Canadian Fertility & Andrology Society

Clinical Practice Guidelines

Ovarian Hyperstimulation Syndrome: Diagnosis, Prevention and Management

Beth Taylor, MD, FRCSC
Jason Min, MD, FRCSC

CFAS Clinical Practice Guideline Committee

William Buckett, MD
Jon Havelock, MD
Hananel Holzer, MD
Neal Mahutte, MD
Jason Min, MD (Chair)
Jeff Roberts, MD
Sony Sierra, MD
Camille Sylvestre, MD
Beth Taylor, MD

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a serious and potentially life-threatening iatrogenic complication of ovarian stimulation. The symptoms of OHSS typically present in the luteal phase or in early pregnancy and range from a mild, self-limiting disorder to a life-threatening illness. While the disease has been reported to occur spontaneously,[1,2,3] or after clomiphene citrate treatment,[4,5,6] it most commonly occurs after gonadotropin administration for ovarian stimulation.

The reported incidence of the mild form of OHSS is 8-33%, between 1-7% for the moderate form and 0.1 to 2% for the severe form.[7,8,9,10]

This guideline reviews our current understanding of the risk factors, pathophysiology, prevention strategies, and management of OHSS; a disease that, if not completely preventable, can be minimized. Evidence is graded as outlined in the report of the Canadian Task Force on Preventative Health Care (Table 1). [11,12]

Table 1. Quality of evidence assessment and classification of recommendations as defined by the Canadian Task Force on Preventative Health Care

Quality of Evidence Assessment[11]		Classification of Recommendations[12]	
I	Evidence obtained from a least one properly randomized controlled trial.	A	There is good evidence to recommend the clinical preventative action.
II-1	Evidence from well-designed controlled trials without randomization.	B	There is fair evidence to recommend the clinical preventative action.
II-2	Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.	C	The existing evidence is conflicting and does not allow making a recommendation for or against use of the clinical preventative action; however, other factors may influence decision-making.
II-3	Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.	D	There is fair evidence to recommend against the clinical preventative action.
		E	There is good evidence recommend against the clinical preventative action.
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.	L	There is insufficient evidence (in quantity and/or quality) to make a recommendation; however, other factors may influence decision-making.

Pathophysiology

Ovarian hyperstimulation syndrome is the clinical manifestation of increased vascular permeability that results in a shift of serum from the intravascular space to the third space. There are two main clinical consequences to this fluid shift: excess fluid in the third space, predominantly the abdominal and pleural cavities, and hemoconcentration with reduced organ perfusion.

While the precise etiology of OHSS remains unclear, the action of luteinizing hormone (LH) or LH-like exposure (e.g. human chorionic gonadotropin, hCG) on granulosa cells of stimulated ovaries is a prerequisite to disease development. LH or hCG induces the release of mediators that increase vascular permeability. The most strongly implicated mediator is vascular endothelial growth factor (VEGF) which acts on endothelial surface receptors to increase cellular junctions between endothelial cells resulting in increased vascular permeability.13 Serum and follicular fluid VEGF concentrations have been observed to predict the occurrence, severity, and progress of OHSS.[14-16] Other mediators that have been implicated in the development of OHSS including interleukin-6 , angiotension II, epidermal growth factor (EGF), transforming growth factors (TGF), and platelet-derived growth factor (PDGF).[17]

Risk Factors

Primary risk factors, those identifiable prior to ovarian stimulation, include:

- young age,[18]
- a history of elevated response to gonadotropins,
- previous OHSS,[19]
- polycystic ovary syndrome,[20]
- high antral follicle count,[21,22] and
- high basal anti-Mullerian hormone level.[18,23]

Secondary risk factors, those identifiable after the onset of ovarian stimulation, include:

- absolute levels or rate of increase of serum estradiol,[24]
- follicular size and number,[24]
- number of oocytes collected,[25] and
- pregnancy.[26]

Clinical Presentation

There is a broad spectrum of clinical manifestations by which OHSS severity is classified and graded. OHSS was first classified by Rabau et al. in 1967.[27] Since then, there have been several classification systems used. The Golan grading system is the most widely referenced and divides OHSS into mild, moderate and severe disease.[9] The most recent modification of the Golan system was published in 2010 (Table 2).[28] This system also divides OHSS into mild, moderate and severe disease but incorporates ultrasound and laboratory parameters into the classification system affording more objectivity.

Mild, moderate, and severe forms are distinguished by the extent of fluid shift into the third space. The symptoms of mild OHSS include abdominal distention and pelvic discomfort, and may include nausea, vomiting, and diarrhea. Progression of illness to moderate OHSS is marked by worsening symptoms, ascites evident on ultrasound examination and moderate hemoconcentration. In severe OHSS, more fluid shifts into the third space (predominately the peritoneal and pleural cavities), leading to hypovolemia and severe hemoconcentration. Life-threatening complications of severe OHSS include hepatorenal failure, acute respiratory distress syndrome, hemorrhage from ovarian rupture and thromboembolism.

Besides disease severity, OHSS is further categorized based on the onset of the syndrome in relation to oocyte retrieval and/or hCG administration. Two distinct clinical forms

of OHSS are recognized: early OHSS and late OHSS. Early OHSS is an acute effect of exogenous hCG administration, occurring within 9 days of administration and correlated with ovarian response to gonadotropins. In contrast, late OHSS occurs more than 10 days after hCG administration and does not correlate to the ovarian response. Late OHSS is related to hCG administered for luteal phase support and/or endogenous hCG produced by an implanting embryo.[24,29,30]

Table 2. Humaidan's proposed new clinical grading system for OHSS.[28]

	Mild	Moderate	Severe
Objective criteria			
Fluid in Douglas pouch	✓	✓	✓
Fluid around uterus (major pelvis)		✓	✓
Fluid around intestinal loops			✓
Hematocrit >45%		✓[a]	✓
White blood cells >15,000/mm3		±[a]	✓
Low urine output		±[a]	✓
<600 mL/24 h		±[a]	±
Creatinine >1.5 mg/dL			±
Elevated transaminases			±c
Clotting disorder			±c
Pleural effusion			
Subjective criteria	✓	✓	✓
Abdominal distention	✓	✓	✓
Pelvic discomfort	±[b]	±[b]	✓
Breathing disorder	±[b]	±[b]	±[b]
Acute pain	±	±	±
Nausea/vomiting	✓	✓	✓
Ovarian enlargement	±	±	✓
Pregnancy occurence			
Note: The ± sign means may or may not be present. a If two of these are present, consider hospitalization. b If present, consider hospitalization. c If present, consider intensive care.			

From Humaidan P, Quartarolo J, Papanikolaou EG. Preventing ovarian hyperstimulation syndrome: guidance for the clinician. Fertil Steril. 2010;94:389-400.28

Prevention

Primary prevention

Primary prevention strategies intend to avoid the development of OHSS by identifying women at high-risk who can benefit from specific preventive strategies.

The selection of the stimulation protocol plays an important role in determining the magnitude of the ovarian response and hence the risk of developing OHSS. Three major aspects of the stimulation protocol could affect the intensity of the ovarian response: the type of gonadotropin-releasing hormone (GnRH) analogue used to suppress ovulation (agonist or antagonist), the starting dose of gonadotropins, and the type of gonadotropins administered.

