

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

Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

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.)

Earn online CME credit related to this document at [www.asrm.org/elearn](http://www.asrm.org/elearn)

**Discuss:** You can discuss this article with its authors and with other ASRM members at <https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/12461-22981>

## 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-1 $\beta$ , angiotensin II, insulin-like growth factor 1, transforming growth factor  $\beta$ , 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

Received August 25, 2016; accepted August 25, 2016; published online September 24, 2016.

Reprint requests: Practice Committee, American Society for Reproductive Medicine, 1209 Montgomery Hwy, Birmingham, Alabama 35216 (E-mail: [ASRM@asrm.org](mailto:ASRM@asrm.org)).

*Fertility and Sterility*® Vol. 106, No. 7, December 2016 0015-0282/\$36.00

Copyright ©2016 American Society for Reproductive Medicine, Published by Elsevier Inc.

<http://dx.doi.org/10.1016/j.fertnstert.2016.08.048>

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	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	Low blood/central venous pressure Pleural effusion Rapid weight gain (>1 kg in 24 h) Syncope Severe abdominal pain Venous thrombosis 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.

Adapted from Navot D, Bergh PA, Laufer N (Ovarian hyperstimulation syndrome in novel reproductive technologies: prevention and treatment. *Fertil Steril* 1992;58:249-61). Terms of use: Fiedler K, Ezcurra D (Predicting and preventing ovarian hyperstimulation syndrome (OHSS): the need for individualized not standardized treatment. *Reprod Biol Endocrinol* 2012;10:32. © 2012 Fiedler and Ezcurra; licensee BioMed Central Ltd. This work is licensed under a Creative Commons Attribution 2.0 Generic License: <http://creativecommons.org/licenses/by/2.0>. It is attributed to Klaus Fiedler and Diego Ezcurra, and the original version can be found at <http://rbej.biomedcentral.com/articles/10.1186/1477-7827-10-32#CR9>).

Practice Committee of the American Society for Reproductive Medicine. Prevention and treatment of moderate and severe OHSS. *Fertil Steril* 2016.

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-periovarian 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  $\geq 4$  days decreases implantation rates (67).

### Summary Statement

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

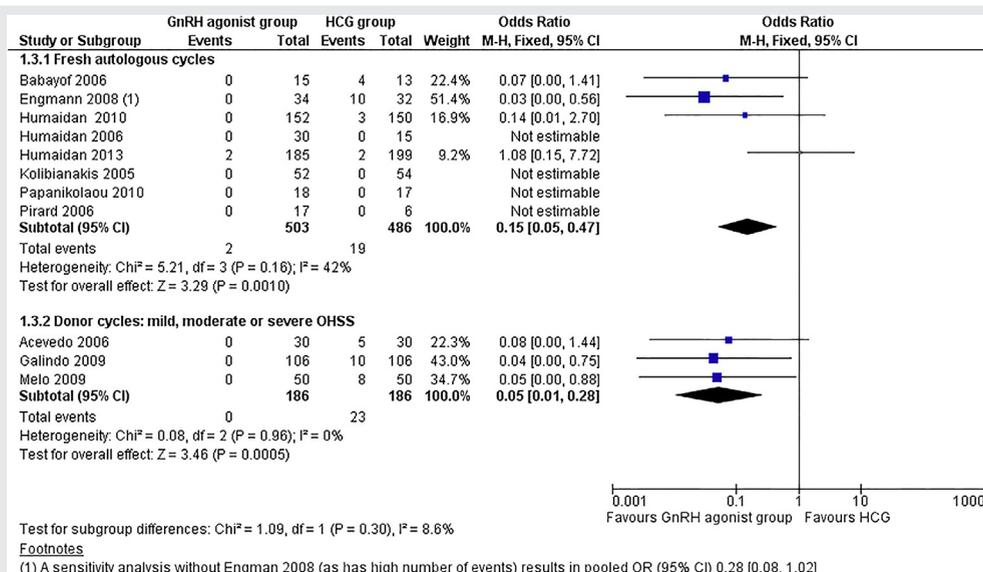
### Choice of Trigger for Final Oocyte Maturation Prior to Retrieval

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).

Practice Committee of the American Society for Reproductive Medicine. Prevention and treatment of moderate and severe OHSS. Fertil Steril 2016.

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  $>9 \text{ cm}^2$  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 coating. 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 coated (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.

