IJMS
Vol 43, No 3, May 2018

Review Article

Ovarian Hyperstimulation Syndrome: A Narrative Review of Its Pathophysiology, Risk Factors, Prevention, Classification, and Management

Bahia Namavar Jahromi[1,2], MD;
Mohammad Ebrahim Parsanezhad[1,2], MD;
Zahra Shomali[2,3], MD;
Pardis Bakhshai[2,3], MD;
Mahshid Alborzi[2,3], MD;
Najmeh Moin Vaziri[1], MD, PhD;
Zahra Anvar[1], PhD

[1]Infertility Research Center, Shiraz University of Medical Sciences, Shiraz, Iran;
[2]Department of Obstetrics and Gynecology, Shiraz Medical School, Shiraz University of Medical Sciences, Shiraz, Iran;
[3]Student Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Correspondence:
Bahia Namavar Jahromi, MD;
Department of Obstetrics and Gynecology, Shahid Faghihi Hospital, Zand Blvd., Shiraz, Iran
Tel: +98 917 3158723
Fax: +98 71 32332365
Email: namavarb@sums.ac.ir
Received: 12 November 2016
Accepted: 01 January 2017

What's Known

- Ovarian hyperstimulation syndrome (OHSS) is the most serious iatrogenic complication of ovulation induction. OHSS is almost always associated with exogenous gonadotropin stimulation, followed by hCG administration, for triggering final oocyte maturation. OHSS can be effectively prevented and managed during the early stages.

What's New

- Since OHSS is an important topic in the field of IVF, we reviewed the relevant articles on the ways to have an OHSS-free clinic. GnRH antagonist protocol, GnRHa triggering, and freeze-all approach for high-risk women and adjuvant therapies, discussed in this manuscript, can effectively prevent OHSS.

Abstract

Ovarian hyperstimulation syndrome (OHSS) is a serious complication of ovulation induction that usually occurs after gonadotropin stimulation, followed by human chorionic gonadotropin administration, for infertility treatment. The existing knowledge about the pathophysiology, risk factors, and primary and secondary methods for the prevention of OHSS is reviewed in this manuscript. The clinical manifestations and characteristics of mild, moderate, severe, and critical forms of the syndrome are defined. The methods of handling affected cases as outpatient or in-hospital management methods as well as indications for hospitalization are summarized in this review. The clinical and biochemical routes of assessing and monitoring hospitalized patients with OHSS, various drugs and medical treatment strategies including indications for aspiration of the ascitic fluid and pleural effusion, and also rare indications for surgery are briefly explained in this article. Severe OHSS, which two decades ago was considered an iatrogenic life-threatening condition, can now be effectively prevented or managed during the early stages. An OHSS-free clinic can be established nowadays by carefully considering the endocrinology of ovulation and using appropriate and dose-adjusted pharmaceutical agents, which are summarized and discussed in this review.

Please cite this article as: Namavar Jahromi B, Parsanezhad ME, Shomali Z, Bakhshai P, Alborzi M, Vaziri MN, Anvar Z. Ovarian Hyperstimulation Syndrome: A Narrative Review of Its Pathophysiology, Risk Factors, Prevention, Classification, and Management. Iran J Med Sci May. 2018;43(3):248-260.

Keywords ● Ovarian hyperstimulation syndrome ● Pathophysiology ● Risk factors ● Prevention ● Classification ● Fertilization in vitro

Introduction

Ovarian hyperstimulation syndrome (OHSS) is considered an iatrogenic consequence of ovulation induction during the management of infertility during in vitro fertilization (IVF) cycles.[1] Controlled ovarian stimulation (COS) is aimed at producing more oocytes; nonetheless, occasionally OHSS, accompanied by its serious complications, develops. We performed this narrative review to summarize the latest knowledge about the pathophysiology, risk factors, prevention, classification, and management of OHSS. Additionally, we sought to introduce the methods whereby OHSS-free infertility clinics can be established.

Pathophysiology

The hallmark of OHSS is an increase in the permeability of the capillaries, resulting in a fluid shift form the intravascular space to the extravascular compartments. Vascular endothelial growth factor (VEGF) plays a critical role in the pathogenesis of OHSS by increasing vascular permeability. VEGF is secreted by the granulosa cells, and human chorionic gonadotropin (hCG) stimulates its secretion. Severe OHSS is associated with higher levels of VEGF.[2]

The other suggested factors that may act directly or indirectly on the development or severity of OHSS are angiotensin II, insulin-like growth factor, epidermal growth factor, transforming growth factor alpha and beta, basic fibroblast growth factor, platelet-derived growth factor, interleukin-1B, and interleukin-6.[3,4]

The intra-ovarian renin-angiotensin system (RAS) is another pathophysiological mechanism implicated in OHSS. Furthermore, hCG activates the RAS, which is confirmed by the association of high renin activity in the follicular fluid of women with OHSS. High levels of the VEGF and the RAS seem to play a role in the development of OHSS.[5]

Prevention of Ovarian Hyperstimulation Syndrome

The prevention of OHSS is based on its prediction. There is no method that can completely abolish OHSS. However, its prevention can be lifesaving and is principally preferred over its treatment.

The primary risk factors for OHSS are young age, low body mass index, polycystic ovarian syndrome (PCOS), and history of previous OHSS.[6]

Serum anti-Müllerian hormone (AMH) is a biomarker that may predict the risk of OHSS. Lee and colleagues[7] suggested that an AMH level >3.36 ng/mL was able to predict the development of OHSS (sensitivity=90.5% and specificity=81.3%). The antral follicle count (AFC) is also predictive of OHSS. In 2012, Jayaprakasan et al.[8] reported that an AFC≥24 correlated with an increased risk of moderate-to-severe OHSS.

The secondary risk factors depend on ovarian response to COS. Ultrasound monitoring and serum E_2 are the vital components of surveillance for OHSS. A large number of growing follicles on the day of triggering (>14 follicles with a diameter of 11 mm) and a large number of oocytes retrieved are the risk factors for OHSS.[9] During COS, serum estradiol monitoring is a significant predictor to control the risk of OHSS. A rapid rise in estradiol levels and serum estradiol concentrations >2500 pg/mL are important predictive factors.[10-12] However, none is capable of independently forecasting OHSS.[13,14]

Primary Prevention

1- Ovulation induction regimens: The risk of OHSS should be assessed individually based on the history, physical examination, ultrasound results, and the AFC.[15] Patients with PCOS are at a higher risk for OHSS. The minimum gonadotropin dose should be used for ovulation induction in patients with PCOS, and step-up regimens are considered superior to step-down regimens. During a step-up regimen, ovulation induction is started with a low dose of gonadotropin (75 IU). Gonadotropin will be increased after 14 days only if an appropriate ovarian response with a growing follicle >10 mm has not been developed. The appropriate dose will be continued until at least 1 follicle ≥18 mm is produced.[16]

2- Metformin: A recent Cochrane Review, which was based on 8 randomized controlled trials with 798 cases, concluded that metformin significantly reduced the risk of OHSS by 63% and increased the clinical pregnancy rates, with no effect on live birth rates.[17] A daily dose between 1000 and 2000 mg at least 2 months prior to COS was recommended to prevent OHSS.[18]