1. Type of protocol

Evidence from a meta-analysis of randomized controlled trials of normo-ovulatory women indicates that the use of GnRH-antagonists instead of GnRH-agonists during ovarian stimulation for IVF reduces the risk of severe OHSS (OR 0.43; 95% CI 0.33, 0.57).[31] Importantly, there was no evidence of a statistically significant difference in live birth rates between women receiving the antagonist compared with the agonist protocols. The reduction in OHSS was particularly pronounced in patients with polycystic ovarian syndrome, a finding replicated in a separate meta-analysis.[31,32] The reduction in OHSS observed with GnRH-antagonist protocols can be partially explained by a lower number of growing follicles in the antagonist protocol. On average, one oocyte less is retrieved after ovarian stimulation in a GnRH-antagonist protocol versus a GnRH-agonist protocol.[33,34] Agonist triggering is feasible in a GnRH-antagonist protocol as the pituitary remains responsive to a bolus dose of GnRH-agonist leading to a reduction in endogenous LH levels, luteolysis and thereby a reduction in the incidence of OHSS.[35-37]

Recommendation

The use of GnRH antagonist protocols should be considered for both normo-ovulatory women and women with polycystic ovarian syndrome undergoing IVF treatment who are at higher risk of OHSS. (IA)

2. Starting dose

Selecting the optimal dose of gonadotropins that will result in an acceptable number of oocytes is complicated. Several studies have observed that the dose of gonadotropins can be reduced without affecting the pregnancy rates in GnRH agonist or GnRH antagonist IVF cycles.38-42 These studies did not examine OHSS incidence, however, one observational study of IVF treatment[43] and one randomized controlled trial of controlled ovarian stimulation with IUI44 observed that a reduction in the dose of gonadotropins significantly reduced the incidence of OHSS.

Attempts to develop a predictive model of gonadotropin effect and OHSS risk using patient variables have been unsuccessful in providing pregnancy rates comparable to physician determined gonadotropin dosing.[45,46]

Recommendation

Administration of the lowest-effective dose of gonadotropins is reasonable to reduce the risk of OHSS. (II-3B)

3. Type of gonadotropin used

Evidence from two meta-analyses indicates that the choice of urinary or recombinant human menopausal gonadotropin or FSH does not influence the incidence of OHSS.[47,48]

Recommendation

As there appears to be no difference in the risk of OHSS with the use of either urinary or recombinant gonadotropins, the choice of gonadotropin preparation should be based on other clinical parameters. (IA)

4. Metformin in women with PCOS

Insulin and insulin-like growth factors (IGFs) promote VEGF production by luteinized granulosa cells synergistically with LH exposure.[49] An increase in serum VEGF levels in women with insulin-resistance, as seen in PCOS, may play a role in the increased risk of OHSS in PCOS women. By increasing insulin sensitivity, metformin may reduce VEGF production and OHSS in women with PCOS.

A meta-analysis of 4 RCTs comparing metformin versus no treatment or placebo in 449 women with PCOS undergoing IVF reported a significant reduction in the risk of OHSS in metformin treated women (OR = 0.27; 95% CI 0.16, 0.47). There was no difference in clinical pregnancy rates or live birth rates.[50] A subsequent RCT comparing metformin to placebo found a similar reduction in the risk of OHSS in metformin treated women with PCOS (OR = 0.28; 95% confidence interval, 0.11, 0.67).[51]

Recommendation

Metformin should be used to reduce the risk of OHSS in women with PCOS undergoing IVF. (IA)

5. Acetyl-salicylic acid (Aspirin)

Platelet activation is known to increase VEGF levels in OHSS.[52] Activated platelets also release substances, such as lysophosphatidic acid and histamine that increase vascular permeability in OHSS.[53] By blocking the formation of thromboxane A2 in platelets, aspirin inhibits platelet activation and the production of such vasoactive substances giving it a potential role in the prevention of OHSS.

In a randomized trial of 3154 women undergoing IVF, low dose aspirin (100mg per day) given during ovarian stimulation was observed to reduce the risk of OHSS in a high risk sub-group.[54]

Recommendation

Low dose aspirin may be considered to reduce the risk of OHSS in women undergoing IVF treatment. (IB)

6. In Vitro Maturation

The only reliable way to eliminate the risk of OHSS is to avoid gonadotropin ovarian stimulation altogether. In vitro maturation (IVM) involves the retrieval of immature oocytes from unstimulated or minimally stimulated ovaries. These immature oocytes are then cultured, matured, and fertilized in vitro.

IVM was first performed on human oocytes by Edwards in 1965.[55] Since that time, widespread application of IVM has been limited as the pregnancy rates from IVM are lower than those of in vivo stimulation cycles.[56]

The incidence of OHSS in women with PCOS undergoing ovarian hyperstimulation can be as high as 30%.[17,23,57] Two case-control studies observed a significant reduction in the risk of OHSS in women with PCOS undergoing IVM compared to IVF. However, there was also a reduction in implantation, clinical pregnancy and live birth rates with IVM.[58,59] No other published studies have compared OHSS rates in women with PCOS undergoing IVM compared to IVF.

Although several centres have reported their IVM experience in ovulatory women with no cases of OHSS occurring,[60-62] no studies have been published comparing OHSS rates with IVM versus IVF in this population.

Recommendation

Although there is a lack of published evidence, in vitro maturation minimizes ovarian stimulation, and therefore, can be considered for the prevention of OHSS. (IIIL)

Secondary prevention

Secondary prevention strategies attempt to diagnose and treat an existing disease in its early stages before it results in significant morbidity.

1. Low dose HCG triggering of final oocyte maturation

Critical to IVF success is the induction of final oocyte maturation and separation of the oocyte from the follicle wall using LH or an LH analogue. This is achieved most commonly with human chorionic gonadotropin (HCG). The most widely used dose of HCG in IVF is 10,000 IU. It can be expected that less aggressive stimulation of the corpora lutea with lower doses of hCG used to induce final oocyte maturation would result in a lower risk of OHSS. A decrease in the HCG serum concentration is associated with a reduced risk of OHSS while remaining sufficient to induce final oocyte maturation and achieve comparable pregnancy rates.[63-65] However, the published literature on the influence of HCG dose on the incidence of OHSS is varied. Three randomized control trials have been published comparing lower to higher doses of HCG. Shaltout et al. compared 5000 IU to 10,000 IU hCG in 100 IVF patients and observed a higher incidence of mild OHSS in the group receiving 10,000 IU (8.3% vs. 2%). There were no cases of moderate or severe OHSS in either group.[66] In contrast, Kolibianakis et al. randomized 80 women with PCOS to receive 10,000IU, 5000IU, or 2500IU HCG and documented no difference in the incidence of severe OHSS.[67] Lin et al. randomized 164 women to receive either 6000 IU or 4000 IU HCG and, similarly, documented no difference in the moderate or severe OHSS risk.[68] Although no statistical difference in moderate and severe OHSS rates was demonstrated, the incidence of OHSS was low in all trials. Reassuringly, the pregnancy rates in all three randomized controlled trials were similar between comparison groups. Non-randomized studies are similarly contradictory.[63,69-72]

While it is biologically plausible that a reduction in the dose of HCG below 10,000 IU will reduce the incidence of OHSS yet not reduce pregnancy rates, further prospective randomized trials are needed before dosing recommendations can be made.

