Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline

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Ovarian hyperstimulation syndrome (OHSS) is an uncommon but serious complication associated with assisted reproductive technology (ART). This systematic review aims to identify who is at high risk, how to prevent OHSS, and the treatment for existing OHSS. (Fertil Steril® 2016;106:1634–47. ©2016 by American Society for Reproductive Medicine.)

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is an uncommon but serious complication associated with controlled ovarian stimulation during assisted reproductive technology (ART). Moderate-to-severe OHSS occurs in approximately 1%–5% of cycles (1–5). However, the true incidence is difficult to delineate as a strict, consensus definition is lacking. The traditional description of the syndrome generally includes a spectrum of findings, such as ovarian enlargement, ascites, hemoconcentration, hypercoagulability, and electrolyte imbalances. Symptoms are often qualified by their severity (mild, moderate, or severe) and by the timing of onset (early or late) (Table 1). Severe OHSS can lead to serious complications, including pleural effusion, acute renal insufficiency, and venous thromboembolism.

Because OHSS is the most serious consequence of controlled ovarian stimulation, every attempt should be made to identify patients who are at highest risk. Understanding the pathophysiology of this condition may aid in identifying measures to prevent its development and treat associated symptoms. Classic physiologic changes of OHSS include arteriolar vasodilation and an increase in capillary permeability that results in fluid shifting from intravascular to extravascular spaces (6, 7). This fluid shift results in a state of hypovolemic hyponatremia. Vascular endothelial growth factor (VEGF) appears to be integral to the development of this condition and is involved in follicular growth, corpus luteum function, angiogenesis, and vascular endothelial stimulation (8–10). In response to human chorionic gonadotropin (hCG), VEGF appears to mediate the vascular permeability of OHSS as systemic hCG levels positively correlate with severity of the disease (10–12). Other systemic and local vasoactive substances, including interleukin-6, interleukin-1β, angiotensin II, insulin-like growth factor 1, transforming growth factor β, and the renin-angiotensin system are also directly and indirectly involved in the pathogenesis of OHSS symptoms (8,12–16). As understanding of stimulation techniques, disease pathophysiology, and monitoring technology improve, an objective of ovulation induction should be near-complete mitigation of the syndrome. The condition is self-limiting and, in patients who do not conceive, typically resolves at the time of the next menstrual period. In patients who do become pregnant, rising hCG levels continue to stimulate the ovaries and symptoms may extend through the end of the first trimester.

A systematic search of the literature was performed in order to answer three questions about OHSS: who is at

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TABLE 1

Classification of OHSS symptoms.

OHSS stage	Clinical feature	Laboratory feature
Mild	Abdominal distension/discomfort Mild nausea/vomiting Mild dyspnea Diarrhea Enlarged ovaries	No important alterations
Moderate	Mild features Ultrasonographic evidence of ascites	Hemoconcentration (Hct >41%) Elevated WBC (>15,000 mL)
Severe	Mild and moderate features Clinical evidence of ascites Hydrothorax Severe dyspnea Oliguria/anuria Intractable nausea/vomiting Low blood/central venous pressure Pleural effusion Rapid weight gain (>1 kg in 24 h) Syncope Severe abdominal pain Venous thrombosis	Severe hemoconcentration (Hct >55%) WBC >25,000 mL CrCl <50 mL/min Cr >1.6 mg/dL Na+ <135 mEq/L K+ >5 mEq/L Elevated liver enzymes
Critical	Anuria/acute renal failure Arrhythmia Thromboembolism Pericardial effusion Massive hydrothorax Arterial thrombosis Adult respiratory distress syndrome Sepsis	Worsening of findings

Note: Hct = hematocrit; WBC = white blood cell; CrCl = creatinine clearance; Cr = creatinine; Na+ = sodium; K+ = potassium.

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high risk, how can it be prevented, and what is the treatment for it? When available, level I data were utilized to address these questions, and when unavailable, level II-1 and II-2 data were analyzed. Although the quality of the data available to address these questions is variable, there are consistent trends in the literature that allow for the guidelines set forth in this document.

METHODS

This clinical practice guideline was based on a systematic review of the literature performed in the electronic database MEDLINE through PubMed, with a filter for human subject and English research, on September 10, 2015. This electronic search and examination of reference lists from primary and review articles yielded 1,245 studies, of which 144 studies were included.

A combination of the following medical subject headings or text words were used: acetylsalicylic acid, age, albumin, ASA, ascites, aspirin, BMI, body mass index, calcium, clinical trial, clomiphene, enoxaparin, freeze, freeze-all, heparin, "last 5 years," Lovenox, obes*, metformin, OHSS, ovarian hyperstimulation syndrome, paracentesis, prevention, prednisolone, prednisone, risk factors, *stimulation, treatment (limited to "clinical trial"), and weight*.

Initially, titles and abstracts of potentially relevant articles were screened and reviewed for inclusion/exclusion criteria. Protocols and results of the studies were examined according to specific inclusion criteria. Only studies that met the inclusion criteria were assessed in the final analysis. Studies were eligible if they met one of the following criteria: primary evidence (clinical trials) that assessed the effectiveness of a procedure correlated with an outcome measure (pregnancy, implantation, or live-birth rates); meta-analyses; and relevant articles from bibliographies of identified articles.

Four members of an independent task force reviewed the full articles of all citations that possibly matched the predefined selection criteria. Final inclusion or exclusion decisions were made on examination of the articles in full. Disagreements about inclusion among reviewers were discussed and solved by consensus or arbitration after consultation with an independent reviewer/epidemiologist.

The quality of the evidence was evaluated using the following grading system and is assigned for each reference in the bibliography:

Level I: Evidence obtained from at least one properly designed randomized, controlled trial.

Level II-1: Evidence obtained from well-designed controlled trials without randomization.

Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III: Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Systematic reviews/meta-analyses were individually considered and included if they followed a strict methodological process and assessed relevant evidence.