3- Aromatase inhibitors for ovulation induction: Aromatase inhibitors act through the downregulation of estrogen production by inhibiting cytochrome p450 enzymes. They eventually increase the pituitary secretion of follicle-stimulating hormone and promote the folliculogenesis. Consequently, the negative feedback mechanisms remain intact and decrease the incidence of OHSS during ovulation induction.[19] However, a recent Cochrane Review failed to show any difference in the rates of OHSS after aromatase inhibitors in contrast to other ovulation induction drugs.[20]

4- Individualizing the treatment regimens of in vitro fertilization: COS should be individualized, and gonadotropin administration should be tailored to every single woman separately to prevent OHSS. A combination of the AFC and AMH is considered to serve as the best biomarker to predict the possibility of an excessive response.[21]

5- Laparoscopic ovarian drilling in patients with polycystic ovarian syndrome: laparoscopic

ovarian drilling (LOD) or cauterization of polycystic ovaries may be regarded as an alternative method to enhance ovulation before ovarian stimulation. The main advantage of LOD is decreasing the dose and duration of gonadotropins required for ovulation induction. LOD may be performed for one or both ovaries, inducing 4–10 cauterization points with the depths of 4–10 mm. Drilling fewer than 4 points on each ovary may lead to lower pregnancy rates, and inducing more than 10 points may cause ovarian damage. The best outcomes have been seen in slim women with high serum levels of luteinizing hormone (LH).[22,23]

6- Human chorionic gonadotropin alternatives for ovulation triggering: The drug of choice to trigger the final maturation of follicles should be selected based on the predicted risk of OHSS development. It should be kept in mind that there is no agent capable of completely eliminating the risk of OHSS. Exogenous hCG has been used to induce LH surge for a long time now. Nonetheless, its prolong half-life leads to long luteotrophic effects, whereas the half-life of LH is approximately 60 minutes and that of hCG exceeds 24 hours.[24]
   a- Reducing human chorionic gonadotropin doses: It should be noted that trial of hCG with lower doses instead of the conventional dose of 10000 IU has not impacted clinical outcomes. Even so, questions still remain over the capacity to reduce the risk of OHSS.[25] It has been suggested that with serum estradiol concentrations >3000 μg/mL, it would be advisable to reduce the dose of hCG to half. There is, however, no definitive consensus on it.[26]
   b- Gonadotropin-releasing hormone agonist (GnRHa): GnRHa induces shorter mid-cycle gonadotropin surge (for 24–36 h) in contrast to hCG by stimulation of the pituitary LH secretion. GnRHa triggering during a GnRH antagonist IVF protocol virtually eliminates the risk of OHSS in a freeze-all approach for high-risk women.[27] In a meta-analysis carried out by Griesinger et al. after the administration of GnRHa to trigger final oocyte maturation in antagonists IVF cycles, the ongoing pregnancy rates were low compared to those in the conventional hCG triggering cycles.[28,29]
   c- Recombinant luteinizing hormone: The administration of recombinant LH to mimic the endogenous LH surge with a half-life of only 10 hours is a theoretically potential strategy for prevention of OHSS in high-risk patients. Nevertheless, Youssef and colleagues[30] did not report any difference in the risk of OHSS between recombinant LH and urinary HCG. Furthermore, recombinant LH has been associated with a lower pregnancy rate and a poor cost-benefit ratio.[31]

7- Gonadotropin-releasing hormone antagonist as an alternative to the long agonist IVF protocol: It has been proven that patients who are at a high risk for developing OHSS would have a minimal risk after undergoing GnRH antagonist protocols.[32,33] However, there have been controversies regarding the efficacy and pregnancy rates after GnRH antagonist protocols during the early years of their utilization.[34,35,36]

Secondary Prevention

Secondary preventive measures should be undertaken in patients with an exaggerated response to COS.

1- Coasting or delaying human chorionic gonadotropin administration: In patients in whom a dangerously high serum E_2 concentration is reached or a large number of follicles are developed, hCG triggering might be delayed for several days until E_2 levels decrease or plateau.[37] During the coasting period, no gonadotropin should be administered. Serum estradiol level usually doubles every 2 days, and follicle diameter rises 1.5–2 mm per day when the leading follicles have reached 8–10 mm and the LH receptors have appeared. After the administration of gonadotropins is stopped, mature follicles continue to grow in size for 4 days and serum estradiol concentrations continue to increase for about 1 or 2 days. Withholding should not last more than 4 days to avoid decreasing the pregnancy rates, which would happen following longer periods of coasting.[32,38] Still, there are controversies regarding the benefits of coasting compared to other interventions.[39]

2- Cryopreservation of all embryos: Although there is inadequate evidence in support of routine cryopreservation in a Cochrane Review with two randomized controlled trials, recent studies have reported that the most effective method in preventing OHSS is the use of a GnRHa trigger and then cryopreservation of all embryos.[40-42]

3- Cancellation of the cycle: Withholding the final HCG triggering is the only definite method for prevention of OHSS,[43] during GnRHa IVF protocoles when ultrasound scans show large numbers of follicles with very high levels of estrogens. The critical values of estradiol for withholding hCG to hamper OHSS have been reported from 2000 pg/mL (for intrauterine insemination) to 4000 pg/mL (for IVF cycles) in different studies.[44-46] However during GnRH antagonist protocols high estrodial levels are well tolerated.

4- Albumin: Intravenous administration of albumin is suggested to prevent OHSS. It is hypothesized that albumin prevents vasoactive materials to be released from the corpus luteum and inhibits the synthesis of other additional substances that may induce OHSS. Also, the oncotic effect of albumin serves to maintain the intravascular volume and can prevent the development of hypovolemia, hemoconcentration, ascites, and pleural effusion. Several large randomized controlled trials have demonstrated the efficacy of prophylactic albumin administration in reducing OHSS.[47-49] The administration of 20–50 g of 25% albumin at the time of oocyte retrieval has been proposed to decrease the risk of OHSS.[50] The disadvantages of albumin, including allergic reactions, and virus/prion transmission, should be considered[51] and its routine use cannot be recommended.[48] However, a systematic review published in 2010 concluded that prophylactic intravenous albumin not only failed to decrease the incidence of severe OHSS but also reduced pregnancy rates.[52]

5- Calcium: Naredi and Karunakaran[53] reported that calcium infusion was able to prevent severe OHSS, but the observed effect was not greater than that of cabergoline. A dose of 10 mL of calcium gluconate solution of 10% in 200 mL of physiologic saline was successfully infused over a 40-minute period during a clinical trial. This infusion was administered 30 minutes after oocyte retrieval on the day of ovum pick-up and the first three days after.[53,54]

6- Hydroxyethyl starch solution: Hydroxyethyl starch (HES) is a synthetic colloid, glycogen-like polysaccharide and is obtained via the hydrolysis and consequent hydroxyethylation of the highly branched amylopectin. HES solutions are available in variable chemical properties with different molecular weights. Although the HES solution is a useful volume expander and perhaps is even more effective than human albumin based on several small studies, the efficacy of HES solutions compared to albumin should be further evaluated.[55] In a study on 100 patients at high risk of OHSS with ≥20 follicles and serum estradiol levels >3000 pg/mL, the administration of 1000 mL of 6% HES during oocyte retrieval and an additional 500 mL 48 hours later led to a significant decrease in severe OHSS.[56,57] Ghahiri et al.[47] also reported that by the administration of 1000 mL of 6% HES on the day of oocyte retrieval, the incidence of OHSS was more effectively reduced compared to the administration of cabergoline and human albumin.[47]