Recommendation

For the prevention of OHSS, effectiveness of the reduction of HGC dose below 10,000 IU for final oocyte maturation is not well established. (IC)

2. GnRH agonist triggering of final oocyte maturation

OHSS occurs after hCG administration as the LH activity of HCG potentiates the activity of corpa lutea. HCG levels remain elevated even after 6 days of administration due to its long half-life affecting the risk of OHSS development.[73] In contrast to HCG, endogenous LH levels after GnRH agonist triggering return to baseline within 24 to 48 hours and thus there is no prolonged stimulation of the corpora lutea.[74] After the endogenous LH levels return to baseline, GnRH agonist are functionally luteolytic due to their prolonged pituitary downregulation and suppression of LH as evidenced by the lower luteal progesterone and estradiol levels compared with cycles triggered with hCG.[75] Such diminution of corpora lutea activity makes the use of a GnRH agonist for triggering oocyte maturation in antagonist IVF cycles a feasible option to reduce the incidence of OHSS.

It has been demonstrated that triggering final oocyte maturation with a GnRH agonist is an effective alternative to hCG for inducing

follicular maturation.[77] However, a significant reduction in pregnancy rates in GnRH agonist triggered cycles was initially reported as GnRH agonist triggering has a negative effect on the function of the corpus luteum and the endometrium.[34,77,78] Luteal phase support with estradiol, progestins and low dose HCG have been shown to equalize pregnancy rates in more recent studies.[36,79-81] Examples of published GnRH agoinst triggering doses are presented in Table 3. [82-86]

Table 3. GnRH agonists used for triggering of final oocyte maturation and luteal support.

Study	GnRH agonist trigger	Luteal Support
Babayof 2006 et al.[82]	Triptorelin 0.2mg sc	50mg IM progesterone, estradiol 4mg
Beckers 2003 et al.[83]	none	none
Fauser 2002 et al.[84]	Triptorelin 0.2mg sc	50mg IM progesterone
Humaidan 2010 et al.[85]	Buserelin 0.5 mg sc	micronized progesterone 90mg od, estradiol 4mg daily and 1500IU HCG 35 hours after trigger
Kolibianakis 2005 et al.[86]	Triptorelin 0.2mg sc	micronized progesterone 600mg

A meta-analysis of 11 randomized controlled trials comparing GnRH agonist with hCG for triggering final oocyte maturation reported a reduction in the incidence of moderate and severe OHSS (OR 0.10; 95% CI 0.01, 0.82).[87] Of the 11 randomized control trials included in the analysis, 8 included fresh autologous IVF cycles and 3 included donor oocyte IVF cycles. In autologous cycles, the ongoing pregnancy rate (OR 0.45; 95% CI 0.31, 0.65) and live birth rates (OR 0.44; 95% CI 0.29, 0.68) were significantly reduced with the use of a GnRH agonist trigger. In the subgroup of donor oocyte IVF cycles, there was no reduction in ongoing pregnancy rates.

GnRH agonist triggering leads to a significant reduction in the circulating endogenous LH level compared with hCG triggering.[73] Luteal LH plays a role not only for the steroidogenic activity of the corpus luteum, but also for the up-regulation of growth factors, such as VEGF, which are important for implantation.[88,89]

Luteal supplementation of low dose HCG (e.g. 1000-1500 IU) has been shown to adequately to support the luteal phase in GnRH agonist triggered cycles. A recent RCT reported a no difference in live birth rates between GnRH agonist triggering with HCG supplementation and hCG triggering and no cases of OHSS were observed in the GnRH agonist triggered group.81 GnRH agonist triggering combined with low-dose hCG supplementation rescues the luteal phase and achieves pregnancy rates similar to that seen after hCG triggering.

Recommendation

In GnRH antagonist protocols, triggering of final oocyte maturation with a GnRH agonist is recommended for the prevention of OHSS in women at higher risk. (IA)

3. Use of dopamine agonists

In OHSS, vascular permeability is increased due to activation of the VEGF-2 receptor. The dopamine agonist cabergoline can prevent this increase in vascular permeability by inactivating the VEGF-2 receptor while not disrupting VEGF-receptor mediated angiogenesis, which is a important for pregnancy development.[90]

Several trials have documented a reduction in the incidence, severity and duration of OHSS with the use of cabergoline around the time of ovulation induction. There is variability in the dose and duration of treatment published. Two recent meta-analyses of randomized controlled trials of carbergoline use in women at high risk of developing OHSS observed a significant reduction in the incidence of moderate OHSS .The reduction in severe OHSS was not significant in either analysis. There was no significant difference in pregnancy rate between those treated with cabergoline or placebo.[91,92] Examples of cabergoline dosing regimes are presented in Table 4.[93-96]

Table 4. Dopamine agonist regimens for the reduction of OHSS.

Study	Dopamine agonist	Timing
Alvarez 2007 et al.[93]	cabergoline 0.5mg po	daily for 8 days from the day of HCG
Carizza 2008 et al.94	cabergoline 0.5mg po	daily for three weeks from day after oocyte retrieval
Salah Edeen 2009 et al.95	cabergoline 0.5mg po	daily for 2 days from the day of HCG and repeated after 1 week
Shaltout 2009 at al.96	cabergoline 0.25mg po	daily for 8 days from the day of HCG

Recommendation

The dopamine agonist cabergoline should be used to reduce the incidence of OHSS in women at higher risk. (IA)

4. Withholding gonadotropins (coasting)

Coasting is defined as withholding gonadotrophins for a variable number of days before administering hCG injection until safe estradiol levels are attained. This approach may prevent severe OHSS by reducing the FSH stimulation of granulosa cells thereby inhibiting their proliferation and reducing the number of granulosa cells and, consequently, the amount of vasoactive substances released in response to hCG.

Coasting was first described as a method to reduce the incidence of OHSS over 20 years ago.[97,98] Since that time over 16 studies have examined coasting; each using different coasting techniques that can be broadly categorized as "early" or "late." Early coasting involves withholding gonadotropins once follicles reach 12-15mm in the presence of an elevated estradiol concentration. Late coasting involves withholding gonadotropins once follicles are >15mm and the estradiol is markedly elevated. There is limited evidence to suggest one technique is superior to the other. A small retrospective study reported that both early and late coasting were equivalent in reducing OHSS, with similar IVF outcomes.[99] Most studies examined late coasting.

A meta-analysis identified four randomized controlled trials of women at high risk of developing OHSS.[100] There was no effect on the incidence of moderate to severe OHSS or in the achievement of clinical pregnancy when coasting was compared with early unilateral follicular aspiration (two trials) or GnRH antagonist administration (one trial). A single trial found a benefit of coasting over no coasting for a reduction in moderate to severe OHSS (OR 0.17; 95% CI 0.03, 0.88) without effect on the clinical pregnancy rate (OR 0.56; 95% CI 0.20, 1.63).