The strength of the evidence was evaluated as follows:

Grade A: There is good evidence to support the recommendations, either for or against.

Grade B: There is fair evidence to support the recommendations, either for or against.

Grade C: There is insufficient evidence to support the recommendations, either for or against.

WHO IS AT HIGH RISK FOR MODERATE AND SEVERE OHSS?

OHSS could theoretically occur in any woman undergoing controlled ovarian stimulation with gonadotropins. However, evidence indicates that there are some women who are at a much higher risk. Identifying these women is essential to lowering, and potentially eliminating, the incidence of OHSS. After a systematic search of the literature was performed, studies comparing prevalence rates among different cohorts of women undergoing controlled ovarian stimulation were evaluated.

Demographics (Age, BMI, Race, Infertility Diagnosis)

Patient characteristics, such as age, body mass index (BMI), and ART indication, should be considered when assessing the risk of developing OHSS. In the largest study to evaluate risk factors for OHSS, data from the Society for Assisted Reproductive Technology (SART) database were utilized and showed that among 214,219 ART cycles, younger age, black race, ovulation, tubal factor, and unexplained infertility were all associated with an increased risk of OHSS (2). This is the only study that evaluates race as a predictor of OHSS. Four retrospective studies (2,17–19) and two prospective studies (20, 21) evaluated the effect of age on the risk of developing OHSS symptoms and demonstrated that a younger age was associated with an increased risk. In the largest of these studies, more than 60% of women who developed OHSS were less than 35 years old. Of the six studies reporting BMI and rates of OHSS, two supported a correlation between a lower BMI and development of OHSS (21, 22), whereas the other four studies showed no predictive value (17, 19, 23, 24). Several observational studies have also shown a higher incidence of OHSS in women with a diagnosis of an ovulation disorder or polycystic ovary syndrome (PCOS) (2, 3, 19, 20, 23, 25).

Ovarian Reserve Markers (AMH, AFC, Inhibin A/B)

Markers for ovarian reserve may also be used to assess risk of OHSS. Using a prospective cohort of 262 women undergoing in vitro fertilization (IVF), higher serum antimüllerian hormone (AMH) levels (cut-off value 3.36 ng/mL) predicted OHSS better than age and BMI with a sensitivity of 90.5% and specificity of 81.3% (24). In another study, AMH levels in women with OHSS were 6-fold higher than age- and weight-matched controls (26). In a retrospective cohort study of 134 women with elevated AMH levels (>5 ng/mL), women with AMH of >10 ng/mL had significantly higher rates (>3-fold) of OHSS (27).

Antral follicle count (AFC) is predictive of OHSS as well (17, 28). In a prospective analysis of 1,012 first ART cycles, the risk of OHSS increased from 2.2% in women with an AFC <24 to 8.6% with an AFC ≥24 (3).

Only two studies have assessed the predictive value of inhibin A and B, and both have shown no correlation between serum (or follicular) inhibin concentrations and the development of OHSS (28, 29).

Ovarian reserve measures, in particular AMH and AFC, have been found to be predictive of OHSS in several studies and may be useful for planning ovarian stimulation protocols and counseling patients regarding risk. However, these measures should be used with caution since clear cut points have not been validated in the literature.

Ovarian Stimulation Parameters (Follicles, Oocytes, Estradiol)

Stimulation characteristics, such as multifollicular development, elevated estradiol levels, and a high number of oocytes retrieved, may aid in the prediction of patients who will develop OHSS. Several prospective studies have demonstrated that a high number of growing follicles is an independent predictor of OHSS (4, 5, 22, 30). Specifically, one study found that developing 20 or more follicles during ART stimulation significantly increases the risk of OHSS (30).

In a prospective cohort study of 624 patients undergoing their first IVF cycle in Sweden, multivariate analysis identified a model to predict the occurrence of OHSS with 82% sensitivity and 90% specificity if the following thresholds were met: >25 follicles at retrieval; >19 large-/medium-sized follicles before hCG; and >24 oocytes retrieved (4). An additional 11 studies support the positive correlation between number of oocytes retrieved and development of OHSS (1, 4, 17–23, 31, 32). Utilizing the SART registry, analysis of 256,381 cycles demonstrated that retrieval of >15 oocytes significantly increases the risk of OHSS without improving live-birth rate in fresh autologous cycles (1).

Finally, serum estradiol concentrations were also significantly associated with OHSS (17–24, 33). In the majority of these studies, the mean estradiol value in patients with OHSS was >3,500 pg/mL.

Summary Statements

- There is fair evidence (level II-2) that PCOS, elevated AMH values, peak estradiol levels, multifollicular development, and a high number of oocytes retrieved are associated with an increased risk of OHSS. (Grade B)
- While cut points require validation, AMH values >3.4 ng/mL, AFC >24, development of ≥25 follicles, estradiol values >3,500 pg/mL, or ≥24 oocytes retrieved are particularly associated with an increased risk of OHSS. (Grade B)

PREVENTION OF OHSS

Does the Type of Stimulation Protocol Influence the Risk of OHSS?