7- Dopamine agonists in the prevention of ovarian hyperstimulation syndrome (cabergoline): VEGF, as the main cause of OHSS, is responsible for an increase in the capillary permeability during the hyperstimulation of the ovarian follicles by binding to VEGF receptor 2.[58-60] Cabergoline is a dopamine agonist that is suggested to successfully reduce the incidence of moderate OHSS (OR=0.38, 95% CI=0.19–0.78), with no significant effect on clinical pregnancy rates and miscarriage rates.[61] A pilot study designed by Alvarez et al.[58] tried to determine whether cabergoline could prevent OHSS and also what its effects were on assisted reproductive technology (ART) outcomes such as implantation and pregnancy rates. The authors' high-risk patients took a daily oral dose of 0.5 mg of cabergoline for 8 days, starting on the day of hCG administration, and were matched to a control group. Their results revealed that cabergoline was safe with comparable results to the ART outcomes. Moreover, research has shown that cabergoline can decrease hematocrit, hemoglobin, amount of ascetic fluid, and rate of moderate OHSS, with no effect on estradiol levels.[62] Similarly, a Cochrane Review by Tang et al.[61] concluded that cabergoline efficiently reduced the rate of moderate OHSS, with no significant effect on clinical pregnancy rates and miscarriage rates, although it was not able to prevent severe OHSS. Thus, the administration of oral cabergoline, starting on the day of hCG triggering at a dose of 0.5 mg for 8 days, is recommended.[58,62,63]

8- Vasopressin-induced vascular endothelial growth factor secretion blockade: Relcovaptan is a non-peptide vasopressin receptor antagonist that has the ability to inhibit the VEGF by adjusting vascular smooth muscle proliferation and vasoconstriction. In a study on hyperstimulated rat models,

with relcovaptan prescription, lower concentrations of the VEGF-A in the peritoneal fluid and lesser ovarian weight gain and decrease in the number of corpora lutea were observed.[64]

9- Low-dose aspirin: Supraphysiological ovarian stimulation may cause platelet hyperstimulation, which is associated with OHSS. Therefore, low-dose aspirin therapy (100 mg daily, starting on the 1st day of ovarian stimulation) may reduce the risk of severe OHSS.[65,66]

10- In vitro maturation (IVM) of immature oocytes: IVM can be considered as another alternative method for fertility treatment in over-responding patients who are at high risk for OHSS.[67,68] Mature and immature oocyte retrieval, followed by IVM, would be an efficient method for the prevention of OHSS during ovarian stimulation. In an IVM protocol, for over-responding women who have >20 growing follicles with a mean diameter >10 mm, gonadotropins should be stopped and 10000 IU of hCG should be administered when the leading follicles reach 12–14 mm in diameter. Oocyte collection is performed 36 hours later followed by IVM.[69,70]

Treatment of Ovarian Hyperstimulation Syndrome

The clinical treatment of OHSS depends on its severity, complications, and absence or presence of pregnancy.[71-73] The treatment involves dealing with electrolytic imbalance, hemodynamic changes, liver dysfunction, pulmonary manifestations, hypoglobulinemia, febrile morbidity, thromboembolic events, adnexal torsion, and neurological manifestations.[2,74]

Clinical Manifestations and Classification

The main event in the pathogenesis of OHSS is ovarian enlargement, secretion of vasoactive substances, ascites, and hypovolemia resulting from an acute extravasation of fluid into the interstitial space.[2,75] OHSS is classified into 4 categories based on the severity of symptoms, signs, and laboratory findings.

1- Mild ovarian hyperstimulation syndrome: It is defined by the enlargement of bilateral ovaries with multiple follicular and corpus luteal cysts, measuring up to 8 cm and accompanied by abdominal bloating and mild abdominal pain.

2- Moderate ovarian hyperstimulation syndrome: It is characterized by the enlargement of the ovaries up to 12 cm, accompanied by abdominal bloating due to an increase in ovarian size and gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhea) as well as ultrasound evidence of ascites. A rapid weight gain of over 3 kg might be the initial sign of moderate hyperstimulation.

3- Severe ovarian hyperstimulation syndrome: About 2% of OHSS cases are classified as severe. The severe form is described by the presence of large ovarian cysts (>12×12 cm), clinical ascites with or without hydrothorax, hyperkalemia (potassium >5 mmol/L), hyponatremia (sodium <135 mmol/L), hypo-osmolarity (osmolarity <282 mOsm/kg), hypoproteinemia (serum albumin <35 g/L), oliguria (<300 mL/d or <30 mL/h), creatinine 1.1–1.5 mg/dL, and hypovolemic shock. Hemoconcentration with hematocrit >45%, white cell count >15000, liver dysfunction, increased blood viscosity, and thromboembolic events occurs in the most severe cases.[2,75-77]

4- Critical ovarian hyperstimulation syndrome: It is diagnosed when there is severe ascites or hydrothorax, hematocrit >55%, white cell count >25000/mL, oliguria or anuria, creatinine ≥1.6 mg/dL, creatinine clearance <50 mL/min, thromboembolism, or acute respiratory distress syndrome.[2,75-78]

Outpatient Management for Moderate Ovarian Hyperstimulation Syndrome

Spontaneous regression occurs over 10 to 14 days in mild-to-moderate cases, but it may take longer if implantation occurs. Mild degrees of OHSS do not need any special treatment. Moderate OHSS may be followed up by daily telephone calls as a minimum in addition to office visits twice weekly. The evaluation consists of liver function tests, pelvic ultrasound, complete blood count, and coagulation profile. The patients should be directed to report to the hospital in case of development of dyspnea, decrease in urine volume, or upon starting any unusual symptoms such as leg swelling, numbness, dizziness, and neurological problems.[71]

In-Hospital Management of Severe Ovarian Hyperstimulation Syndrome

1- Indications for admission: Patients with severe OHSS should be admitted to the hospital for treatment if they suffer from severe abdominal pain, nausea and vomiting, hemoconcentration, severe ascites, profound oliguria or anuria,

decrease in blood pressure, tachypnea or dyspnea, light-headedness or syncope, electrolyte disturbances (hyponatremia and hyperkalemia), or abnormal liver function test. Careful observation of an OHSS patient is highly recommended because a mild disease may suddenly progress to the advanced stages.[74,77]

2- Biochemical monitoring in the hospital: The laboratory results of severely affected OHSS patients are comprised of hemoconcentration (hematocrit >45%), decreased creatinine clearance (serum creatinine >1.2 and creatinine clearance <50 mL/min), electrolyte imbalances (hyponatremia [sodium <135 mEq/L] and hyperkalemia [potassium >5.0 mEq/L]), leukocytosis (white blood cell count >15000), and elevated liver enzymes.[77,79,80,81]

3- Suggestions for the assessment and monitoring of hospitalized patients with ovarian hyperstimulation syndrome:
   - Vital signs (every 2–8 hours, according to clinical status)[78]
   - Complete physical examination (daily, avoiding bimanual pelvic examination)
   - Weight (recorded daily)
   - Abdominal circumference (at the navel, recorded daily)
   - Ultrasound evaluation of ascites and ovarian size (repeated as necessary to guide management or paracentesis)
   - Daily monitoring of fluid intake and output
   - Pulse oximetry (for patients with symptoms of pulmonary compromise)
   - Chest X-ray and echocardiogram when pleural or pericardial effusion is suspected (repeated as necessary)
   - Pregnancy test
   - Electrolytes (daily)
   - Complete blood count (daily, or more often as needed to guide fluid management)
   - Liver enzymes (repeated as necessary)
   - Serum creatinine or creatinine clearance and urine specific gravity (repeated as necessary)