Many, but not all observational studies have reported a significant reduction in OHSS with coasting compared to no coasting,[101-103] and some have documented a decrease in clinical pregnancy rates after coasting, particularly if the duration of coast exceeds 3 days.[104-106]

Recommendation

Coasting can be useful to reduce the incidence of moderate and severe OHSS. (IB)

5. Freezing all embryos

OHSS occurs in the luteal phase as a consequence of ovulatory or exogenous hCG, and in early gestation when endogenous hCG is produced. When OHSS develops in the luteal phase and pregnancy does not occur, the syndrome resolves spontaneously with the onset of the menses and only rarely progresses into severe disease. The elective cryopreservation of all embryos to avoid pregnancy and therefore, severe OHSS was first described in 1990.[107]

A meta-analysis of two randomized controlled trials examined the effect of embryo cryopreservation on the risk of OHSS.[108] One trial compared cryopreservation of all embryos with intravenous albumin infusion and subsequent fresh ET,[109] and the second compared elective cryopreservation of all embryos with fresh ET, with both groups receiving albumin infusion on the day of egg retrieval.[110] Both studies were of poor methodological quality with limited numbers of participants. Neither showed a statistically significant difference in the incidence of moderate or severe OHSS with cryopreservation of all embryos versus fresh embryo transfer in women at risk of OHSS.

While several non-randomized studies have highlighted similar pregnancy rates whether using elective cryopreservation of all embryos or fresh embryo transfer, the influence of a policy of elective cryopreservation of all embryos on cumulative pregnancy rate is unclear as embryo cryopreservation techniques and success rates vary among centres.[110-112]

Recommendation

There is insufficient evidence to support the routine cryopreservation of all embryos to prevent the development of OHSS. (IIIL)

6. IV Colloid infusions

In the pathogenesis of OHSS, elevated levels of VEGF, and other vasoactive mediators, leads to increased vascular permeability. The administration of intravenous fluids such as human albumin is hypothesized to restore intravascular volume by increasing plasma colloid oncotic pressure preventing the sequelae of hypovolaemia, ascites and haemoconcentration. Albumin may also bind and inactivate VEGF and other such mediators of OHSS.[113]

Two meta-analyses published in 2011 examined the use of intravenous albumin in women at high risk of developing OHSS for prevention of severe OHSS.[114,115] Venetis et al. reported no difference in the risk of severe OHSS (OR, 0.80; 95% CI, 0.52, 1.22), early or late onset, and no difference was noted with varying albumin doses. Youssef et al. reported a borderline, statistically significantly lower incidence of severe OHSS in women that received IV albumin (OR 0.67; 95% CI 0.45, 0.99). While both meta-analyses included eight trials, Venetis et al. excluded one study included in Youssef et al. on the basis of overlapping publication,[116] while Youssef et al. excluded one trial due to quasi-randomization.[117] Sensitivity analysis with exclusion of potentially duplicated data was performed in the Youssef et al. meta-analysis showing a loss of significance in the reduction of severe OHSS with intravenous albumen (OR 0.75; 95% CI 0.47, 1.21).[115]

In three randomized control trials there was evidence of a statistically significant reduction in the incidence of severe OHSS in women who received hydroxyethyl starch (HES) compared to placebo (OR 0.12; 95% CI 0.04, 0.40); however, two of the included trials may have overlapping data.[115]

Recommendation

There is insufficient evidence to support the use of intravenous albumin or hydroxyethyl starch to prevent the development of severe OHSS. (IC)

Management

Patients with mild to moderate OHSS can generally be managed on an outpatient basis. Treatment usually requires only oral analgesics and counseling regarding the signs and symptoms of progressing illness. Fluid intake and weight should be monitored daily and the woman should be in regular communication with someone experienced in monitoring and managing OHSS.

1. Hospitalization

Hospitalization for severe OHSS is uncommon but should be considered if there is severe abdominal pain, intractable nausea and vomiting, dyspnea and tachypnea, elevated liver enzymes, decreased urine output (< 600 mL/24hours), abnormal elevation of liver enzymes or other significant biochemical abnormality.

The inpatient management of OHSS includes careful monitoring of the woman's vital signs, weight, fluid balance, abdominal circumference and oxygen saturation. A chest X-ray and echocardiogram should be considered if pleural or pericardial fluid is suspected. Frequent assessment of hematocrit, electrolytes, liver enzymes and creatinine levels will assist in monitoring disease progression and response to treatment.

2. Fluid management

A balance is made between intravascular volume maintenance to ensure adequate organ perfusion and minimizing third space fluid accumulation. Fluids should be strictly monitored and IV fluids titrated to maintain adequate urine output.

Crystalloids and colloids are commonly used but have not been compared in the management of OHSS. As colloid solutions are more effective in expanding the intravascular volume, if adequate volume expansion is not achieved with an initial crystalloid administration, IV colloids should be initiated. Both albumin and hydroxyethyl starch (HES) have been used in the treatment of severe OHSS. A single study of 16 women with severe OHSS compared human albumin and 6% HES. Women who received 6% HES had a higher urine output, needed less abdominal paracentesis and drainage of pleural effusions, and had a shortened hospital stay.[118]

Recommendation

If volume depletion persists despite IV crystalloids, IV 6% HES may be considered. (II-3C)

3. Paracentesis

Ultrasound guided paracentesis or culdocentesis is indicated if there is tense ascites, or compromised renal or pulmonary function. Several case reports have documented an improvement in severe OHSS after drainage of ascites. A randomized trial of 21 women comparing culdocentesis and expectant management with IV fluids observed more rapid improvement of symptoms, and a shorter hospital stay in the culdocentesis group.

No major complications were reported.[119] Further, culdocentesis may reduce the progression of moderate to severe disease.[120]

Recommendation

Paracentesis or culdocentesis should be considered in the management of moderate and severe OHSS. (IB)

4. Thromboprophlaxis

Thromboembolism is a rare, but life-threatening complication of severe OHSS. There are no comparative trials of the effectiveness of thromboprophlaxis in women with OHSS.

Recommendation

Venous support stockings and daily prophylactic heparin therapy should be considered. (IIIL)

Complications

Thromboembolism, pericardial effusion, renal failure and adult respiratory distress syndrome are potential life-threatening complications of OHSS. Prompt identification and management of such complications are critical to the successful management of OHSS.

Conclusion

OHSS is a serious and preventable, potentially life-threatening complication of ovarian stimulation. In the primary prevention of OHSS, the use of modest ovarian stimulation in a GnRH antagonist protocol and triggering final oocyte maturation with a GnRH agonists is an effective strategy. Metformin should be considered in women with PCOS and low-dose aspirin can be considered for those at high risk of developing OHSS. Secondarily, coasting and the use of cabergoline are currently supported by the available evidence.

Mild and moderate OHSS can generally be managed on an outpatient basis with close monitoring. Severe OHSS may require hospitalization.

The implementation of evidence-based prevention and management strategies should enable clinicians to significantly reduce the occurrence and severity of OHSS.