GnRH agonist vs. GnRH antagonist protocols. There are multiple studies demonstrating that stimulation protocols utilizing gonadotropin-releasing hormone (GnRH) antagonists for ovulation suppression are associated with a lower incidence of OHSS compared with protocols that use a GnRH agonist. The mechanism is thought to be related to a reduction in circulating estradiol levels seen with GnRH antagonist suppression. The largest randomized study addressing this question was a two-center, open-label superiority trial of 1,050 patients comparing GnRH antagonist to GnRH agonist designed to detect a difference in severe OHSS (34). The incidence of severe OHSS was significantly lower in the GnRH antagonist group compared with the agonist group (5.1% [27/528] versus 8.9% [44/495]; 95% confidence interval [CI], −7.1 to −0.4; $P=.02$). Live-birth rates were no different between groups, 22.8% (122/534) vs 23.8% (123/516), respectively. These findings are corroborated by multiple smaller randomized controlled studies (35–38), including a study in which 235 patients undergoing ART for the first time were randomized to a standard long protocol with GnRH agonist compared with GnRH antagonist (39). Similar to the previous study, the incidence of OHSS was significantly lower in the antagonist protocol compared with agonist, 2.7% vs 12%, respectively (39). Of interest, studies looking specifically at IVF in women with PCOS found that suppression with antagonist as opposed to agonist also appears to be beneficial in this high-risk subset of patients (40, 41). It is worth noting that hCG trigger (no GnRH agonist) was used for all of these randomized controlled trials (RCTs). In addition, multiple systematic reviews have supported the use of GnRH antagonist for ovarian suppression and subsequent reduction in OHSS (42–45). A Cochrane review compiled data from 29 RCTs that evaluated live birth (45 studies total in Cochrane) and demonstrated a statistically significant lower incidence of OHSS in the GnRH antagonist group (odds ratio [OR] 0.43, 95% CI, 0.33 to 0.57) and no difference in live-birth rates compared with GnRH agonist (46).

It is unclear whether the addition of clomiphene as part of a GnRH antagonist stimulation protocol influences the risk of OHSS. Two RCTs demonstrate that the addition of clomiphene to controlled ovarian stimulation results in fewer OHSS events compared with GnRH agonist protocols without clomiphene (47, 48). Two systematic reviews concluded that clomiphene-antagonist protocols have a significant reduction of OHSS compared with either non-clomiphene protocols (0.5% vs 4.1%, $P=.01$) (49) or GnRH agonist cycles (OR 0.23, 95% CI 0.10–0.52) (50). However, these studies are difficult to interpret since the reduction in OHSS risk is confounded by different stimulation protocols where "minimal stimulation" may be the goal.

Summary Statements

- There is good evidence to support the use of ovarian stimulation protocols using GnRH antagonists in order to reduce the risk of OHSS. (Grade A)
- There is insufficient evidence that clomiphene independently reduces OHSS risk. (Grade C)

Can Aspirin Reduce the Risk of OHSS?

There are two randomized trials on the use of aspirin for OHSS prevention. Increased platelet activation due to VEGF levels may lead to release of substances, such as histamine, serotonin, platelet-derived growth factor, or lysophosphatidic acid, that can further potentiate the physiologic cascade of OHSS. Based on this theory, aspirin has been considered in the risk reduction of OHSS (51). In one study, patients were randomized to receive low-dose aspirin and prednisolone (n = 97) or nothing (n = 298), in addition to the routinely used IVF medications. Patients randomized to the treatment arm received a daily dose of 100 mg aspirin from the first day of stimulation until the day of the pregnancy test, and prednisolone in varying doses (10 mg to 30 mg) for the same time frame. Patients who received the combination of aspirin and prednisolone had more retrieved oocytes, but a lower incidence of severe OHSS (1.7% vs 6.5%) (52). In a second trial, women at high risk for OHSS (defined as a prior history of OHSS, polycystic ovaries, and age under 30 years) benefited from 100 mg aspirin given from the first day of the menstrual cycle when IVF was performed, and continued until menstruation, a negative pregnancy test, or the ultrasonographic detection of embryonic cardiac activity. Women taking aspirin had a lower incidence of severe OHSS requiring hospital admission compared with women who were not on aspirin (2/780 women, 0.25% vs 43/412 women, 8.4%, $P<.001$) (51). The authors did not see a difference in pregnancy outcomes between the two groups.

Summary Statement

- There is fair evidence that aspirin reduces the incidence of OHSS based on a single randomized trial comparing aspirin alone with no treatment and another study comparing combined acetylsalicylic acid and steroid treatment with no treatment. (Grade B)

Can Metformin Reduce the Risk of OHSS?

Metformin is an insulin-sensitizing drug that is commonly used for treating type 2 diabetes and has been widely studied in patients with PCOS. "Androgen priming" is the concept that androgens increase the ovarian response to gonadotropin

stimulation by enhancing early follicular growth. By improving intraovarian hyperandrogenism, it is theorized that metformin can affect the ovarian response by reducing the number of non-periovulatory follicles and thereby reduce estradiol secretion. Studies have addressed the question of whether metformin (500 mg three times daily or 850 mg twice daily) during ovarian stimulation for IVF in PCOS patients can reduce OHSS in this high-risk group. The first RCT in 2006 showed that metformin from the start of down-regulation until oocyte retrieval for GnRH protocols decreased the incidence of OHSS in PCOS patients (3.8% vs 20.4%, $P=.023$) (53). Subsequent RCTs have supported this conclusion (54, 55). More recently, a systematic review of 10 RCTs concluded that metformin decreases the incidence of OHSS in PCOS patients (OR 0.27, 95% CI 0.16–0.46) (56). A recent meta-analysis included 12 studies of 1,516 participants and showed that there were no differences in pregnancy rates, live-birth rates, and spontaneous abortion rates between the metformin group and placebo group, but that OHSS risk was significantly lower with metformin use (relative risk [RR] 0.44, 95% CI 0.26–0.77) (57). There have been attempts to identify the subset of PCOS patients who may benefit most from metformin to reduce OHSS risk. Some studies suggest that metformin does not decrease OHSS risk in non-obese PCOS patients (58) or those with PCO morphology only (59).

Summary Statement

- There is good evidence that metformin decreases the risk of OHSS risk in PCOS patients. (Grade A)

Can Coasting Reduce the Risk of OHSS?