A- Medical Treatment

1- Circulatory volume correction: The key line of treatment is to correct the circulatory volume and electrolyte imbalance. Every effort should be made to maintain a normal intravascular volume and to conserve adequate renal function. Volume replacement should be started with intravenous crystalloid fluids at a rate of 125–150 mL/h. Rapid initial hydration may be done with a bolus of intravenous fluids (500–1000 mL). Fluids should be administered thoughtfully, in the volumes required, to retain an adequate urine output (>20–30 mL/h) and to reverse hemoconcentration. Dextrose 5% in normal saline is preferable to lactated Ringer's solution. Plasma colloid expanders may be used if necessary. The useful effect of plasma expanders may be transient because they will redistribute into the extravascular space and may exacerbate the ascites. The use of albumin, mannitol, dextran, HES, or fresh frozen plasma with the aim of increasing the intravascular oncotic pressure in order to maintain the intravascular volume is recommended. The advantages of HES solutions over albumin are their high molecular weight (200–1000 kDa vs. 69 kDa) and a nonbiological origin, lower possibility of anaphylactic reactions, and viral contaminations. A clinical trial demonstrated fewer necessary paracenteses, higher urine output, and shorter hospital stays after HES utilization for patients with severe OHSS compared to albumin.[54] Another clinical trial showed comparable results after the administration of HES and HAEMACCEL. However, HAEMACCEL was more cost-effective than HES.[82]

2- Electrolyte replacement: Salt and water restriction is not broadly advocated since sodium and water restriction does not affect the patient's weight, peripheral edema, or abdominal circumference.[74] Hyperkalemia may lead to cardiac dysrhythmia, and acute management includes treatments that shift potassium into the intracellular space (sodium bicarbonate, insulin and glucose, and albuterol). Calcium gluconate may be used to protect the cardiac tissue against hyperkalemia. ECG signs of hyperkalemia show the need for urgent treatment with calcium gluconate. Kayexalate also may be used to remove potassium from the body slowly with the onset of action in 1–2 hours and can be administered orally or rectally as a retention enema.[79,80,81]

3- Anticoagulant therapy: Venous thrombosis is the most significant life-threatening complication of OHSS. When there is a risk of thrombosis, preventive measures are indicated. The risk factors for thromboembolism in moderate-to-severe OHSS are as follows:[83-85] immobilization, pressure induced by large ovaries or ascites on pelvic vessels, and hypercoagulable states due to pregnancy or high estrogen

levels. The incidence of deep vein thrombosis is obviously increased in patients with Leiden factor V mutation, antithrombin III deficiency, protein C and S deficiency, and personal or familial history of thrombosis.[84]

The utilization of low-molecular weight heparin improves the risk of thrombotic complications. Enoxaparin (40 mg/d) or dalteparin (5000 IU/d) is recommended for thromboprophylaxis with easy administration and no need for monitoring.[86] Anticoagulation is recommended for pregnant women and should be continued at least to the end of the first trimester.[74] There are reports on late thrombosis even up to 20 weeks post embryo transfer and many researchers are in favor of the continuation of heparin therapy for many weeks. Venous thromboemboli may develop even in a moderate OHSS, which might be related to the activation of the intrinsic coagulation cascade.[87,88]

4- Antibiotic treatment: The administration of antibiotics is not unusual in the treatment of OHSS because of repeated catheterizations, venipuncture, pleural drainage, and transvaginal aspiration of the ascitic fluid. Preoperative antibiotic prophylaxis is highly recommended.[88]

5- Diuretics: Diuretic therapy without previous volume expansion might be harmful inasmuch as it may further constrict the intravascular volume and worsen hypotension and its squeals. Diuretics may raise blood viscosity and increase the risk of venous thrombosis. The administration of diuretics is usually limited to the management of pulmonary edema.[88]

6- Dopamine: Dopamine is used in oliguric patients with severe OHSS and confers a notable improvement in renal function.[85,89] Dopamine acts through increasing renal blood flow and the glomerular filtration rate.[89]

7- Indomethacin: Indomethacin, a prostaglandin synthesis inhibitor, is also hypothesized to perform potential roles in the pathophysiology of OHSS. However, in clinical practice, indomethacin cannot induce clinical improvement in the amount of the ascitic fluid in severe OHSS patients. In addition, indomethacin may interfere with renal perfusion, leading to oliguria and renal failure; thus, it is not recommended for the treatment of patients with OHSS.[74]

8- Aspiration of the ascitic fluid and pleural effusion in severe ovarian hyperstimulation syndrome: The development of ascites is the hallmark of OHSS. The most common reason for hospitalization is symptoms due to ascites. Aspiration is not suggested for all patients. Paracentesis is applied via the transabdominal or transvaginal method for severe abdominal pain, respiratory compromise as shown by tachypnea and pulse oximetry, and renal compromise as demonstrated by oliguria and increased creatinine concentrations.[90-92]

a- Abdominal paracentesis: Soon after the paracentesis procedure, urinary output increases together with a decrease in the patient's weight, lower extremity edema, and abdominal circumference. In addition, the creatinine clearance rate is raised following the procedure. Paracentesis decreases respiratory and abdominal distress but since the fluid tends to return, some patients need frequent paracenteses and drainage of effusions. The amount of fluid drainage can vary between 200 and 4000 mL. Ultrasonographic guidance minimizes the risk of damage to the ovaries. The percutaneous placement of a pigtail catheter may be a safe and effective alternative to multiple vaginal or abdominal paracenteses in severe OHSS patients. The monitoring of plasma proteins is necessary, and HES or human albumin should be infused whenever needed.[74]

b- Transvaginal aspiration under ultrasound guidance: Transvaginal aspiration under ultrasound guidance is an effective and safe procedure. Injury to the ovaries is avoided when the puncture is performed under ultrasonic visualization. Since the pouch of Douglas is the best site for the drainage of ascites, no anesthesia is required.[87,88]

c- Autotransfusion of the ascetic fluid: Aspiration of the ascitic fluid under transvaginal ultrasound guidance and autotransfusion of the aspirated fluid have been recommended for the management of severe OHSS. The procedure is safe and easy and demonstrates a prominent physiological achievement in correcting the maldistribution of the fluid and proteins to the circulation without the use of heterogeneous biological material. However, some researchers do not advocate the autotransfusion of the ascitic fluid because it possibly contains active cytokines, which would be reinjected into the circulation and might prolong the symptoms.[87,88]

d- Treatment of pulmonary complications and pleurocentesis: The assessment and treatment of patients with dyspnea in severe OHSS starts with a complete physical examination, chest X-ray and ultrasound, and arterial blood gases. It is necessary to assess any pulmonary condition that may lead to hypoxia. Severe ascites may be accompanied by hydrothorax, particularly on the right side, due to the transfer of the abdominal fluid to the chest through the thoracic duct. Paracentesis will usually be effective in the resolution of hydrothorax, and thoracentesis may be reserved for those with bilateral or severe persistent pleural effusions. Pericardial effusion rarely occurs but if it does, drainage may be necessary by an expert physician.[92,93]