References

1. Akerman FM, Lei Z, Rao CV, Nakajima ST. A case of spontaneous ovarian hyperstimulation syndrome with a potential mutation in the hCG/LH receptor gene. Fertil Steril 2000;74:403–404.
2. Ayhan A, Tuncer ZS and Aksu AT. Ovarian hyperstimulation syndrome associated with spontaneous pregnancy. Hum Reprod 1996;11:1600–1601.
3. Michaelson-Cohen R, Altarescu G, Beller U, Reens R, Halevy-Shalem T, Eldar-Geva T. Does elevated human chorionic gonadotropin alone trigger spontaneous ovarian. Fertil Steril. 2008;90:1869-74.
4. Chow KK, Choo HT. Ovarian hyperstimulation with clomiphene citrate. Case report. Br J Obstet Gynaecol 1984;91:1051–2.
5. Morgan H, Paredes RA, Lachelin GC. Severe ovarian hyperstimulation after clomiphene citrate in a hypothyroid patient. Case report. Br J Obstet Gynaecol 1983;90:977–82.
6. Morris RS, Paulson RJ. Increased angiotensin-converting enzyme activity in a patient with severe ovarian hyperstimulation syndrome. Fertil Steril. 1999;71:562-3.
7. Delvigne A, Rozenberg S. Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS):a review. Hum Reprod Update 2002;8;559-577.
8. Gunby J, Bissonnette F, Librach C, Cowan L; IVF Directors Group of the Canadian Fertility and Andrology Society. Assisted reproductive technologies (ART) in Canada: 2007 results from the Canadian ART Register. Fertil Steril. 2011;95:542-7.e1-10.
9. Golan A, Ron-El R, Herman A, Soffer Y, Weinraub Z, Caspi E. Ovarian hyperstimulation syndrome: an update review. Obstet Gynecol Surv 1989;44:430-440.
10. Schenker JG, Weinstein D. Ovarian hyperstimulation syndrome: a current survey. Fertil Steril 1978;30:255–268.
11. Woolf SH, Battista RN, Angerson GM, Logan AG, Eel W. Canadian Task Force on the Periodic Health Exam. Ottawa: Canada Communication Group p.xxxvii, 1994.
12. New grades for recommendations from the Canadian Task Force on Preventive Health Care. CMAJ 169:207, 2003.
13. Roberts WG, Palade GE. Increased microvascular permeability and endothelial fenestration induced by vascular endothelial growth factor. J Cell Sci 1995;108(Pt 6):2369–2379.
14. Ajonuma LC. Is vascular endothelial growth factor (VEGF) the main mediator in ovarian hyperstimulation syndrome (OHSS)? Med Hypotheses 2008;70:1174–8.
15. Gao MZ, Zhao XM, Sun ZG, Hong Y, Zhao LW, Zhang HQ. Endocrine gland-derived vascular endothelial growth factor concentrations in follicular fluid and serum may predict ovarian hyperstimulation syndrome in women undergoing controlled ovarian hyperstimulation. Fertil Steril. 2011;95:673-8.
16. Rizk B, Aboulghar M, Smitz J, Ron-El R. The role of vascular endothelial growth factor and interleukins in the pathogenesis of severe ovarian hyperstimulation syndrome. Hum Reprod Update. 1997;3:255–66.
17. Whelan JG 3rd, Vlahos NF. The ovarian hyperstimulation syndrome. Fertil Steril 2000;73:883–96.
18. 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.
19. Navot D, Relou A, Birkenfeld A, Rabinowitz R, Brzezinski A, Mar- galioth EJ. Risk factors and prognostic variables in the ovarian hyper- stimulation syndrome. Am J Obstet Gynecol 1988;159:210–5.
20. European Orgalutran Study Group. Treatment with the gonadotrophin-releasing hormone antagonist ganirelix in women undergoing ovarian stimulation with recombinant follicle stimulating hormone is effective, safe and convenient: results of a controlled, randomized, multicentre trial. Hum Reprod 2000;15:1490–8.
21. Kwee J, Elting ME, Schats R, McDonnell J, Lambalk CB. Ovarian volume and antral follicle count for the prediction of low and hyper responders with in vitro fertilization. Reprod Biol Endocrinol 2007;5:9
22. North American Ganirelix Study Group. Efficacy and safety of ganirelix acetate versus leuprolide acetate in women undergoing controlled ovarian hyperstimulation. Fertil Steril 2001;75:38–45.

23. Broer SL, Dólleman 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.
24. 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.
25. Enskog A, Henriksson M, Unander M, Nilsson L, Brannstrom M. Prospective study of the clinical and laboratory parameters of patients in whom ovarian hyper- stimulation syndrome developed during controlled ovarian hyperstimulation for in vitro fertilization. Fertil Steril 1999;71:808–814.
26. MacDougall MJ, Tan SL, Jacobs HS. In-vitro fertilization and the ovarian hyperstimulation syndrome. Hum Reprod 1992;7:597–600
27. Rabau E, Serr DM, David A et al. (1967). Human menopausal gonadotrophin for anovulation and sterility. Am J Obstet Gynecol 98:92–8.
28. Humaidan P, Quartarolo J, Papanikolaou EG. Preventing ovarian hyperstimulation syndrome: guidance for the clinician. Fertil Steril. 2010;94:389-400.
29. Lyons CA, Wheeler CA, Frishman GN, Hackett RJ, Seifer DB, Haning RV Jr. Early and late presentation of the ovarian hyperstimulation syndrome: two distinct entities with different risk factors. Hum Reprod 1994;9:792–9.
30. Mathur R, Kailasam C, Jenkins J. Review of the evidence base strategies to prevent ovarian hyperstimulation syndrome. Hum Fertil 2007;10:75-85.
31. Al-Inany HG, Youssef MA, Aboulghar M, Broekmans F, Sterrenburg M, Smit J, Abou-Setta AM. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. Cochrane Database Syst Rev. 2011;5:CD001750.
32. Mancini F, Tur R, Martinez F, Coroleu B, Rodríguez I, Barri PN. Gonadotrophin-releasing hormone-antagonists vs long agonist in in-vitro fertilization patients with polycystic ovary syndrome: a meta-analysis. Gynecol Endocrinol. 2011;27:150-5.
33. Al-Inany HG, Abou-Setta AM, Aboulghar M. Gonadotrophin-releasing hormone antagonists for assisted conception: a Cochrane review. Reprod Biomed Online 2007;14(5): 640–649.
34. 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;12:651–671.
35. Bodri D, Guille´ n JJ, Galindo A, Mataro´ D, Pujol A, Coll O. Triggering with human chorionic gonadotropin or a gonadotropin-releasing hormone agonist in gonadotropin- releasing hormone antagonist-treated oocyte donor cycles: findings of a large retrospective cohort study. Fertil Steril 2009;91:365–371.
36. Engmann L, DiLuigi A, Schmidt D, Nulsen J, Maier D, Benadiva C. The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients under- going in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized con- trolled study. Fertil Steril 2008;89:84–91.
37. Galindo A, Bodri D, Guille´ n JJ, Colodro´ n M, Vernaeve V, Coll O. Triggering with HCG or GnRH agonist in GnRH antagonist treated oocyte donation cycles: a randomised clinical trial. Gynecol Endocrinol 2009;25:60–66
38. Latin-American Puregon IVF Study Group. A double-blind clinical trial comparing a fixed daily dose of 150 and 250 IU of recombinant follicle-stimulating hormone in women undergoing in vitro fertilization. Fertil Steril 2001;76(5): 950–956.
39. Out HJ, Lindenberg S, Mikkelsen AL, et al. A prospective, randomized, double-blind clinical trial to study the efficacy and efficiency of a fixed dose of recombinant follicle stimulating hormone (Puregon) in women undergoing ovarian stimulation. Hum Reprod 1999;14:622–627.
40. Out HJ, Rutherford A, Fleming R, et al. A randomized, double-blind, multicentre clinical trial comparing starting doses of 150 and 200 IU of recombinant FSH in women treated with the GnRH antagonist ganirelix for assisted reproduction. Hum Reprod 2004;19:90–95.