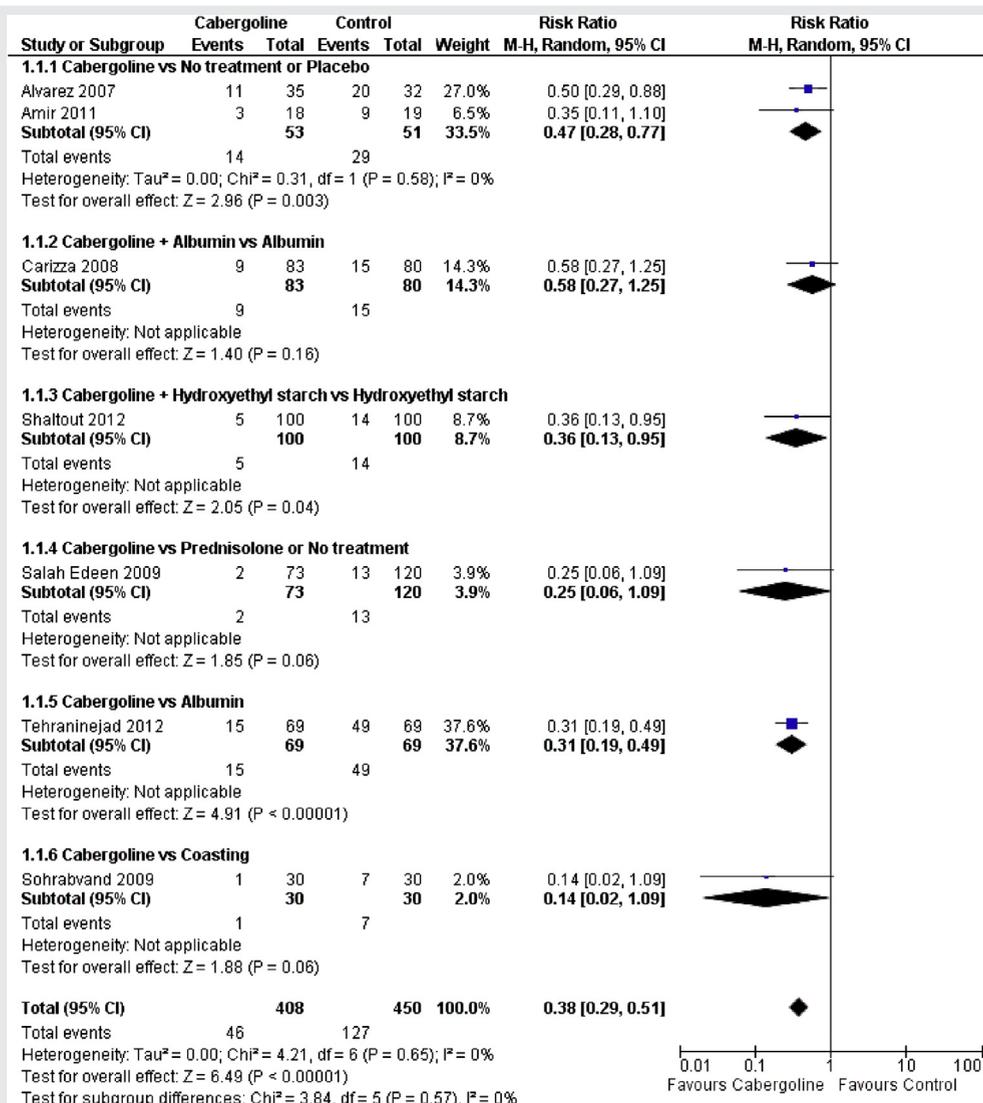
### Summary Statement

- 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).

Practice Committee of the American Society for Reproductive Medicine. Prevention and treatment of moderate and severe OHSS. Fertil Steril 2016.

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 hospital-

ization 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  $\geq 25$  follicles, estradiol values  $>3,500$  pg/mL, or  $\geq 24$  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)

**Acknowledgments:** This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual

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.

This document was reviewed by ASRM members and their input was considered in the preparation of the final document. The Practice Committee acknowledges the special contribution of Rebecca Usadi, M.D., Suleena Kalra, M.D., M.S.C.E., Erica Wang, M.D., and Christina Boots, M.D. in the preparation of this document. The following members of the ASRM Practice Committee participated in the development of this document. All Committee members disclosed commercial and financial relationships with manufacturers or distributors of goods or services used to treat patients. Members of the Committee who were found to have conflicts of interest based on the relationships disclosed did not participate in the discussion or development of this document.

Samantha Pfeifer, M.D.; Samantha Butts, M.D., M.S.C.E.; Daniel Dumesic, M.D.; Gregory Fossum, M.D.; Clarisa Gracia, M.D., M.S.C.E.; Andrew La Barbera, Ph.D.; Jennifer Mersereau, M.D., M.S.C.I.; Randall Odem, M.D.; Richard Paulson, M.D.; Alan Penzias, M.D.; Margareta Pisarska, M.D.; Robert Rebar, M.D.; Richard Reindollar, M.D.; Mitchell Rosen, M.D.; Jay Sandlow, M.D.; Michael Vernon, Ph.D.; Eric Widra, M.D.