B- Surgical Treatment

1- Surgery for ruptured cysts: Laparotomy should usually be avoided in OHSS. When proven necessary in cases with hemorrhagic ovarian cysts, it should be done by skilled gynecologists to perform hemostasis and to save the ovaries.[94]
2- Surgery for ovarian torsion: Ovarian torsion is a rare complication of ovulation induction and leads to the loss of one or both ovaries if not diagnosed and treated surgically on time. The symptoms of ovarian torsion include severe unilateral colicky adnexal pain. Ultrasonography with Doppler flow study can be diagnostic; nevertheless, a result of a normal blood flow does not rule out ovarian torsion.[94]
3- Surgery for ectopic or heterotopic pregnancy associated with ovarian hyperstimulation syndrome: The association between OHSS and ectopic or heterotopic pregnancy is not common, and the diagnosis needs a high index of suspicion. However, in ART cycles, due to the presence of multiple oocytes or multiple embryos and special manipulations, ectopic or heterotopic pregnancies may occur more than usual. The diagnosis of tubal pregnancy is not always possible via vaginal ultrasound examination at early stages. The presence of enlarged OHSS ovaries also obscures the vision during ultrasound scanning. Also, the presence of fluid in the pouch of Douglas is of limited diagnostic importance in the presence of ascites.[74] All the aforementioned issues make the diagnosis difficult. However, when ectopic or heterotopic pregnancies are diagnosed, surgery is indicated in the majority of the cases.
4- Pregnancy termination: Pregnancy termination is done in extreme cases to save the mother's life. The termination of pregnancy in critical and prolonged cases is performed in order to stop hormone production and to terminate the cascade of events leading to OHSS. The termination of pregnancy has been stated to improve the clinical respiratory, cardiological, nephrological, hematological, and vascular complications.[74]

Conclusion

Nowadays, the establishment of OHSS-free clinics is feasible through careful primary evaluation of infertile couples, paying special attention to the risk factors for OHSS development and considering the aforementioned primary preventive measures. Even after the commencement of ovulation induction, it is possible to prevent severe OHSS in almost all patients by careful monitoring, early prediction of an ongoing ovarian hyper-responsiveness, and utilization of appropriate management strategies. Severe OHSS, which was deemed an iatrogenic life-threatening condition two decades ago, can now be effectively prevented and managed during the early stages. This advancement should be considered a great revolution in ovulation induction and infertility management, achieved on the basis of increasing endocrinology knowledge and advances in the field of pharmaceutics.

Conflict of Interest: None declared.

References

1. Mathur RS, Akande AV, Keay SD, Hunt LP, Jenkins JM. Distinction between early and late ovarian hyperstimulation syndrome. Fertil Steril. 2000;73:901-7. PubMed PMID: 10785214.
2. Pellicer A, Albert C, Mercader A, Bonilla-Musoles F, Remohi J, Simon C. The pathogenesis of ovarian hyperstimulation syndrome: In vivo studies investigating the role of interleukin-1beta, interleukin-6, and vascular endothelial growth factor. Fertil Steril. 1999;71:482-9. PubMed PMID: 10065786.
3. Whelan JG, 3rd, Vlahos NF. The ovarian hyperstimulation syndrome. Fertil Steril. 2000;73:883-96. PubMed PMID: 10785212.
4. Naredi N, Talwar P, Sandeep K. VEGF antagonist for the prevention of ovarian hyperstimulation syndrome: Current status. Med J Armed Forces India. 2014;70:58-63. doi: 10.1016/j.mjafi.2012.03.005. PubMed

PMID: 24623949; PubMed Central PMCID: PMCPMC3946416.
5. Herr D, Bekes I, Wulff C. Local Renin-Angiotensin system in the reproductive system. Front Endocrinol (Lausanne). 2013;4:150. doi: 10.3389/fendo.2013.00150. PubMed PMID: 24151488; PubMed Central PMCID: PMCPMC3798827.
6. Practice Committee of American Society for Reproductive M. Ovarian hyperstimulation syndrome. Fertil Steril. 2008;90:S188-93. doi: 10.1016/j.fertnstert.2008.08.034. PubMed PMID: 19007627.
7. Lee TH, Liu CH, Huang CC, Wu YL, Shih YT, Ho HN, et al. Serum anti-Mullerian hormone and estradiol levels as predictors of ovarian hyperstimulation syndrome in assisted reproduction technology cycles. Hum Reprod. 2008;23:160-7. doi: 10.1093/humrep/dem254. PubMed PMID: 18000172.
8. Jayaprakasan K, Chan Y, Islam R, Haoula Z, Hopkisson J, Coomarasamy A, et al. Prediction of in vitro fertilization outcome at different antral follicle count thresholds in a prospective cohort of 1,012 women. Fertil Steril. 2012;98:657-63. doi: 10.1016/j.fertnstert.2012.05.042. PubMed PMID: 22749225.
9. Mathur RS, Tan BK. British Fertility Society Policy and Practice Committee: Prevention of ovarian hyperstimulation syndrome. Hum Fertil (Camb). 2014;17:257-68. doi: 10.3109/14647273.2014.961745. PubMed PMID: 25380089.
10. Grochowski D, Wolczynski S, Kuczynski W, Domitrz J, Szamatowicz J, Szamatowicz M. Correctly timed coasting reduces the risk of ovarian hyperstimulation syndrome and gives good cycle outcome in an in vitro fertilization program. Gynecol Endocrinol. 2001;15:234-8. PubMed PMID: 11447736.
11. Papanikolaou EG, Pozzobon C, Kolibianakis EM, Camus M, Tournaye H, Fatemi HM, et al. Incidence and prediction of ovarian hyperstimulation syndrome in women undergoing gonadotropin-releasing hormone antagonist in vitro fertilization cycles. Fertil Steril. 2006;85:112-20. doi: 10.1016/j.fertnstert.2005.07.1292. PubMed PMID: 16412740.
12. Al-Shawaf T, Zosmer A, Hussain S, Tozer A, Panay N, Wilson C, et al. Prevention of severe ovarian hyperstimulation syndrome in IVF with or without ICSI and embryo transfer: A modified 'coasting' strategy based on ultrasound for identification of high-risk patients. Hum Reprod. 2001;16:24-30. PubMed PMID: 11139531.
13. Delvigne A, Rozenberg S. Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): A review. Hum Reprod Update. 2002;8:559-77. PubMed PMID: 12498425.
14. Humaidan P, Quartarolo J, Papanikolaou EG. Preventing ovarian hyperstimulation syndrome: Guidance for the clinician. Fertil Steril. 2010;94:389-400. doi: 10.1016/j.fertnstert.2010.03.028. PubMed PMID: 20416867.
15. Lamazou F, Legouez A, Letouzey V, Grynberg M, Deffieux X, Trichot C, et al. [Ovarian hyperstimulation syndrome: Pathophysiology, risk factors, prevention, diagnosis and treatment]. J Gynecol Obstet Biol Reprod (Paris). 2011;40:593-611. doi: 10.1016/j.jgyn.2011.06.008. PubMed PMID: 21835557.
16. Howles CM, Alam V, Tredway D, Homburg R, Warne DW. Factors related to successful ovulation induction in patients with WHO group II anovulatory infertility. Reprod Biomed Online. 2010;20:182-90. doi: 10.1016/j.rbmo.2009.11.017. PubMed PMID: 20113956.
17. Tso LO, Costello MF, Albuquerque LE, Andriolo RB, Freitas V. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2009:CD006105. doi: 10.1002/14651858.CD006105.pub2. PubMed PMID: 19370625.
18. El-Faissal Y. Approaches to complete prevention of OHSS. Middle East Fertil Soc J. 2014;19:13-5.
19. Lee VC, Ledger W. Aromatase inhibitors for ovulation induction and ovarian stimulation. Clin Endocrinol (Oxf). 2011;74:537-46. doi: 10.1111/j.1365-2265.2011.04006.x. PubMed PMID: 21470277.
20. Franik S, Kremer JA, Nelen WL, Farquhar C. Aromatase inhibitors for subfertile women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2014:CD010287. doi: 10.1002/14651858.CD010287.pub2. PubMed PMID: 24563180.
21. Bosch E, Ezcurra D. Individualised controlled ovarian stimulation (iCOS): Maximising success rates for assisted reproductive technology patients. Reprod Biol Endocrinol. 2011;9:82. doi: 10.1186/1477-7827-9-82. PubMed PMID: 21693025; PubMed Central PMCID: PMCPMC3150250.
22. Homburg R. Management of infertility and prevention of ovarian hyperstimulation in women with polycystic ovary syndrome. Best Pract Res Clin Obstet Gynaecol.