41. Wikland M, Bergh C, Borg K, et al. A prospective, randomized comparison of two starting doses of recombinant FSH in combination with cetrorelix in women undergoing ovarian stimulation for IVF/ICSI. Hum Reprod 2001;16: 1676–1681.
42. Yong PY, Brett S, Baird DT, Thong KJ. A prospective randomized clinical trial comparing 150 IU and 225 IU of recombinant follicle-stimulating hormone (Gonal-F*) in a fixed-dose regimen for controlled ovarian stimulation in in vitro fertilization treatment. Fertil Steril 2003;79:308–315.
43. Marci R, Senn A, Dessole S, Chanson A, Loumaye E, De Grandi P, Germond M. A low-dose stimulation protocol using highly purified follicle-stimulating hormone can lead to high pregnancy rates in in vitro fertilization patients with polycystic ovaries who are at risk of a high ovarian response to gonadotropins. Fertil Steril. 2001;75:1131-5.
44. Sengoku K, Tamate K, Takaoka Y, Horikawa M, Goishi K, Komori H, Okada R, Tsuchiya K, Ishikawa M. The clinical efficacy of low-dose step-up follicle stimulating hormone administration for treatment of unexplained infertility. Hum Reprod. 1999;14:349-53.
45. Olivennes F, Howles CM, Borini A, et al; CONSORT study group. Individualizing FSH dose for assisted reproduction using a novel algorithm: the CONSORT study. Reprod Biomed Online 2009;18:195–204.
46. Popovic-Todorovic B, Loft A, Bredkjaeer HE, Bangsbøll S, Nielsen IK, Andersen AN. A prospective randomized clinical trial comparing an individual dose of recombinant FSH based on predictive factors versus a 'standard' dose of 150 IU/day in 'standard' patients undergoing IVF/ICSI treatment. Hum Reprod 2003;18:2275–2282.
47. Daya S. Updated meta-analysis of recombinant follicle- stimulating hormone (FSH) versus urinary FSH for ovarian stimulation in assisted reproduction. Fertil Steril 2002;77: 711–714.
48. van Wely M, Kwan I, Burt AL, Thomas J, Vail A, Van der Veen F, Al-Inany HG. Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproductive technology cycles. Cochrane Database Syst Rev. 2011 16;(2):CD005354.
49. Stanek MB, Borman SM, Molskness TA, Larson JM, Stouffer RL, Patton PE. Insulin and insulin-like growth factor stimulation of vascular endothelial growth factor production by luteinized granulosa cells: comparison between polycystic ovarian syndrome (PCOS) and non-PCOS women. J Clin Endocrinol Metab. 2007;92:2726-33.
50. Tso LO, Costello MF, Albuquerque LE, Andriolo RB, Freitas V. treatment before and during IVF or ICSI in women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD006105.
51. Palomba S, Falbo A, Carrillo L, Villani MT, Orio F, Russo T, Di Cello A, Cappiello F, Capasso S, Tolino A, Colao A, Mastrantonio P, La Sala GB, Zullo F, Cittadini E; METformin in High Responder Italian Group. Metformin reduces risk of ovarian hyperstimulation syndrome in patients with polycystic ovary syndrome during gonadotropin-stimulated in vitro fertilization cycles: a randomized, controlled trial. Fertil Steril. 2011;96:1384-1390.e4.
52. Choudhury A, Freestone B, Patel J, Lip GY. Relationship of soluble CD40 sig and to vascular endothelial growth factor, angiopoietins, and tissue factor in atrial fibrillation: a link among platelet activation, angiogenesis, and thrombosis? Chest 2007;132:1913–9.
53. Chen SU, Chou CH, Lee H, Ho CH, Lin CW, Yang YS. Lysophosphatidic acid up-regulates expression of interleukin-8 and -6 in granulosa-lutein cells through its receptors and NF-{kappa}B-dependent pathways: implications for angiogenesis of corpus luteum and ovarian hyperstimula- tion syndrome. J Clin Endocrinol Metab 2008;93:935–43.
54. Várnagy A, Bódis J, Mánfai Z, Wilhelm F, Busznyák C, Koppán M. Low-dose aspirin therapy to prevent ovarian hyperstimulation syndrome. Fertil Steril. 2010;93:2281-4.
55. Edwards RG. Maturation in vitro of human ovarian oocytes. Lancet 1965;2:926 –9.
56. Banwell KM, Thompson JG. In vitro maturation of Mammalian oocytes: outcomes and consequences. Semin Reprod Med 2008;26:162–174.
57. Dor J, Shulman A, Levran D, Ben-Rafael Z, Rudak E, Mashiach S. The treatment of patients with polycystic ovarian syndrome by in-vitro fertilization and embryo transfer: a comparison of results with those of patients with tubal infertility. Hum Reprod 1990;5:816–8.
58. Child TJ, Phillips SJ, Abdul-Jalil AK, et al. A comparison of in vitro maturation and in vitro fertilization for women with polycystic ovaries. Obstet Gynecol 2002;100:665–670.