## REFERENCES

1. Steward RG, Lan L, Shah AA, Yeh JS, Price TM, Goldfarb JM, et al. Oocyte number as a predictor for ovarian hyperstimulation syndrome and live birth: an analysis of 256,381 in vitro fertilization cycles. *Fertil Steril* 2014;101:967–73. Level II-2.
2. Luke B, Brown MB, Morbeck DE, Hudson SB, Coddington CC 3rd, Stern JE. Factors associated with ovarian hyperstimulation syndrome (OHSS) and its effect on assisted reproductive technology (ART) treatment and outcome. *Fertil Steril* 2010;94:1399–404. Level II-2.
3. Jayaprakasan K, Chan Y, Islam R, Haoula Z, Hopkisson J, Coomarasamy A, et al. Prediction of in vitro fertilization outcome at different antral follicle count thresholds in a prospective cohort of 1,012 women. *Fertil Steril* 2012;98:657–63. Level II-2.
4. Kahnberg A, Enskog A, Brännström M, Lundin K, Bergh C. Prediction of ovarian hyperstimulation syndrome in women undergoing in vitro fertilization. *Acta Obstet Gynecol Scand* 2009;88:1373–81. Level II-2.
5. 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. Level II-2.
6. Goldsman MP, Pedram A, Dominguez CE, Ciuffardi I, Levin E, Asch RH. Increased capillary permeability induced by human follicular fluid: a hypothesis for an ovarian origin of the hyperstimulation syndrome. *Fertil Steril* 1995;63:268–72. Level II-2.
7. Bergh PA, Navot D. Ovarian hyperstimulation syndrome: a review of pathophysiology. *J Assist Reprod Genet* 1992;9:429–38. Level III.
8. Geva E, Jaffe RB. Role of vascular endothelial growth factor in ovarian physiology and pathology. *Fertil Steril* 2000;74:429–38. Level III.
9. Levin ER, Rosen GF, Cassidenti DL, Yee B, Meldrum D, Wisot A, et al. Role of vascular endothelial cell growth factor in ovarian hyperstimulation syndrome. *J Clin Invest* 1998;102:1978–85. Level II-2.
10. Neulen J, Yan Z, Raczek S, Weindel K, Keek C, Weich HA, et al. Human chorionic gonadotropin-dependent expression of vascular endothelial growth factor/vascular permeability factor in human granulosa cells: importance in ovarian hyperstimulation syndrome. *J Clin Endocrinol Metab* 1995;80:1967–71. Level II-3.
11. McClure N, Healy DL, Rogers PA, Sullivan J, Beaton L, Haning RV, et al. Vascular endothelial growth factor as capillary permeability agent in ovarian hyperstimulation syndrome. *Lancet* 1994;344:235–6. Level II-2.
12. Pellicer A, Albert C, Mercader A, Bonilla-Musoles F, Remohi J, Simon C. The pathogenesis of ovarian hyperstimulation syndrome: in vivo studies investigating the role of interleukin-1b, interleukin-6, and vascular endothelial growth factor. *Fertil Steril* 1999;71:482–9. Level II-2.
13. Whelan JG 3rd, Vlahos NF. The ovarian hyperstimulation syndrome. *Fertil Steril* 2000;73:883–96. Level III.
14. Revel A, Barak V, Lavy Y, Anteby E, Abramov Y, Schenker JJ, et al. Characterization of intraperitoneal cytokines and nitrites in women with severe ovarian hyperstimulation syndrome. *Fertil Steril* 1996;66:66–71. Level II-1.
15. Delbaere A, Bergmann PJM, Gervy-Decoster C, Deschodt-Lanckman M, de Maertelaer V, Staroukine M, et al. Increased angiotensin II in ascites during severe ovarian hyperstimulation syndrome: role of early pregnancy and ovarian gonadotropin stimulation. *Fertil Steril* 1997;67:1038–45. Level II-2.
16. Morris RS, Wong IL, Kirkman E, Gentschein E, Paulson RJ. Inhibition of ovarian-derived prorenin to angiotensin cascade in the treatment of ovarian hyperstimulation syndrome. *Hum Reprod* 1995;10:1355–8.
17. Ashrafi M, Bahmanabadi A, Akhond MR, Arabipour A. Predictive factors of early moderate/severe ovarian hyperstimulation syndrome in non-polycystic ovarian syndrome patients: a statistical model. *Arch Gynecol Obstet* 2015;292:1145–52. Level II-2.
18. Johnson MD, Williams SL, Seager CK, Liu JH, Barker NM, Hurd WW. Relationship between human chorionic gonadotropin serum levels and the risk of ovarian hyperstimulation syndrome. *Gynecol Endocrinol* 2014;30:294–7. Level II-2.
19. Sousa M, Cunha M, Teixeira da Silva J, Oliveira C, Silva J, Viana P, et al. Ovarian hyperstimulation syndrome: a clinical report on 4894 consecutive ART treatment cycles. *Reprod Biol Endocrinol* 2015;13:66. Level II-2.
20. Mathur RS, Akande AV, Keay SD, Hunt LP, Jenkins JM. Distinction between early and late ovarian hyperstimulation syndrome. *Fertil Steril* 2000;73:901–7. Level II-2.
21. Aramwit P, Pruksananonda K, Kasettrat N, Jammeechai K. Risk factors for ovarian hyperstimulation syndrome in Thai patients using gonadotropins for in vitro fertilization. *Am J Health Syst Pharm* 2008;65:1148–53. Level II-2.
22. Danninger B, Brunner M, Obruca A, Feichtinger W. Prediction of ovarian hyperstimulation syndrome by ultrasound volumetric assessment [corrected] of baseline ovarian volume prior to stimulation. *Hum Reprod* 1996;11:1597–9. Level II-2.
23. Delvigne A, Demoulin A, Smitz J, Donne J, Koninckx P, Dhont M, et al. The ovarian hyperstimulation syndrome in in-vitro fertilization: a Belgian multicentric study. I. Clinical and biological features. *Hum Reprod* 1993;8:1353–60. Level II-2.
24. 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. Level II-2.
25. Swanton A, Storey L, McVeigh E, Child T. IVF outcome in women with PCOS, PCO and normal ovarian morphology. *Eur J Obstet Gynecol Reprod Biol* 2010;149:68–71. Level II-2.
26. Nakhuda GS, Chu MC, Wang JG, Sauer MV, Lobo RA. Elevated serum mullerian-inhibiting substance may be a marker for ovarian hyperstimulation syndrome in normal women undergoing in vitro fertilization. *Fertil Steril* 2006;85:1541–3. Level II-2.
27. Tal R, Seifer DB, Khanimov M, Malter HE, Grazi RV, Leader B. Characterization of women with elevated antimullerian hormone levels (AMH): correlation of AMH with polycystic ovarian syndrome phenotypes and assisted reproductive technology outcomes. *Am J Obstet Gynecol* 2014;211:59.e1–8. Level II-2.
28. Ocal P, Sahmay S, Cetin M, Irez T, Guralp O, Cepni I. Serum anti-Mullerian hormone and antral follicle count as predictive markers of OHSS in ART cycles. *J Assist Reprod Genet* 2011;28:1197–203. Level II-2.
29. Moos J, Rezbek K, Filova V, Moosova M, Pavelkova J, Peknicova J. Comparison of follicular fluid and serum levels of Inhibin A and Inhibin B with calculated indices used as predictive markers of Ovarian Hyperstimulation Syndrome in IVF patients. *Reprod Biol Endocrinol* 2009;7:86. Level II-2.