2004;18:773-88. doi: 10.1016/j.bpobgyn.2004.05.006. PubMed PMID: 15380146.
23. Pirwany I, Tulandi T. Laparoscopic treatment of polycystic ovaries: Is it time to relinquish the procedure? Fertil Steril. 2003;80:241-51. PubMed PMID: 12909478.
24. Castillo JC, Humaidan P, Bernabeu R. Pharmaceutical options for triggering of final oocyte maturation in ART. Biomed Res Int. 2014;2014:580171. doi: 10.1155/2014/580171. PubMed PMID: 25133168; PubMed Central PMCID: PMCPMC4123594.
25. Kashyap S, Parker K, Cedars MI, Rosenwaks Z. Ovarian hyperstimulation syndrome prevention strategies: Reducing the human chorionic gonadotropin trigger dose. Semin Reprod Med. 2010;28:475-85. doi: 10.1055/s-0030-1265674. PubMed PMID: 21082506.
26. Chen X, Chen SL, He YX, Ye DS. Minimum dose of hCG to trigger final oocyte maturation and prevent OHSS in a long GnRHa protocol. J Huazhong Univ Sci Technolog Med Sci. 2013;33:133-6. doi: 10.1007/s11596-013-1085-z. PubMed PMID: 23392722.
27. Kol S, Humaidan P. GnRH agonist triggering: Recent developments. Reprod Biomed Online. 2013;26:226-30. doi: 10.1016/j.rbmo.2012.11.002. PubMed PMID: 23337420.
28. Griesinger G, Diedrich K, Devroey P, Kolibianakis EM. GnRH agonist for triggering final oocyte maturation in the GnRH antagonist ovarian hyperstimulation protocol: A systematic review and meta-analysis. Hum Reprod Update. 2006;12:159-68. doi: 10.1093/humupd/dmi045. PubMed PMID: 16254001.
29. Kolibianakis EM, Schultze-Mosgau A, Schroer A, van Steirteghem A, Devroey P, Diedrich K, et al. A lower ongoing pregnancy rate can be expected when GnRH agonist is used for triggering final oocyte maturation instead of HCG in patients undergoing IVF with GnRH antagonists. Hum Reprod. 2005;20:2887-92. doi: 10.1093/humrep/dei150. PubMed PMID: 15979994.
30. Youssef MA, Al-Inany HG, Aboulghar M, Mansour R, Abou-Setta AM. Recombinant versus urinary human chorionic gonadotrophin for final oocyte maturation triggering in IVF and ICSI cycles. Cochrane Database Syst Rev. 2011:CD003719. doi: 10.1002/14651858.CD003719.pub3. PubMed PMID: 21491386.
31. Papanikolaou EG, Verpoest W, Fatemi H, Tarlatzis B, Devroey P, Tournaye H. A novel method of luteal supplementation with recombinant luteinizing hormone when a gonadotropin-releasing hormone agonist is used instead of human chorionic gonadotropin for ovulation triggering: A randomized prospective proof of concept study. Fertil Steril. 2011;95:1174-7. doi: 10.1016/j.fertnstert.2010.09.023. PubMed PMID: 20979997.
32. Al-Inany HG, Abou-Setta AM, Aboulghar M. Gonadotrophin-releasing hormone antagonists for assisted conception. Cochrane Database Syst Rev. 2006:CD001750. doi: 10.1002/14651858.CD001750.pub2. PubMed PMID: 16855976.
33. Kolibianakis EM, Collins J, Tarlatzis BC, Devroey P, Diedrich K, Griesinger G. Among patients treated for IVF with gonadotrophins and GnRH analogues, is the probability of live birth dependent on the type of analogue used? A systematic review and meta-analysis. Hum Reprod Update. 2006;12:651-71. doi: 10.1093/humupd/dml038. PubMed PMID: 16920869.
34. Xing W, Lin H, Li Y, Yang D, Wang W, Zhang Q. Is the GnRH Antagonist Protocol Effective at Preventing OHSS for Potentially High Responders Undergoing IVF/ICSI? PLoS One. 2015;10:e0140286. doi: 10.1371/journal.pone.0140286. PubMed PMID: 26468951; PubMed Central PMCID: PMCPMC4607293.
35. Devroey P, Aboulghar M, Garcia-Velasco J, Griesinger G, Humaidan P, Kolibianakis E, et al. Improving the patient's experience of IVF/ICSI: A proposal for an ovarian stimulation protocol with GnRH antagonist co-treatment. Hum Reprod. 2009;24:764-74. doi: 10.1093/humrep/den468. PubMed PMID: 19153090.
36. Hershko Klement A, Berkovitz A, Wiser A, Gonen O, Amichay K, Cohen I, et al. GnRH-antagonist programming versus GnRH agonist protocol: A randomized trial. Eur J Obstet Gynecol Reprod Biol. 2015;185:170-3. doi: 10.1016/j.ejogrb.2014.12.021. PubMed PMID: 25594526.
37. Delvigne A, Rozenberg S. A qualitative systematic review of coasting, a procedure to avoid ovarian hyperstimulation syndrome in IVF patients. Hum Reprod Update. 2002;8:291-6. PubMed PMID: 12078839.
38. Griesinger G. Ovarian hyperstimulation syndrome prevention strategies: Use of gonadotropin-releasing hormone antagonists. Semin Reprod Med. 2010;28:493-9. doi: 10.1055/s-0030-1265676. PubMed PMID: 21082508.