Coasting is the practice of withholding gonadotropins at the end of controlled ovarian stimulation for up to 4 days to decrease OHSS risk. Early cohort studies showed that coasting is associated with a lower risk of OHSS without compromising the pregnancy rate (60, 61). Cohort studies showed a comparable reduction in OHSS when coasting is compared with cryopreservation (62), albumin (63), or, in one RCT, early unilateral follicular aspiration (64). However, these results were not supported by RCTs. A systematic review of four RCTs concluded that coasting does not decrease risk of OHSS, but is associated with fewer oocytes retrieved (65). An additional cohort study suggested that coasting may lead to a higher incidence of severe OHSS, though the absolute numbers were small (66). The optimal length of coasting has not been determined, with limited cohort studies suggesting that coasting ≥ 4 days decreases implantation rates (67).

Summary Statement

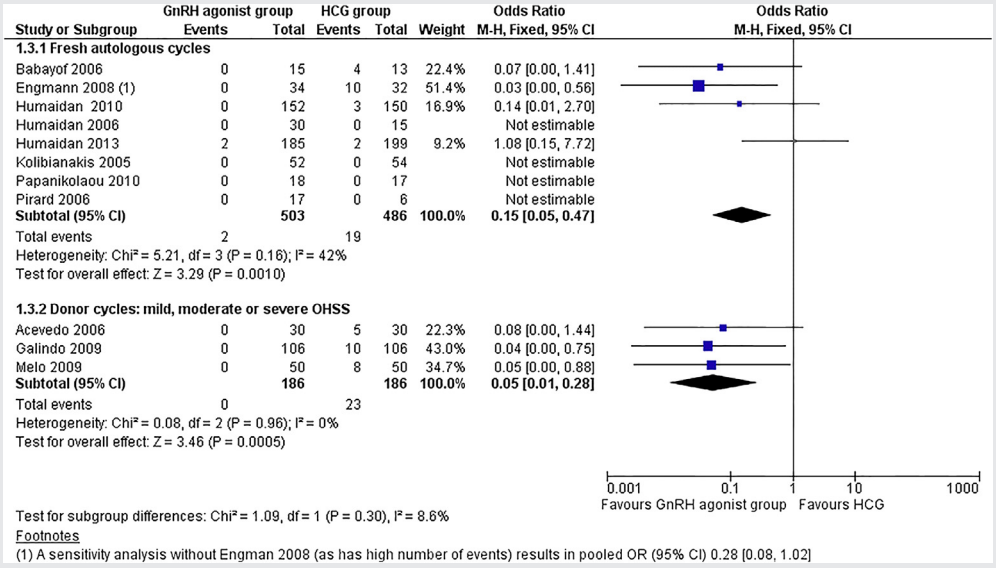
- There is insufficient evidence to recommend coasting for the prevention of OHSS. (Grade C)

Choice of Trigger for Final Oocyte Maturation Prior to Retrieval

Utilization of hCG for trigger prior to oocyte retrieval for final oocyte maturation in ART cycles to mimic the endogenous preovulatory luteinizing hormone (LH) surge has been the standard of care for decades. However, the longer half-life of hCG results in sustained LH-like activity post-retrieval. This resultant stimulation of LH receptors on the multiple post-retrieval corpora lutea may lead to the development of OHSS. Modification of the "trigger" shot or dose used for oocyte maturation has been an active area of investigation to reduce OHSS. Several studies have assessed whether lowering the dose of hCG results in a lower risk of OHSS. An RCT evaluated 5,000 IU vs 10,000 IU of hCG in 100 high-risk patients and reported a lower risk of OHSS in the low-dose group, 2% (one reported case) vs 8.3% (four reported cases), but the results did not meet statistical significance (68). The authors found no difference in oocyte recovery, fertilization, or pregnancy rate. An RCT of 164 patients randomized to 4,000 IU vs 6,000 IU dose found no difference in the rate of OHSS, 3.6% vs 4.9%, respectively (69). Lowering the dose of hCG is a strategy with conflicting results and may or may not consistently reduce OHSS in high-risk patients. Given that lowering the hCG dose is not a perfect solution, alternate strategies continue to be investigated.

There are multiple studies that assess development of OHSS in women who receive GnRH agonist trigger compared with hCG trigger for final oocyte maturation. This includes several RCTs that provide strong evidence that the use of a GnRH agonist trigger results in a significant reduction in the development of OHSS. The majority of these studies were conducted in women at high risk for OHSS, including oocyte donors or women with PCOS. In an RCT of 66 women at high risk for the development of OHSS that compared GnRH agonist to hCG trigger, none of the patients in the GnRH agonist trigger group developed any form of OHSS compared with 31% (10/32) of the patients who received hCG. Furthermore, the study found no significant differences in the implantation rate (22/61 [36.0%] vs 20/64 [31.0%]), clinical pregnancy rate (17/30 [56.7%] vs 15/29 [51.7%]), and ongoing pregnancy rate (16/30 [53.3%] vs 14/29 [48.3%]) in the GnRH agonist vs hCG trigger groups, respectively (70). Subsequently, three separate RCTs were performed in an oocyte donor population at high risk for OHSS and found that GnRH agonist trigger almost eliminated the development of OHSS in these women (0% risk of OHSS with GnRH agonist vs 7%–16% with hCG trigger) (71–73). One of the largest studies assessed a cohort of oocyte donors over 4,052 stimulation cycles in which hCG or GnRH agonist was administered based on physician discretion (74). Consistent with other reports, the incidence of moderate/severe OHSS was lower in the women who received GnRH agonist trigger compared with hCG (0% [0/1,519] vs 0.87% [22/2,533], respectively) (74). Multiple cohort studies in the literature corroborate the reduction in OHSS following GnRH agonist as compared with hCG trigger (74–77). A Cochrane review published in 2014 summarized the results of 17 RCTs that assessed GnRH agonist as compared with hCG trigger (n = 1,847) and found that final oocyte triggering with an agonist resulted in a lower incidence of OHSS in fresh autologous cycles (OR 0.15, 95% CI 0.05–0.47; eight RCTs, 989 women, moderate-quality evidence) as well as in donor-recipient cycles (OR 0.05, 95% CI 0.01–

FIGURE 1



Summary of risk comparing GnRH agonist with HCG trigger. Used with permission from Youssef 2014, The Cochrane Collection (78).