30. Jayaprakasan K, Herbert M, Moody E, Stewart JA, Murdoch AP. Estimating the risks of ovarian hyperstimulation syndrome (OHSS): implications for egg donation for research. *Hum Fertil (Camb)* 2007;10:183–7. Level II-2.
31. D'Angelo A, Davies R, Salah E, Nix BA, Amso NN. Value of the serum estradiol level for preventing ovarian hyperstimulation syndrome: a retrospective case control study. *Fertil Steril* 2004;81:332–6. Level II-2.
32. Reljic M, Vlasisavljevic V, Gavric V, Kovacic B. Number of oocytes retrieved and resulting pregnancy. Risk factors for ovarian hyperstimulation syndrome. *J Reprod Med* 1999;44:713–8. Level II-2.
33. Hendriks DJ, Klinkert ER, Bancsi LF, Looman CW, Habbema JD, te Velde ER, et al. Use of stimulated serum estradiol measurements for the prediction of hyperresponse to ovarian stimulation in in vitro fertilization (IVF). *J Assist Reprod Genet* 2004;21:65–72. Level II-2.
34. Toftager M, Bogstad J, Bryndorf T, Løssl K, Roskær J, Holland T, et al. Risk of severe ovarian hyperstimulation syndrome in GnRH antagonist versus GnRH agonist protocol: RCT including 1050 first IVF/ICSI cycles. *Hum Reprod* 2016 [Epub ahead of print]. Level I.
35. Ludwig M, Felberbaum RE, Devroey P, Albano C, Riethmuller-Winzen H, Schuler A, et al. Significant reduction of the incidence of ovarian hyperstimulation syndrome (OHSS) by using the LHRH antagonist Cetrorelix (Cetrotide) in controlled ovarian stimulation for assisted reproduction. *Arch Gynecol Obstet* 2000;264:29–32. Level I.
36. Qiao J, Lu G, Zhang HW, Chen H, Ma C, Olofsson JJ, et al. A randomized controlled trial of the GnRH antagonist ganirelix in Chinese normal responders: high efficacy and pregnancy rates. *Gynecol Endocrinol* 2012;28:800–4. Level I.
37. Borm G, Mannaerts B. 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. The European Orgalutran Study Group. *Hum Reprod* 2000;15:1490–8. Level I.
38. Borges E Jr, Braga DP, Setti AS, Vingris LS, Figueira RC, Iaconelli A Jr. Strategies for the management of OHSS: Results from freezing-all cycles. *JBRA Assist Reprod* 2016;20:8–12. Level II-2.
39. Firouzabadi RD, Ahmadi S, Oskouian H, Davar R. Comparing GnRH agonist long protocol and GnRH antagonist protocol in outcome the first cycle of ART. *Arch Gynecol Obstet* 2010;281:81–5. Level I.
40. Hosseini MA, Aleyasin A, Saeedi H, Mahdavi A. Comparison of gonadotropin-releasing hormone agonists and antagonists in assisted reproduction cycles of polycystic ovarian syndrome patients. *J Obstet Gynaecol Res* 2010;36:605–10. Level I.
41. Lainas TG, Sfontouris IA, Zorzovilis IZ, Petsas GK, Lainas GT, Alexopoulou E, et al. Flexible GnRH antagonist protocol versus GnRH agonist long protocol in patients with polycystic ovary syndrome treated for IVF: a prospective randomised controlled trial (RCT). *Hum Reprod* 2010;25:683–9. Level I.
42. Ludwig M, Katalinic A, Diedrich K. Use of GnRH antagonists in ovarian stimulation for assisted reproductive technologies compared to the long protocol. Meta-analysis. *Arch Gynecol Obstet* 2001;265:175–82. Level III.
43. Mancini F, Tur R, Martinez F, Coroleu B, Rodriguez 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. Level III.
44. Xiao J, Chen S, Zhang C, Chang S. Effectiveness of GnRH antagonist in the treatment of patients with polycystic ovary syndrome undergoing IVF: a systematic review and meta analysis. *Gynecol Endocrinol* 2013;29:187–91. Level III.
45. Xiao JS, Su CM, Zeng XT. Comparisons of GnRH antagonist versus GnRH agonist protocol in supposed normal ovarian responders undergoing IVF: a systematic review and meta-analysis. *PLoS One* 2014;9:e106854. Level III.
46. Al-Inany HG, Youssef MA, Aboulghar M, Broekmans F, Sterrenburg M, Smit J, et al. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. *Cochrane Database Syst Rev* 2011:CD001750. Level III.