39. D'Angelo A, Brown J, Amso NN. Coasting (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome. Cochrane Database Syst Rev. 2011:CD002811. doi: 10.1002/14651858.CD002811.pub3. PubMed PMID: 21678336.
40. Devroey P, Adriaensen P. OHSS Free Clinic. Facts Views Vis Obgyn. 2011;3:43-5. PubMed PMID: 24753847; PubMed Central PMCID: PMCPMC3991410.
41. D'Angelo A. Ovarian hyperstimulation syndrome prevention strategies: Cryopreservation of all embryos. Semin Reprod Med. 2010;28:513-8. doi: 10.1055/s-0030-1265679. PubMed PMID: 21082511.
42. D'Angelo A, Amso N. Embryo freezing for preventing ovarian hyperstimulation syndrome. Cochrane Database Syst Rev. 2007:CD002806. doi: 10.1002/14651858.CD002806.pub2. PubMed PMID: 17636707.
43. Mathur R, Sumaya W. Prevention and management of ovarian hyperstimulation syndrome. Obstetrics, Gynaecology & Reproductive Medicine. 2008;18:18-22. doi: 10.1016/j.ogrm.2007.11.004.
44. Friedman CI, Schmidt GE, Chang FE, Kim MH. Severe ovarian hyperstimulation following follicular aspiration. Am J Obstet Gynecol. 1984;150:436-7. PubMed PMID: 6435453.
45. Forman RG, Frydman R, Egan D, Ross C, Barlow DH. Severe ovarian hyperstimulation syndrome using agonists of gonadotropin-releasing hormone for in vitro fertilization: A European series and a proposal for prevention. Fertil Steril. 1990;53:502-9. PubMed PMID: 2106456.
46. Kummer NE, Feinn RS, Griffin DW, Nulsen JC, Benadiva CA, Engmann LL. Predicting successful induction of oocyte maturation after gonadotropin-releasing hormone agonist (GnRHa) trigger. Hum Reprod. 2013;28:152-9. doi: 10.1093/humrep/des361. PubMed PMID: 23077235.
47. Ghahiri A, Mogharehabed N, Movahedi M, Hosseini N. Evaluation of intravenous hydroxylethyl starch, intravenous albumin 20%, and oral cabergoline for prevention of ovarian hyperstimulation syndrome in patients undergoing ovulation induction. J Res Med Sci. 2015;20:692-6. doi: 10.4103/1735-1995.166228. PubMed PMID: 26622260; PubMed Central PMCID: PMCPMC4638073.
48. Venetis CA, Kolibianakis EM, Toulis KA, Goulis DG, Papadimas I, Tarlatzis BC. Intravenous albumin administration for the prevention of severe ovarian hyperstimulation syndrome: A systematic review and metaanalysis. Fertil Steril. 2011;95:188-96, 96 e1-3. doi: 10.1016/j.fertnstert.2010.05.026. PubMed PMID: 20579987.
49. Ben-Chetrit A, Eldar-Geva T, Gal M, Huerta M, Mimon T, Algur N, et al. The questionable use of albumin for the prevention of ovarian hyperstimulation syndrome in an IVF programme: A randomized placebo-controlled trial. Hum Reprod. 2001;16:1880-4. PubMed PMID: 11527892.
50. Isikoglu M, Berkkanoglu M, Senturk Z, Ozgur K. Human albumin does not prevent ovarian hyperstimulation syndrome in assisted reproductive technology program: A prospective randomized placebo-controlled double blind study. Fertil Steril. 2007;88:982-5. doi: 10.1016/j.fertnstert.2006.11.170. PubMed PMID: 17313946.
51. Tehraninejad ES, Hafezi M, Arabipoor A, Aziminekoo E, Chehrazi M, Bahmanabadi A. Comparison of cabergoline and intravenous albumin in the prevention of ovarian hyperstimulation syndrome: A randomized clinical trial. J Assist Reprod Genet. 2012;29:259-64. doi: 10.1007/s10815-011-9708-4. PubMed PMID: 22231013; PubMed Central PMCID: PMCPMC3288141.
52. Jee BC, Suh CS, Kim YB, Kim SH, Choi YM, Kim JG, et al. Administration of intravenous albumin around the time of oocyte retrieval reduces pregnancy rate without preventing ovarian hyperstimulation syndrome: A systematic review and meta-analysis. Gynecol Obstet Invest. 2010;70:47-54. doi: 10.1159/000286379. PubMed PMID: 20173327.
53. Naredi N, Karunakaran S. Calcium gluconate infusion is as effective as the vascular endothelial growth factor antagonist cabergoline for the prevention of ovarian hyperstimulation syndrome. J Hum Reprod Sci. 2013;6:248-52. doi: 10.4103/0974-1208.126293. PubMed PMID: 24672164; PubMed Central PMCID: PMCPMC3963308.
54. Yakovenko S, Sivozhelezov V, Zorina I, Dmitrieva N, Apryshko V, Voznesenskaya J. Prevention of OHSS by intravenous calcium. Hum Reprod. 2009;24:i61.
55. 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. PubMed PMID: 11384657.
56. 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 placebo controlled study. Eur J Obstet Gynecol Reprod Biol. 2001;96:187-92. PubMed PMID: 11384805.
57. Aboulghar MA, Mansour RT. Ovarian hyperstimulation syndrome: Classifications and critical analysis of preventive measures. Hum Reprod Update. 2003;9:275-89. PubMed PMID: 12859048.
58. Alvarez C, Marti-Bonmati L, Novella-Maestre E, Sanz R, Gomez R, Fernandez-Sanchez M, et al. Dopamine agonist cabergoline reduces hemoconcentration and ascites in hyperstimulated women undergoing assisted reproduction. J Clin Endocrinol Metab. 2007;92:2931-7. doi: 10.1210/jc.2007-0409. PubMed PMID: 17456571.
59. Alvarez C, Alonso-Muriel I, Garcia G, Crespo J, Bellver J, Simon C, et al. Implantation is apparently unaffected by the dopamine agonist Cabergoline when administered to prevent ovarian hyperstimulation syndrome in women undergoing assisted reproduction treatment: A pilot study. Hum Reprod. 2007;22:3210-4. doi: 10.1093/humrep/dem315. PubMed PMID: 17921134.
60. Garcia-Velasco JA. How to avoid ovarian hyperstimulation syndrome: A new indication for dopamine agonists. Reprod Biomed Online. 2009;18 Suppl 2:71-5. PubMed PMID: 19406035.
61. Tang H, Hunter T, Hu Y, Zhai SD, Sheng X, Hart RJ. Cabergoline for preventing ovarian hyperstimulation syndrome. Cochrane Database Syst Rev. 2012:CD008605. doi: 10.1002/14651858.CD008605.pub2. PubMed PMID: 22336848.
62. Moll E, van der Veen F, van Wely M. The role of metformin in polycystic ovary syndrome: A systematic review. Hum Reprod Update. 2007;13:527-37. doi: 10.1093/humupd/dmm026. PubMed PMID: 17767003.
63. Kasum M, Vrcic H, Stanic P, Jezek D, Oreskovic S, Beketic-Oreskovic L, et al. Dopamine agonists in prevention of ovarian hyperstimulation syndrome. Gynecol Endocrinol. 2014;30:845-9. doi: 10.3109/09513590.2014.943716. PubMed PMID: 25093428.
64. Cenksoy C, Cenksoy PO, Erdem O, Sancak B, Gursoy R. A potential novel strategy, inhibition of vasopressin-induced VEGF secretion by relcovaptan, for decreasing the incidence of ovarian hyperstimulation syndrome in the hyperstimulated rat model. Eur J Obstet Gynecol Reprod Biol. 2014;174:86-90. doi: 10.1016/j.ejogrb.2013.12.001. PubMed PMID: 24405730.
65. Varnagy A, Bodis J, Manfai Z, Wilhelm F, Busznyak C, Koppan M. Low-dose aspirin therapy to prevent ovarian hyperstimulation syndrome. Fertil Steril. 2010;93:2281-4. doi: 10.1016/j.fertnstert.2009.01.085. PubMed PMID: 19261278.
66. Varnagy A, Koppan M, Manfai Z, Busznyak C, Bodis J. Low-dose aspirin for prophylaxis of ovarian hyperstimulation syndrome. Fertil Steril. 2008;89:1035-6. doi: 10.1016/j.fertnstert.2008.01.077. PubMed PMID: 18353319.
67. Roque M, Lattes K, Serra S, Sola I, Geber S, Carreras R, et al. Fresh embryo transfer versus frozen embryo transfer in in vitro fertilization cycles: A systematic review and meta-analysis. Fertil Steril. 2013;99:156-62. doi: 10.1016/j.fertnstert.2012.09.003. PubMed PMID: 23040524.
68. Son WY, Yoon SH, Lim JH. Effect of gonadotrophin priming on in-vitro maturation of oocytes collected from women at risk of OHSS. Reprod Biomed Online. 2006;13:340-8. PubMed PMID: 16984762.
69. Lim K, Lee W, Lim J. IVM after interruption of COH for the prevention of OHSS. Fertility and Sterility. 2005;84:S84-S5.
70. Lim KS, Chae SJ, Choo CW, Ku YH, Lee HJ, Hur CY, et al. In vitro maturation: Clinical applications. Clin Exp Reprod Med. 2013;40:143-7. doi: 10.5653/cerm.2013.40.4.143. PubMed PMID: 24505559; PubMed Central PMCID: PMCPMC3913892.
71. Delvigne A, Rozenberg S. Review of clinical course and treatment of ovarian hyperstimulation syndrome (OHSS). Hum Reprod Update. 2003;9:77-96. PubMed PMID: 12638783.
72. Brinsden PR, Wada I, Tan SL, Balen A, Jacobs HS. Diagnosis, prevention and management of ovarian hyperstimulation syndrome. Br J Obstet Gynaecol. 1995;102:767-72. PubMed PMID: 7547731.
73. Son WY, Yoon SH, Lee SW, Ko Y, Yoon HG, Lim JH. Blastocyst development and pregnancies after IVF of mature oocytes retrieved from unstimulated patients with PCOS after in-vivo HCG priming. Hum