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0.28; three RCTs, 374 women) (Fig. 1) (78). The authors also reported, however, that agonist trigger was associated with a lower live-birth rate (OR 0.47, 95% CI 0.31–0.70; five RCTs, 532 women, moderate-quality evidence) in fresh autologous cycles (78).

The mechanism by which pregnancy rate is lowered in GnRH agonist trigger cycles is not completely elucidated; however, the more rapid and dramatic post-luteal drop in hormonal LH support, as compared with hCG for maturation, has been well described and results in luteal phase insufficiency. There are several strategies that have been used to mitigate the lower pregnancy rates after GnRH trigger for oocyte maturation: cryopreserving embryos and transferring in a subsequent frozen embryo transfer cycle rather than performing a fresh embryo transfer; adding a co-trigger with low-dose hCG; or supplementing hormones (hCG or estradiol) during the luteal phase in addition to progesterone. Several groups have investigated whether co-administration of low-dose hCG may improve pregnancy rates and still reduce OHSS (70, 79). One study used GnRH agonist with administration of low-dose hCG for luteal support (1,000 IU, 500 IU, or 250 IU every third day after retrieval) and reported that supplementation with low-dose hCG restored the clinical pregnancy rate (80). The overall rates of moderate and severe OHSS were 4.2% and 3.6%, respectively. It should be noted that the authors reported a trend toward a higher rate of moderate OHSS with the 1,000 IU dosing compared to the lower doses, but this was not significant and there was no difference in the incidence of severe OHSS with the different hCG regimens. An RCT of 384 patients found that GnRH agonist trigger with a single bolus of 1,500 IU of hCG after oocyte retrieval reduced OHSS in high-risk patients (0%), and when patients received a second bolus of 1,500 IU of hCG (one the day of retrieval and one the subsequent day), there was an increase in moderate-to-late onset of OHSS (3.4%) (79). These studies suggest that co-administration of low-dose hCG at the time of GnRH agonist administration can support the post-retrieval luteal phase to help mitigate the reported reduction in pregnancy rate when GnRH agonist is administered alone.

It should be noted that certain subgroups of patients exhibit a poor response to GnRH agonist for final oocyte maturation. A retrospective cohort analysis of 500 cycles attempted to identify patients at risk for suboptimal LH surge (LH <15) after trigger with GnRH agonist alone ($n = 73$) or in combination with low-dose hCG ($n = 427$) (81). The authors reported a 5.2% rate of suboptimal response overall and found it was correlated with lower follicle-stimulating hormone (FSH) and LH levels at baseline as well as lower LH levels on the day of GnRH agonist trigger. Specifically, they reported a 25% chance of suboptimal response if the LH level was undetectable on the day of trigger. In addition, irregular menses and prolonged oral contraceptive pill use, as well as a trend to lower body mass, were also reported to be associated with suboptimal response to GnRH agonist trigger or co-trigger. As such, patients who exhibit signs of significant suppression of the hypothalamic-pituitary axis may not be good candidates for GnRH agonist for final maturation; this strategy should be avoided or used with caution in this patient population.

Summary Statements

- There is insufficient evidence to recommend a lower dose of hCG to trigger oocyte maturation for reduction in

OHSS risk based on one underpowered randomized trial. (Grade C)

- There is good evidence to recommend the use of a GnRH agonist to trigger oocyte maturation prior to oocyte retrieval in order to reduce the risk of OHSS. (Grade A)
- There is good evidence that live-birth rates are lower in fresh autologous cycles after GnRH trigger, but not donor-recipient cycles. (Grade A)
- There is fair evidence that reproductive outcomes are improved when a low dose of hCG is co-administered at the time of GnRH agonist trigger for luteal support. (Grade B)

Dopamine Agonist

The pathophysiology of ovarian OHSS is largely attributed to an increased vascular permeability of the ovarian and peritoneal capillaries caused by ovarian hypersecretion of VEGF. It has been postulated that treatment with a dopamine-receptor agonist such as cabergoline may result in a reduction of VEGF production and a subsequent reduction in OHSS. To that end, there is a growing body of evidence evaluating the administration of dopamine agonist (cabergoline) to reduce the severity and incidence of OHSS. This includes eight randomized controlled studies (82–89). A prospective, randomized, double-blind study assessed oocyte donors who were administered cabergoline 0.5 mg/day (n = 37) or placebo (n = 32) from the day of hCG for 8 days. The incidence of moderate OHSS was 20.0% in the cabergoline group and 43.8% in the placebo group (P=.04) (84). The authors also assessed ascites as an endpoint and found a lower rate of a fluid pocket exceeding >9 cm^2 in women treated with cabergoline (25.7%), compared with those who did not receive treatment (59.4%, P=.005) (84). Subsequently, another prospective, randomized trial of cabergoline vs no treatment in 40 women at high risk (estradiol >4,000; >20 follicles) found that the incidence of moderate OHSS was also reduced in the cabergoline-treated group vs controls, 15% vs 50%, respectively (P=.04), with the incidence of severe OHSS not significantly different between treated and control groups (0% and 10%, respectively) (85). Several systematic reviews have assessed cabergoline compared with placebo. A review of seven studies in 858 women found that administration of cabergoline reduced the incidence of OHSS compared with no treatment (RR 0.38, CI 0.29–0.51, P<.00001), without impacting pregnancy rates (RR 1.02, 95% CI 0.78–1.34, four studies, 561 women) (Fig. 2) (90).

Summary Statement

- There is good evidence that dopamine agonist administration starting at the time of hCG trigger for several days reduces the incidence of OHSS. (Grade A)

Can Albumin Prevent OHSS Risk?