47. Weigert M, Krischker U, Pohl M, Poschalko G, Kindermann C, Feichtinger W. Comparison of stimulation with clomiphene citrate in combination with recombinant follicle-stimulating hormone and recombinant luteinizing hormone to stimulation with a gonadotropin-releasing hormone agonist protocol: a prospective, randomized study. *Fertil Steril* 2002;78:34–9. Level I.
48. Karimzadeh MA, Ahmadi S, Oskouian H, Rahmani E. Comparison of mild stimulation and conventional stimulation in ART outcome. *Arch Gynecol Obstet* 2010;281:741–6. Level I.
49. Figueiredo JB, Nastro CO, Vieira AD, Martins WP. Clomiphene combined with gonadotropins and GnRH antagonist versus conventional controlled ovarian hyperstimulation without clomiphene in women undergoing assisted reproductive techniques: systematic review and meta-analysis. *Arch Gynecol Obstet* 2013;287:779–90. Level III.
50. Gibreel A, Maheshwari A, Bhattacharya S. Clomiphene citrate in combination with gonadotropins for controlled ovarian stimulation in women undergoing in vitro fertilization. *Cochrane Database Syst Rev* 2012;11:CD008528. Level III.
51. Varnagy A, Bodis J, Manfai Z, Wilhelm F, Busznyák C, Koppán M. Low-dose aspirin therapy to prevent ovarian hyperstimulation syndrome. *Fertil Steril* 2010;93:2281–4. Level I.
52. Revelli A, Dolfin E, Gennarelli G, Lantieri T, Massobrio M, Holte JG, et al. Low-dose acetylsalicylic acid plus prednisolone as an adjuvant treatment in IVF: a prospective, randomized study. *Fertil Steril* 2008;90:1685–91. Level I.
53. Tang T, Glanville J, Orsi N, Barth JH, Balen AH. The use of metformin for women with PCOS undergoing IVF treatment. *Hum Reprod* 2006;21:1416–25. Level I.
54. Palomba S, Falbo A, Carrillo L, Villani MT, Orio F, Russo T, et al. 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;96:1384–90.e4. Level I.
55. Qublan HS, Al-Khaderei S, Abu-Salem AN, Al-Zpoon A, Al-Khateeb M, Al-Ibrahim N, et al. Metformin in the treatment of clomiphene citrate-resistant women with polycystic ovary syndrome undergoing in vitro fertilisation treatment: a randomised controlled trial. *J Obstet Gynaecol* 2009;29:651–5. Level I.
56. Palomba S, Falbo A, La Sala GB. Effects of metformin in women with polycystic ovary syndrome treated with gonadotrophins for in vitro fertilisation and intracytoplasmic sperm injection cycles: a systematic review and meta-analysis of randomised controlled trials. *BJOG* 2013;120:267–76. Level III.
57. Huang X, Wang P, Tal R, Lv F, Li Y, Zhang X. A systematic review and meta-analysis of metformin among patients with polycystic ovary syndrome undergoing assisted reproductive technology procedures. *Int J Gynaecol Obstet* 2015;131:111–6. Level III.
58. Kumbak B, Kahraman S. Efficacy of metformin supplementation during ovarian stimulation of lean PCOS patients undergoing in vitro fertilization. *Acta Obstet Gynecol Scand* 2009;88:563–8. Level II-2.
59. Swanton A, Lighten A, Granne I, McVeigh E, Lavery S, Trew G, et al. Do women with ovaries of polycystic morphology without any other features of PCOS benefit from short-term metformin co-treatment during IVF? A double-blind, placebo-controlled, randomized trial. *Hum Reprod* 2011;26:2178–84. Level I.
60. Al-Shawaf T, Zosmer A, Hussain S, Tozer A, Panay N, Wilson C, et al. Prevention of severe ovarian hyperstimulation syndrome in IVF with or without ICSI and embryo transfer: a modified 'coasting' strategy based on ultrasound for identification of high-risk patients. *Hum Reprod* 2001;16:24–30. Level II-2.
61. Dhont M, Van der Straeten F, De Sutter P. Prevention of severe ovarian hyperstimulation by coasting. *Fertil Steril* 1998;70:847–50. Level II-2.
62. 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. Level II-2.
63. 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. Level II-2.