Reprod. 2002;17:134-6. PubMed PMID: 11756376.
74. Rizk B. Ovarian hyperstimulation syndrome: Epidemiology, pathophysiology, prevention and management. 1 st ed. Cambridge: Cambridge University Press; 2006.
75. Navot D, Bergh PA, Laufer N. Ovarian hyperstimulation syndrome in novel reproductive technologies: Prevention and treatment. Fertil Steril. 1992;58:249-61. PubMed PMID: 1633889.
76. Mathur R, Evbuomwan I, Jenkins J. Prevention and management of ovarian hyperstimulation syndrome. Curr Obstet Gynaecol. 2005;15:132-8. doi: 10.1016/j.curobgyn.2005.01.003.
77. Department of Health, Government of South Australia. South Australian Paediatric Clinical Guidelines: Ovarian hyperstimulation syndrome. South Australia: GoSA; 2007.
78. Shmorgun D, Claman P, Joint Sogc-Cfas Clinical Practice Guidelines C. The diagnosis and management of ovarian hyperstimulation syndrome. J Obstet Gynaecol Can. 2011;33:1156-62. doi: 10.1016/S1701-2163(16)35085-X. PubMed PMID: 22082791.
79. Budev MM, Arroliga AC, Falcone T. Ovarian hyperstimulation syndrome. Crit Care Med. 2005;33:S301-6. PubMed PMID: 16215351.
80. Alper MM, Smith LP, Sills ES. Ovarian hyperstimulation syndrome: Current views on pathophysiology, risk factors, prevention, and management. J Exp Clin Assist Reprod. 2009;6:3. PubMed PMID: 20485578; PubMed Central PMCID: PMCPMC2868304.
81. Kumar P, Sait SF, Sharma A, Kumar M. Ovarian hyperstimulation syndrome. J Hum Reprod Sci. 2011;4:70-5. doi: 10.4103/0974-1208.86080. PubMed PMID: 22065820; PubMed Central PMCID: PMCPMC3205536.
82. Gamzu R, Almog B, Levin Y, Avni A, Lessing JB, Baram A. Efficacy of hydroxyethyl starch and haemaccel for the treatment of severe ovarian hyperstimulation syndrome. Fertil Steril. 2002;77:1302-3. PubMed PMID: 12057749.
83. Rizk B, Meagher S, Fisher AM. Severe ovarian hyperstimulation syndrome and cerebrovascular accidents. Hum Reprod. 1990;5:697-8. PubMed PMID: 2254402.
84. Fabregues F, Tassies D, Reverter JC, Carmona F, Ordinas A, Balasch J. Prevalence of thrombophilia in women with severe ovarian hyperstimulation syndrome and cost-effectiveness of screening. Fertil Steril. 2004;81:989-95. doi: 10.1016/j.fertnstert.2003.09.042. PubMed PMID: 15066453.
85. Mikhail S, Rizk B, Nawar M, Rizk C. Thrombophilia and implantation failure. Infertility and assisted reproduction. Cambridge: Cambridge University Press; 2008.
86. Nelson SM, Greer IA. The potential role of heparin in assisted conception. Hum Reprod Update. 2008;14:623-45. doi: 10.1093/humupd/dmn031. PubMed PMID: 18701511.
87. Chen CD, Chen SU, Yang YS. Prevention and management of ovarian hyperstimulation syndrome. Best Pract Res Clin Obstet Gynaecol. 2012;26:817-27. doi: 10.1016/j.bpobgyn.2012.04.004. PubMed PMID: 22647872.
88. Jakimiuk AJ, Fritz A, Grzybowski W, Walecka I, Lewandowski P. Diagnosing and management of iatrogenic moderate and severe ovarian hyperstymulation syndrome (OHSS) in clinical material. Folia Histochem Cytobiol. 2007;45 Suppl 1:S105-8. PubMed PMID: 18292845.
89. Zhang Q, Xia L, Gao G. A new effective method in the treatment of severe ovarian hyperstimulation syndrome. Iran J Reprod Med. 2012;10:589-94. PubMed PMID: 25246931; PubMed Central PMCID: PMCPMC4169854.
90. Ferraretti AP, Gianaroli L, Diotallevi L, Festi C, Trounson A. Dopamine treatment for severe ovarian hyperstimulation syndrome. Hum Reprod. 1992;7:180-3. PubMed PMID: 1577929.
91. Tsunoda T, Shibahara H, Hirano Y, Suzuki T, Fujiwara H, Takamizawa S, et al. Treatment for ovarian hyperstimulation syndrome using an oral dopamine prodrug, docarpamine. Gynecol Endocrinol. 2003;17:281-6. PubMed PMID: 14503971.
92. Abramov Y, Elchalal U, Schenker JG. Pulmonary manifestations of severe ovarian hyperstimulation syndrome: A multicenter study. Fertil Steril. 1999;71:645-51. PubMed PMID: 10202873.
93. Rinaldi ML, Spirtos NJ. Chest tube drainage of pleural effusion correcting abdominal ascites in a patient with severe ovarian hyperstimulation syndrome: A case report. Fertil Steril. 1995;63:1114-7. PubMed PMID: 7720927.
94. Dickey RP, Brinsden PR, Pyrzak R. Manual of intrauterine insemination and ovulation induction. Cambridge: Cambridge University Press; 2009.