Albumin has a low molecular weight and an average half-life of 20 days. Its binding and transport properties may play a role in OHSS prevention. As albumin increases plasma oncotic pressure, it may counteract the permeability effect of angiotensin II. Albumin may also bind to vasoactive substances, such as factors related to the renin-angiotensin system and VEGF. However, the data evaluating the efficacy of albumin in the prevention of OHSS are mixed. Initially, early RCTs demonstrated that 20% human albumin administered around the time of oocyte retrieval decreased the incidence of moderate-to-severe OHSS compared with no treatment (91–93). One such RCT randomized women at high risk for OHSS based on a serum estradiol cutoff of 3,000 pg/mL to albumin treatment or none after using 5,000 IU hCG as a trigger. In this study, five patients developed moderate or severe OHSS in the control group vs no patients in the albumin group (P=.028) (91). However, more recent studies have not found albumin to be effective in decreasing the incidence of OHSS (94–96). Two systematic reviews concluded that albumin does not prevent OHSS (97, 98). One review in particular reported that intravenous (IV) albumin around oocyte retrieval not only does not decrease the incidence of severe OHSS compared with no treatment (RR 0.8, 95% CI 0.57–1.12), but it also lowers the pregnancy rate (RR 0.85, 95% CI 0.74–0.98) (97). In addition, other studies have compared the use of human albumin to other methods for reducing OHSS risk and found that human albumin does not offer a significant benefit over hydroxyethyl starch solution (HES) or coasting. In a Cochrane review of nine RCTs, although albumin decreased the odds of OHSS compared with placebo (OR 0.67, 95% CI 0.45–0.99), the point estimate for HES compared with placebo was lower than that of albumin (OR 0.12, 95% CI 0.04–0.40) (99). In a cohort study of 162 women undergoing IVF who were considered to be at high risk for OHSS, the incidence of OHSS was comparable between those who received albumin and those who were coasted (63). It is also important to note that albumin is a blood-derived product, and can lead to allergic reactions, anaphylactic reactions, and the transmission of viral or unidentified diseases.

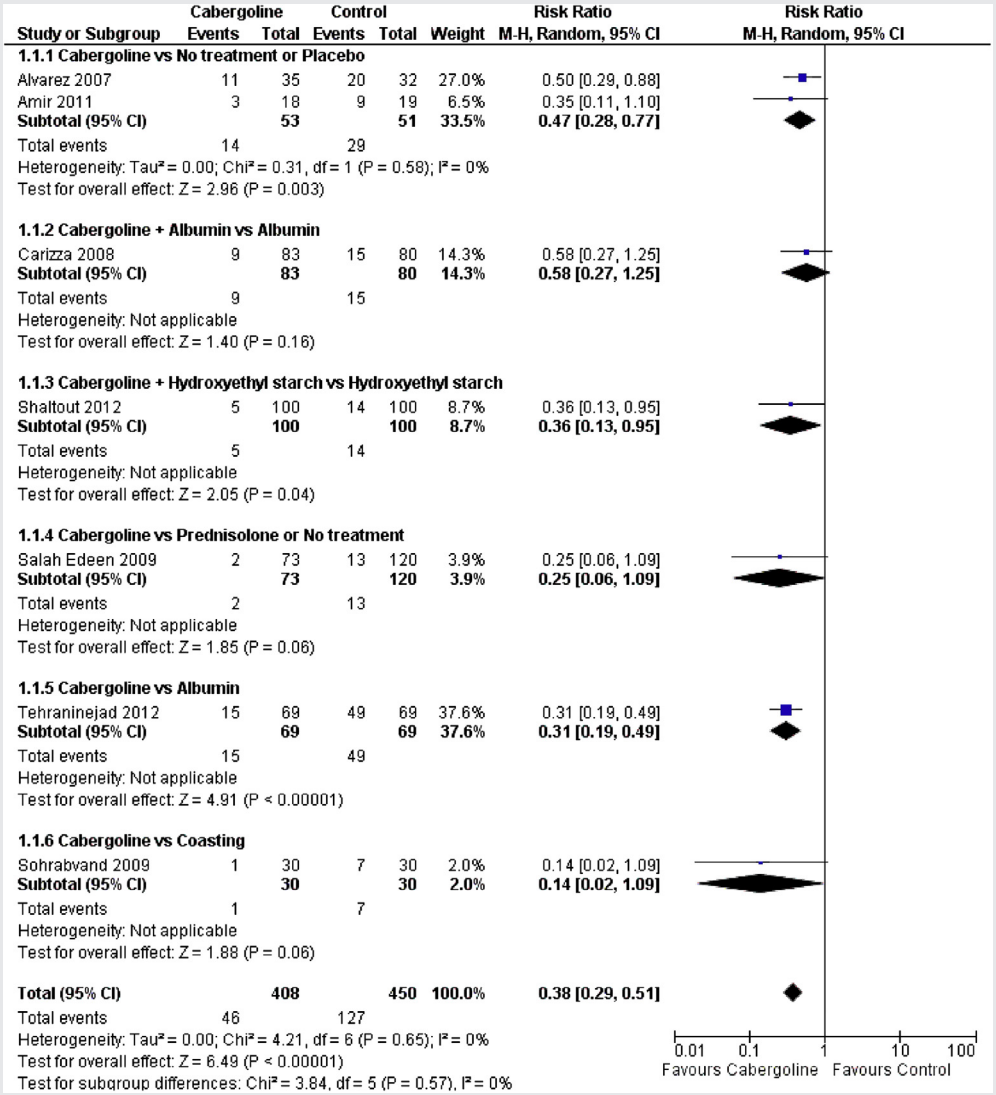
Summary Statement

- Given mixed results in the literature, there is insufficient evidence to conclusively state that albumin lowers the risk of OHSS. (Grade C)

Can Calcium Prevent OHSS Risk?