64. Egbase PE, Sharhan MA, Grudzinskas JG. Early unilateral follicular aspiration compared with coasting for the prevention of severe ovarian hyperstimulation syndrome: a prospective randomized study. *Hum Reprod* 1999;14:1421–5. Level I.
65. D'Angelo A, Brown J, Amso NN. Coasting (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome. *Cochrane Database Syst Rev* 2001:CD002811. Level III.
66. Lee C, Tummon I, Martin J, Nisker J, Power S, Tekpetey F. Does withholding gonadotrophin administration prevent severe ovarian hyperstimulation syndrome? *Hum Reprod* 1998;13:1157–8. Level II-2.
67. Nardo LG, Cheema P, Gelbaya TA, Horne G, Fitzgerald CT, Pease EH, et al. The optimal length of 'coasting protocol' in women at risk of ovarian hyperstimulation syndrome undergoing in vitro fertilization. *Hum Fertil (Camb)* 2006;9:175–80. Level II-2.
68. 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. Level I.
69. 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. Level I.
70. 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 undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized controlled study. *Fertil Steril* 2008;89:84–91. Level I.
71. Galindo A, Bodri D, Guillen JJ, Colodron M, Vernaev V, Coll O. Triggering with HCG or GnRH agonist in GnRH antagonist treated oocyte donation cycles: a randomised clinical trial. *Gynecol Endocrinol* 2009;25:60–6. Level I.
72. Melo M, Busso CE, Bellver J, Alama P, Garrido N, Meseguer M, et al. GnRH agonist versus recombinant HCG in an oocyte donation programme: a randomized, prospective, controlled, assessor-blind study. *Reprod Biomed Online* 2009;19:486–92. Level I.
73. Sismanoglu A, Tekin HI, Erden HF, Ciray NH, Ulug U, Bahceci M. Ovulation triggering with GnRH agonist vs hCG in the same egg donor population undergoing donor oocyte cycles with GnRH antagonist: a prospective randomized cross-over trial. *J Assist Reprod Genet* 2009;26:251–6. Level I.
74. Bodri D, Guillen JJ, Polo A, Trullenque M, Esteve C, Coll O. Complications related to ovarian stimulation and oocyte retrieval in 4052 oocyte donor cycles. *Reprod Biomed Online* 2008;17:237–43. Level II-2.
75. Imbar T, Kol S, Lossos F, Bdolah Y, Hurwitz A, Haimov-Kochman R. Reproductive outcome of fresh or frozen-thawed embryo transfer is similar in high-risk patients for ovarian hyperstimulation syndrome using GnRH agonist for final oocyte maturation and intensive luteal support. *Hum Reprod* 2012;27:753–9. Level II-2.
76. Oktay K, Turkcuoglu I, Rodriguez-Wallberg KA. GnRH agonist trigger for women with breast cancer undergoing fertility preservation by aromatase inhibitor/FSH stimulation. *Reprod Biomed Online* 2010;20:783–8. Level II-2.
77. Orvieto R, Rabinson J, Meltzer S, Zohav E, Anteby E, Homburg R. Substituting HCG with GnRH agonist to trigger final follicular maturation—a retrospective comparison of three different ovarian stimulation protocols. *Reprod Biomed Online* 2006;13:198–201. Level II-2.
78. Youssef MA, Van der Veen F, Al-Inany HG, Mochtar MH, Griesinger G, Nagi Mohesen M, et al. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology. *Cochrane Database Syst Rev* 2014:CD008046. Level III.
79. Humaidan P, Polyzos NP, Alsbjerg B, Erb K, Mikkelsen AL, Elbaek HO, et al. GnRH trigger and individualized luteal phase hCG support according to ovarian response to stimulation: two prospective randomized controlled multi-centre studies in IVF patients. *Hum Reprod* 2013;28:2511–21. Level I.
80. Castillo JC, Dolz M, Bienvenido E, Abad L, Casan EM, Bonilla-Musoles F. Cycles triggered with GnRH agonist: exploring low-dose HCG for luteal support. *Reprod Biomed Online* 2010;20:175–81. Level II-2.
81. Meyer L, Murphy LA, Gumer A, Reichman DE, Rosenwaks Z, Cholst IN. Risk factors for a suboptimal response to gonadotropin-releasing hormone agonist trigger during in vitro fertilization cycles. *Fertil Steril* 2015;104:637–42. Level II-2.