59. Gremeau AS, Andreadis N, Fatum M, Craig J, Turner K, McVeigh E, Child T. In vitro maturation or in vitro fertilization for women with polycystic ovaries? A case-control study of 194 treatment cycles. Fertil Steril. 2012 May 31. Epub.
60. Buckett W, Chian R-C, Tan SL. Can we eliminate severe ovarian hyperstimulation syndrome? Not completely. Hum Reprod 2005;20:2367.
61. Child TJ, Abdul-Jalil AK, Tan SL. Embryo morphology, cumulative embryo score, and outcome in an oocyte in vitro maturation program. Fertil Steril 2002;77:424–425.
62. Le Du A, Kadoch IJ, Bourcigaux N, et al. In vitro oocyte maturation for the treatment of infertility associated with polycystic ovarian syndrome: the French experience. Hum Reprod 2005;20:420–424.
63. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Ross R, Morris S. Effects of the ovulatory serum concentration of human chorionic gonadotropin on the incidence of ovarian hyperstimulation syndrome and success rates for in vitro fertilization. Fertil Steril 2005;84:93–8.
64. Abdalla HI, Ah-Moye M, Brinsden P, Howe DL, Okonofua F, Craft I. The effect of the dose of human chorionic gonadotropin and the type of gonadotropin stimulation on oocyte recovery rates in an in vitro fertilization program. Fertil Steril 1987;48:958–963
65. Wikland M, Borg J, Forsberg AS, Jakobsson AH, Svalander P, Waldenstrom U. Human chorionic gonadotrophin self-administered by the subcutaneous route to induce oocyte maturation in an in-vitro fertilization and embryo transfer programme. Hum Reprod 1995;10:1667–1670.
66. Shaltout AM, Eid M, Shohayeb A. Does triggering ovulation by 5000 IU of uhCG affect ICSI outcome? Middle East Fertil Soc J 2006;11:99–103.
67. Kolibianakis EM, Papanikolaou EG, Tournaye H, Camus M, Van Steirteghem AC, Devroey P. Triggering final oocyte maturation using different doses of human chorionic gonadotropin: a randomized pilot study in patients with polycystic ovary syndrome treated with gonadotropin-releasing hormone antagonists and recombinant follicle-stimulating hormone. Fertil Steril 2007;88:1382–1388.
68. Lin H, Wang W, Li Y, Chen X, Yang D, Zhang Q. Triggering final oocyte maturation with reduced doses of hCG in IVF/ICSI: a prospective, randomized and controlled study. Eur J Obstet Gynecol Reprod Biol. 2011;159:143-7.
69. Detti L, Mitwally MF, Rode A, et al. Serum human chorionic gonadotropin level after ovulation triggering is influenced by the patient's body mass index and the number of larger follicles. Fertil Steril 2007;88:152–155.
70. 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.
71. Nargund G, Hutchison L, Scaramuzzi R, Campbell S. Low- dose HCG is useful in preventing OHSS in high-risk women without adversely affecting the outcome of IVF cycles. Reprod Biomed Online 2007;14:682–685.
72. Schmidt DW, Maier DB, Nulsen JC, Benadiva CA. Reducing the dose of human chorionic gonadotropin in high responders does not affect the out- comes of in vitro fertilization. Fertil Steril 2004;82:841–6.
73. Gonen Y, Balakier H, Powell W, Casper RF. Use of gonadotropin-releasing hormone agonist to trigger follicular maturation for in vitro fertilisation. J Clin Endocrinol Metab 1990;71:918–922.
74. Fauser BC, de Jong D, Olivennes F, et al. Endocrine profiles after triggering of final oocyte maturation with GnRH agonist after cotreatment with the GnRH antagonist ganirelix during ovarian hyperstimulation for in vitro fertilization. J Clin Endocrinol Metab 2002;87:709–715.
75. Kol S, Kol S. Luteolysis induced by a gonadotropin-releasing hormone agonist is the key to prevention of ovarian 73. hyperstimulation syndrome. Fertil Steril 2004;81:1–5.
76. Segal S, Casper RF. Gonadotropin-releasing hormone agonist versus human chorionic gonadotropin for triggering follicular maturation in in vitro fertilisation. Fertil Steril 1992;57:1254–1258.
77. Humaidan P, Bredkjaer HE, Bungum L, Bungum M, Grøndahl ML, Westergaard L, Andersen CY. GnRH agonist (buserelin) or hCG for ovulation induction in GnRH antagonist IVF/ICSI cycles: a prospective randomised study. Hum Reprod 2005;20:1213–1220.
78. Humaidan P, Papanikolaou EG, Tarlatzis BC. GnRHa to trigger final oocyte maturation: a time to reconsider. Hum Reprod 2009;24:2389–2394.

79. DiLuigi AJ, Engmann L, Schmidt DW, Maier DB, Nulsen JC, Benavida CA. Gonadotropin-releasing hormone agonist to induce final oocyte maturation prevents the development of ovarian hyperstimulation syndrome in high-risk patients and leads to improved clinical outcomes compared with coasting. Fertil Steril 2010; 94:1111 – 1114.
80. Humaidan P, Bungum L, Bungum M, Yding Andersen C. Rescue of corpus luteum function with peri-ovulatory HCG supplementation in IVF/ICSI GnRH antagonist cycles in which ovulation was triggered with a GnRH agonist: a pilot study. Reprod Biomed Online 2006;13:173–178.
81. Humaidan P, Ejdrup Bredkjaer H, Westergaard LG, Yding Andersen C. 1,500IU human chorionic gonadotropin administered at oocyte retrieval rescues the luteal phase when gonadotropin-releasing hormone agonist is used for ovulation induction: a prospective, randomised, controlled study. Fertil Steril 2010;93:847–854.
82. Babayof R, Margalioth JE, Huleihel M, Amash A, Zylber-Haran E, Gal M, Brooks B, Mimoni T, Eldar-Geva T. Serum inhibin A, VEGF and TNFa levels after triggering oocyte maturation with GnRH agonist compared with HCG in women with polycystic ovaries undergoing IVF treatment: a prospective randomized trial. Hum Reprod 21:1260, 2006.
83. Beckers NG, Macklon NS, Eijkemans MJ, Ludwig M, Felberbaum RE, Diedrich K, Bustion S, Loumaye E, Fauser BC. Non supplemented luteal phase characteristics after the administration of recombinant human chorionic gonadotropin, recombinant luteinizing hormone, or gonadotropin-releasing hormone (GnRH) agonist to induce final oocyte maturation in in vitro fertilization patients after ovarian stimulation with recombinant follicle-stimulating hormone and GnRH antagonist cotreatment. J Clin Endocrinol Metab 88:4186, 2003.
84. Fauser BC, De Jong D, Olivennes F,Warmsby H, Tay CJ, Itskovitz-Eldor J, Van Hooren HG. Endocrine profiles after triggering of final oocyte maturation with GnRH agonist after cotreatment with the GnRH antagonist ganirelix during ovarian hyperstimulation for in vitro fertilization. J Clin Endocrinol Metab 87:709, 2002
85. Humaidan P, Bredkjær HE, Westergaard L, Andersen CY. 1500 IU hCG secures a normal clinical pregnancy outcome in IVF/ICSI GnRH antagonist cycles in which ovulation was triggered with a GnRH agonist. Fertil Steril 93:847, 2010.
86. Kolibianakis EM, Schultze-Mosgau A, Schroer A, Van Steirteghem A, Devroey P, Diedrich K, Griesinger G. 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 20:2887, 2005.
87. Youssef MA, Van der Veen F, Al-Inany HG, Griesinger G, Mochtar MH, AboulfoutouhI, Khattab SM, van Wely M. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist assisted reproductive technology cycles. Cochrane Database Syst Rev. 2011;(1):CD008046.
88. Tesarik J, Hazout A, Mendoza C. Luteinizing hormone affects uterine receptivity independently of ovarian function. Reprod Biomed Online 2003;7:59–64.
89. Wang TH, Horng SG, Chang, Wu HM, Tsai YJ, Wang HS, et al. Human chorionic gonadotropin-induced hyperstimulation syndrome is associated with up-regulation of vascular endothelial growth factor. J Clin Endocrinol Metab 2002;87:3300–8.
90. Gomez R, Gonzalez-Izquierdo M, Zimmermann RC, Novella-Maestre E, Alonso-Muriel I, Sanchez-Criado J, Remohi J, Simon C, Pellicer A. Low-dose dopamine agonist administration blocks vascular endothelial growth factor (VEGF)-mediated vascular hyperpermeability without altering VEGF receptor 2-dependent luteal angiogenesis in a rat ovarian hyperstimulation model. Endocrinology. 2006;147:5400-11.
91. Tang H, Hunter T, Hu Y, Zhai SD, Sheng X, Hart RJ. Cabergoline for preventing ovarian hyperstimulation syndrome. Cochrane Database Syst Rev. 2012 Feb 15;2:CD008605.
92. 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.
93. Alvarez C, Martí-Bonmatí L, Novella-Maestre E, Sanz R, Gómez R, Fernández-Sánchez M, Simón C, Pellicer A. Dopamine agonist cabergoline reduces hemoconcentration and ascites in hyperstimulated women undergoing assisted reproduction. J Clin Endocrinol Metab. 2007 Aug;92(8):2931-7.
94. Carizza C, Abdelmassih V, Abdelmassih S, Ravizzini P, Salgueiro L, Salgueiro PT, Jine LT, Nagy P, Abdelmassih R. Cabergoline reduces the early onset of ovarian hyperstimulation syndrome: a prospective randomized study. Reprod Biomed Online. 2008 Dec;17(6):751-5.