Studies have investigated whether an IV calcium infusion (10 mL of 10% calcium gluconate in 200 mL normal saline) on the day of oocyte retrieval and days 1, 2, and 3 after oocyte retrieval can decrease OHSS risk. Increased calcium is postulated to inhibit cAMP-stimulated renin secretion, which decreases angiotensin II synthesis and its subsequent effect on VEGF production. One RCT of 200 women at risk for OHSS demonstrated that the incidence of moderate and severe OHSS was higher in women who received normal saline compared with the IV calcium group (23% vs 7%, P=.002) (100). There was no difference in clinical pregnancy or ongoing

FIGURE 2



Risk ratio when comparing cabergoline and controls. Reprinted from Leitao et al., Fertil Steril 2014 (90).

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pregnancy rate between the two groups. A retrospective cohort study concluded that IV calcium was effective in reducing OHSS risk in PCOS women (101). Another case-control study suggested that IV calcium is as effective as cabergoline in preventing OHSS (102). In this study, 202 women at risk for OHSS underwent a GnRH down-regulated protocol and received either 0.5 mg/day cabergoline from the day of ovulation trigger for 8 days, or 10 mL of 10% calcium gluconate solution within 30 minutes of oocyte retrieval and on days 1, 2, and 3 after retrieval. OHSS occurred in 9 patients in the calcium-infusion group compared with 16 patients in the cabergoline group, and the authors reported that this was not statistically significant. Three patients had severe OHSS, two in the cabergoline group and one in the calcium-infusion group. Pregnancy outcomes were not reported.

Summary Statement

- There is fair evidence that calcium lowers OHSS risk. (Grade B)

Can Cryopreservation Prevent OHSS Risk?

Elective cryopreservation of all embryos and their subsequent transfer in nonstimulated cycles may be used to avoid the endogenous hCG rise in fresh transfer cycles, which can exacerbate late-onset OHSS symptoms and duration. Two RCTs have concluded that elective cryopreservation prevents OHSS. In one small study, cryopreservation was as effective as IV albumin in preventing mild, moderate, and severe OHSS in 26 patients considered to be at high risk of

developing OHSS, but with a higher pregnancy rate (103). The cryopreservation group had three cases of moderate OHSS and no cases of severe OHSS, with a pregnancy rate of 38%, compared with the albumin group that had four cases of moderate OHSS and no cases of severe OHSS, with a pregnancy rate of 0%. Another larger RCT of 125 patients showed that cryopreservation at the pronucleate stage resulted in a lower incidence of OHSS than controls with fresh embryo transfers (0 events vs 4 events, respectively) (104). This study showed that there were no differences in pregnancy rates (46% controls vs 48% cryopreservation of zygotes) or live-birth rates (39% controls vs 40% cryopreservation). Interestingly, a systematic review that included only these same two studies came to the conclusion that there was insufficient evidence to support cryopreservation as a method to reduce OHSS risk (105).

Summary Statement

- Based on the results of two small RCTs, there is fair evidence that cryopreservation prevents OHSS. (Grade B)

Can Miscellaneous Treatments Prevent OHSS Risk?

There are insufficient data to make recommendations regarding the use of luteal antagonist administration, letrozole, methylprednisolone, intramuscular progesterone, or ketoconazole to mitigate OHSS risk.

TREATMENT OF OHSS

Symptomatic moderate or severe OHSS is a hypovolemic-hyponatremic state. Treatment usually involves fluid replacement to maintain intravascular perfusion and supportive care. A rare but life-threatening risk for patients with severe hypovolemia involves arterial or venous thromboembolism; therefore, prophylactic anticoagulation is warranted in cases of severe OHSS from the time of diagnosis through the first trimester of pregnancy (106).

The majority of studies examining the treatment of OHSS are retrospective cohort studies. These studies evaluated both volume expanders and surgical interventions utilized when patients had already exhibited signs and symptoms of OHSS. There are more robust data supporting surgical intervention, such as paracentesis and culdocentesis, than fluid management.

Does Outpatient Paracentesis of Women with OHSS Improve Their Outcome?

Several cohort studies have compared management of OHSS with paracentesis, either as in- or outpatient with nonsurgical management. Some authors expressed concern for potential vascular injury or injury to the enlarged ovaries with paracentesis (107, 108). However, studies using ultrasound-guided aspiration did not report these injuries.

A cohort study of 48 women with OHSS and ascites treated all the patients with repeated outpatient transvaginal culdocentesis and rehydration with IV crystalloids and albumin every 1–3 days until resolution of symptoms or hospitalization was required (109). The average number of outpatient treatments was 3.4 (1–14); 91.6% of patients were managed as outpatients and avoided hospitalization. A large cohort study reported the effect of repeated transvaginal aspiration on reproductive outcome in patients with severe OHSS (110). Sixty-five women with severe early OHSS were hospitalized and managed with transvaginal fluid aspiration either in <3 occasions (historic control group; n = 29) or ≥ 3 occasions (multiple aspirations) (study group; n = 36). Patients in both groups received IV fluid, human albumin, and thromboprophylaxis. Patients in the study group had significantly fewer days of hospitalization compared with the control group (4.2 ± 1.3 vs 6.7 ± 2.4 days, respectively, $P<.01$). The pregnancy rate increased significantly along with a significant decrease in the abortion rate that was observed after multiple aspirations compared with <3 aspirations. In a cohort study of 18 women with severe OHSS, eight were managed with hospitalization and IV fluid (111). The average length of stay was 11 days. The other 10 women had outpatient ultrasound-guided transabdominal paracentesis. While patients were hydrated intravenously, 1–3 liters of fluid were removed over 2–3 hours. None of these patients required a second procedure, and none were admitted to the hospital. The authors concluded that outpatient ultrasound-guided paracentesis is a safe alternative to hospitalization in patients with severe OHSS.

Summary Statement

- There is fair evidence to recommend paracenteses or culdocenteses for the management of OHSS in an outpatient setting. (Grade B)

Do Volume Expanders Improve Outcome for Women with OHSS?