82. Tehraninejad ES, Hafezi M, Arabipour A, Azimineko E, Chehrizi M, Bahmanabadi A. Comparison of cabergoline and intravenous albumin in the prevention of ovarian hyperstimulation syndrome: a randomized clinical trial. *J Assist Reprod Genet* 2012;29:259–64. Level I.
83. Torabizadeh A, Vahidroodsari F, Ghorbanpour Z. Comparison of albumin and cabergoline in the prevention of ovarian hyperstimulation syndrome: A clinical trial study. *Iran J Reprod Med* 2013;11:837–42. Level I.
84. Alvarez C, Marti-Bonmati L, Novella-Maestre E, Sanz R, Gomez R, Fernandez-Sanchez M, et al. Dopamine agonist cabergoline reduces hemoconcentration and ascites in hyperstimulated women undergoing assisted reproduction. *J Clin Endocrinol Metab* 2007;92:2931–7. Level I.
85. Amir H, Yaniv D, Hasson J, Amit A, Gordon D, Azem F. Cabergoline for reducing ovarian hyperstimulation syndrome in assisted reproductive technology treatment cycles. A prospective randomized controlled trial. *J Reprod Med* 2015;60:48–54. Level I.
86. Carizza C, Abdelmassih V, Abdelmassih S, Ravizzini P, Salgueiro L, Salgueiro PT, et al. Cabergoline reduces the early onset of ovarian hyperstimulation syndrome: a prospective randomized study. *Reprod Biomed Online* 2008;17:751–5. Level I.
87. Matorras R, Andrés M, Mendoza R, Prieto B, Pijoan JJ, Expósito A. Prevention of ovarian hyperstimulation syndrome in GnRH agonist IVF cycles in moderate risk patients: randomized study comparing hydroxyethyl starch versus cabergoline and hydroxyethyl starch. *Eur J Obstet Gynecol Reprod Biol* 2013;170:439–43. Level I.
88. Seow KM, Lin YH, Bai CH, Chen HJ, Hsieh BC, Huang LW, et al. Clinical outcome according to timing of cabergoline initiation for prevention of OHSS: a randomized controlled trial. *Reprod Biomed Online* 2013;26:562–8. Level I.
89. Shaltout A, Shohyab A, Youssef MA. Can dopamine agonist at a low dose reduce ovarian hyperstimulation syndrome in women at risk undergoing ICSI treatment cycles? A randomized controlled study. *Eur J Obstet Gynecol Reprod Biol* 2012;165:254–8. Level I.
90. Leitao VM, Moroni RM, Seko LM, Nastro CO, Martins WP. Cabergoline for the prevention of ovarian hyperstimulation syndrome: systematic review and meta-analysis of randomized controlled trials. *Fertil Steril* 2014;101:664–75. Level III.
91. Isik AZ, Gokmen O, Zeyneloglu HB, Kara S, Keles G, Gulekli B. Intravenous albumin prevents moderate-severe ovarian hyperstimulation in in-vitro fertilization patients: a prospective, randomized and controlled study. *Eur J Obstet Gynecol Reprod Biol* 1996;70:179–83. Level I.
92. Shalev E, Giladi Y, Matilsky M, Ben-Ami M. Decreased incidence of severe ovarian hyperstimulation syndrome in high risk in-vitro fertilization patients receiving intravenous albumin: a prospective study. *Hum Reprod* 1995;10:1373–6. Level I.
93. Shoham Z, Weissman A, Barash A, Borenstein R, Schachter M, Insler V. Intravenous albumin for the prevention of severe ovarian hyperstimulation syndrome in an in vitro fertilization program: a prospective, randomized, placebo-controlled study. *Fertil Steril* 1994;62:137–42. Level I.
94. Bellver J, Munoz EA, Ballesteros A, Soares SR, Bosch E, Simón C, et al. Intravenous albumin does not prevent moderate-severe ovarian hyperstimulation syndrome in high-risk IVF patients: a randomized controlled study. *Hum Reprod* 2003;18:2283–8. Level I.
95. Ben-Chetrit A, Eldar-Geva T, Gal M, Huerta M, Mimon T, Algur N, et al. The questionable use of albumin for the prevention of ovarian hyperstimulation syndrome in an IVF programme: a randomized placebo-controlled trial. *Hum Reprod* 2001;16:1880–4. Level I.
96. Isikoglu M, Berkkanoglu M, Senturk Z, Ozgur K. Human albumin does not prevent ovarian hyperstimulation syndrome in assisted reproductive technology program: a prospective randomized placebo-controlled double blind study. *Fertil Steril* 2007;88:982–5. Level I.
97. Jee BC, Suh CS, Kim YB, Kim SH, Choi YM, Kim JG, et al. Administration of intravenous albumin around the time of oocyte retrieval reduces