95. Salah Edeen AMR, Alhelou YM. Can cabergoline prevent ovarian hyperstimulation syndrome in PCO patients undergoing gonadotropin stimulation? Comparative study with prednisolone. Abstracts of the 25th Annual Meeting of ESHRE, Amsterdam, The Netherlands, 28 June–1 July 2009.
96. Shaltout A, Shohayeb A, Eid M, Abbas S. Role of cabergoline in preventing ovarian hyperstimulation syndrome in high risk intracytoplasmic sperm injection (ICSI) patients and effect on outcome. Abstracts of the 25th Annual Meeting of ESHRE, Amsterdam, The Netherlands, 28 June–1 July 2009.
97. Rabinovici J, Kushnir O, Shalev J, Goldenberg M, Blankstein J. Rescue of menotrophin cycles prone to develop ovarian hyperstimulation. Br J Obstet Gynaecol 1987; 94:1098–1102.
98. Sher G,SalemR,FeinmanM,DodgeS,ZouvesC,Knutzen V. Eliminating the risk of life-endangering complications following overstimulation with menotropin fertility agents: a report on women undergoing in vitro fertilization and embryo transfer. Obstet Gynecol 1993;81:1009–1011.
99. Chen CD, Chao KH, Yang JH, Chen SU, Ho HN, Yang YS. Comparison of coasting and intravenous albumin in the prevention of ovarian hyperstimulation syndrome. Fertil Steril 2003;80:86–90.
100. D'Angelo A, Brown J, Amso NN. Coasting (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome. Cochrane Database Syst Rev. 2011 Jun 15;(6):CD002811.
101. Gera PS, Tatpati LL, Allemand MC, Wentworth MA, Coddington CC. Ovarian hyperstimulation syndrome: steps to maximize success and minimize effect for assisted reproductive outcome. Fertil Steril. 2010;94:173-8.
102. Ulug U, Ben-Shlomo I, Bahceci M. Predictors of success during the coasting period in high-responder patients undergoing controlled ovarian stimulation for assisted conception. Fertil Steril. 2004;82:338-42.
103. Yilmaz N, Uygur D, Ozgu E, Batioglu S. Does coasting, a procedure to avoid ovarian hyperstimulation syndrome, affect assisted reproduction cycle outcome? Fertil Steril. 2010;94:189-93.
104. Isaza V, Garcia-Velasco JA, Aragonés M, Remoh J, Simon C, Pellicer A. Oocyte and embryo quality after coasting: the experience from oocyte donation. Hum Reprod 2002;17: 1777–1782.
105. Mansour R, Aboulghar M, Serour G, Amin Y, Abou-Setta AM. Criteria of a successful coasting protocol for the prevention of severe ovarian hyperstimulation syndrome. Hum Reprod. 2005;20:3167-72.
106. Ulug U, Bahçeci 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;17:310–313.
107. Amso NN, Ahuja KK, Morris N, Shaw RW. The management of predicted ovarian hyperstimulation involving gonado- tropin-releasing hormone analog with elective cryopreservation of all pre-embryos. Fertil Steril 1990;53:1087–1090.
108. D'Angelo A, Amso N. Embryo freezing for preventing ovarian hyperstimulation syndrome. Cochrane Database Syst Rev. 2007;(3):CD002806.
109. Shaker AG, Zosmer A, Dean N, Bekir SJ, Jacobs HS, Tan S. Comparison of intravenous albumin and transfer of fresh embryos with cryopreservation of all embryos for subsequent transfer in prevention of ovarian hyperstimulation syndrome. Fertility and Sterility 1996;65:992-6.
110. Ferraretti AP, Gianaroli L, Magli C, Fortini D, Selman HA, Feliciani E. Elective cryopreservation of all pronucleate embryos in women at risk of ovarian hyperstimulation syndrome:efficiency and safety. Human Reproduction 1999;14:1457-60.
111. Aflatoonian A, Oskouian H, Ahmadi S, Oskouian L. Can fresh embryo transfers be replaced by cryopreserved-thawed embryo transfers in assisted reproductive cycles? A randomised controlled trial. J Assist Reprod Genet 2010;27:357–363.
112. Surrey E, Keller J, Stevens J, Gustofson R, Minjarez D, Schoolcraft W. Freeze-all: enhanced outcomes with cryopreservation at the blastocyst stage versus pronuclear stage using slow-freeze techniques. Reprod Biomed Online 2010;21:411–417.
113. Asch RH, Ivery G, Goldsman M, Frederick JL, Stone SC, Balmaceda JP. The use of intravenous albumin in patients at high risk for severe ovarian hyperstimulation syndrome. Hum Reprod 1993;8: 1015–20.
114. 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.

115. Youssef MA, Al-Inany HG, Evers JL, Aboulghar M. Intra-venous fluids for the prevention of severe ovarian hyperstimulation syndrome. Cochrane Database Syst Rev. 2011;(2):CD001302.
116. 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.
117. Ben-Chetrit A, Eldar-Geva T, Gal M, Huerta M, Mimon T, Algur N, Diamant YZ, Margalioth EJ. 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.
118. Abramov Y, Fatum M, Abrahamov D, Schenker JG. Hydroxyethyl starch versus human albumin for the treatment of severe ovarian hyperstimulation syndrome: a preliminary report. Fertil Steril 2001;75(6):1228–1230
119. Aboulghar MA, Mansour RT, Serour GI, Amin Y. Ultra- sonically guided vaginal aspiration of ascites in the treatment of severe ovarian hyperstimulation syndrome. Fertil Steril 1990;53:933–935
120. Fluker M, Copeland J, Yuzpe A. An ounce of prevention: outpatient management of ovarian hyperstimulation syndrome. Fertil Steril 2000;73:821–4.