One small, retrospective cohort study compared the efficacy and safety of 6% HES and human albumin as colloid solutions for treatment of severe OHSS in 16 patients (112). Six patients received HES and 10 patients received human albumin. Patients who received HES had higher urine output, needed fewer abdominal paracenteses and pleural thoracocenteses (33% vs 80%), and had a shorter hospital stay (15.7 ± 5.7 vs 19.0 ± 8.2 days) than those who received human albumin. No difference in adverse effects was reported. These results suggest that 6% HES may be superior to albumin as a colloid solution for the treatment of severe OHSS, but due to the small sample size and cohort design, the results are not definitive. A small, prospective observational trial reported nonsurgical inpatient management of 13 patients with severe OHSS (113). This trial employed a fairly aggressive use of volume expanders (25% albumin 250 mL) with diuretic (furosemide 20 mg or bumetanide 1 mg) and dopamine IV (2–3 μg/kg/min) every 8 hours in oliguric patients. This protocol was reported to have a comparable length of hospital stay compared to prior published studies. These small studies evaluating the use of volume expanders in women already exhibiting symptoms of OHSS were not RCTs. It is not clear whether the patients' course would have resolved in a similar way with

crystalloid alone. The concomitant use of diuretics in some patients in these trials further confuses the therapeutic assessment.

Summary Statement

- There is insufficient evidence to support the use of volume expanders alone for the treatment of OHSS (Grade C). The studies reporting use of volume expanders in OHSS treatment have not been uniform in treatment protocols. Some use diuretics and others include dopamine.

CONCLUSIONS

OHSS is a known complication of controlled ovarian stimulation. Ideally, women at risk for this disorder should be identified prior to stimulation, and stimulation protocols should be selected that minimize the risk of OHSS. The use of GnRH antagonist protocols with a GnRH agonist (with or without low-dose hCG) to trigger final oocyte maturation of oocytes is a particularly effective strategy. Other strategies that show some benefit include the use of cabergoline and cryopreservation of all embryos rather than transfer. If OHSS prevention strategies are not effective and a patient experiences severe OHSS, fluid resuscitation, supportive care, paracentesis, and prophylactic anticoagulation are recommended.

SUMMARY

- There is fair evidence (level II-2) that PCOS, elevated AMH values, peak estradiol levels, multifollicular development, and a high number of oocytes retrieved increase the risk of OHSS. (Grade B)
- While cut points require validation, AMH values >3.4 ng/mL, AFC >24, development of ≥ 25 follicles, estradiol values $>3{,}500$ pg/mL, or ≥ 24 oocytes retrieved are particularly associated with an increased risk of OHSS. (Grade B)
- There is good evidence to support the use of ovarian stimulation protocols using GnRH antagonists in order to reduce the risk of OHSS. (Grade A)
- There is insufficient evidence that clomiphene independently reduces OHSS risk. (Grade C)
- There is fair evidence that aspirin reduces the incidence of OHSS based on a single, randomized trial comparing aspirin alone with no treatment and another study comparing combined acetylsalicylic acid and steroid treatment with no treatment. (Grade B)
- There is good evidence that metformin decreases the risk of OHSS risk in PCOS patients. (Grade A)
- There is insufficient evidence to recommend coasting for the prevention of OHSS. (Grade C)
- There is insufficient evidence to recommend a lower dose of hCG to trigger oocyte maturation for reduction in OHSS risk based on one underpowered randomized trial. (Grade C)
- There is good evidence to recommend the use of a GnRH agonist to trigger oocyte maturation prior to oocyte retrieval in order to reduce the risk of OHSS. (Grade A)
- There is good evidence that live-birth rates are lower in fresh autologous cycles after GnRH trigger, but not donor-recipient cycles. (Grade A)
- There is fair evidence that reproductive outcomes are improved when a low dose of hCG is co-administered at the time of GnRH agonist trigger for luteal support. (Grade B)
- There is good evidence that dopamine agonist administration starting at the time of hCG trigger for several days reduces the incidence of OHSS. (Grade A)
- There is insufficient evidence to conclusively state that albumin lowers OHSS risk. (Grade C)
- There is fair evidence that calcium lowers OHSS risk. (Grade B)
- There is fair evidence that cryopreservation prevents OHSS, based on the results of two small RCTs. (Grade B)
- There is fair evidence to recommend paracentesis or culdocentesis for the management of OHSS in an outpatient setting. (Grade B)
- There is insufficient evidence to support the use of volume expanders alone in treatment of OHSS. (Grade C)

RECOMMENDATIONS

- Women with PCOS, elevated AMH values, and elevated AFC may benefit from ovarian stimulation protocols that reduce the risk of OHSS. (Grade B)
- Ovarian stimulation protocols using GnRH antagonists are preferable in women at high risk of OHSS. (Grade A)
- The use of a GnRH agonist to trigger oocyte maturation prior to oocyte retrieval is recommended to reduce the risk of OHSS if peak estradiol levels are high or multifollicular development occurs during stimulation. (Grade A) Low-dose hCG co-trigger, luteal hormonal support, or cryopreservation of embryos are strategies that may improve pregnancy rates in this setting. (Grade B)
- Dopamine agonist administration starting at the time of hCG trigger for several days also may be used to reduce the incidence of OHSS. (Grade A)
- Additional strategies to prevent OHSS which may be helpful include the use of metformin in PCOS patients (Grade A), aspirin administration (Grade A), and cryopreservation of embryos (Grade B).
- The mainstay of OHSS treatment includes fluid resuscitation and prophylactic anticoagulation. Paracentesis or culdocentesis may be recommended for management of OHSS when a large amount of ascites is present. (Grade B)

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patient, available resources, and institutional or clinical practice limitations. The Practice Committee and the Board of Directors of the American Society for Reproductive Medicine have approved this report.

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