- pregnancy rate without preventing ovarian hyperstimulation syndrome: a systematic review and meta-analysis. *Gynecol Obstet Invest* 2010;70:47–54. Level III.
98. 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 meta-analysis. *Fertil Steril* 2011;95:188–96, 196 e1–3. Level III.
  99. 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:CD001302. Level III.
  100. El-Khayat W, Elsadek M. Calcium infusion for the prevention of ovarian hyperstimulation syndrome: a double-blind randomized controlled trial. *Fertil Steril* 2015;103:101–5. Level I.
  101. Gurgan T, Demiroglu A, Guven S, Benkhalifa M, Girgin B, Li TC. Intravenous calcium infusion as a novel preventive therapy of ovarian hyperstimulation syndrome for patients with polycystic ovarian syndrome. *Fertil Steril* 2011;96:53–7. Level II-2.
  102. Naredi N, Karunakaran S. Calcium gluconate infusion is as effective as the vascular endothelial growth factor antagonist cabergoline for the prevention of ovarian hyperstimulation syndrome. *J Hum Reprod Sci* 2013;6:248–52. Level II-1.
  103. Shaker AG, Zosmer A, Dean N, Bekir JS, Jacobs HS, Tan SL. Comparison of intravenous albumin and transfer of fresh embryos with cryopreservation of all embryos for subsequent transfer in prevention of ovarian hyperstimulation syndrome. *Fertil Steril* 1996;65:992–6. Level I.
  104. 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. *Hum Reprod* 1999;14:1457–60. Level I.
  105. D'Angelo A, Amso N. Embryo freezing for preventing ovarian hyperstimulation syndrome. *Cochrane Database Syst Rev* 2007:CD002806. Level III.
  106. Rova K, Passmark H, Lindqvist PG. Venous thromboembolism in relation to in vitro fertilization: an approach to determining the incidence and increase in risk in successful cycles. *Fertil Steril* 2012;97:95–100. Level II-2.
  107. Borenstein R, Elhalah U, Lunenfeld B, Schwartz ZS. Severe ovarian hyperstimulation syndrome: a reevaluated therapeutic approach. *Fertil Steril* 1989;51:791–5. Level II-2.
  108. Casals G, Fabregues F, Pavesi M, Arroyo V, Balasch J. Conservative medical treatment of ovarian hyperstimulation syndrome: a single center series and cost analysis study. *Acta Obstet Gynecol Scand* 2013;92:686–91. Level II-3.
  109. Lincoln SR, Opsahl MS, Blauer KL, Black SH, Schulman JD. Aggressive outpatient treatment of ovarian hyperstimulation syndrome with ascites using transvaginal culdocentesis and intravenous albumin minimizes hospitalization. *J Assist Reprod Genet* 2002;19:159–63. Level II-2.
  110. Qublan HS, Al-Taani MI, Megdadi MF, Metri RM, Al-Ahmad N. Multiple transvaginal ascitic fluid aspirations improves the clinical and reproductive outcome in patients undergoing in vitro fertilisation treatment complicated by severe early ovarian hyperstimulation syndrome. *J Obstet Gynaecol* 2012;32:379–82. Level II-2.
  111. Shrivastav P, Nadkarni P, Craft I. Day care management of severe ovarian hyperstimulation syndrome avoids hospitalization and morbidity. *Hum Reprod* 1994;9:812–4. Level II-2.
  112. Abramov Y, Fatum M, Abrahamov D, Schenker JG. Hydroxyethylstarch versus human albumin for the treatment of severe ovarian hyperstimulation syndrome: a preliminary report. *Fertil Steril* 2001;75:1228–30. Level II-2.
  113. Morris RS, Miller C, Jacobs L, Miller K. Conservative management of ovarian hyperstimulation syndrome. *J Reprod Med* 1995;40:711–4. Level II-3.