Prevention of moderate and severe ovarian hyperstimulation syndrome: a guideline

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Ovarian hyperstimulation syndrome is a serious complication associated with assisted reproductive technology. This systematic review aims to identify who is at high risk for developing ovarian hyperstimulation syndrome, along with evidence-based strategies to prevent it and replaces the document of the same name last published in 2016. (Fertil Steril® 2024;121:230-45. ©2023 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Key Words: Controlled ovarian stimulation, assisted reproductive technology, gonadotropins, risk, clomiphene citrate

RECOMMENDATIONS

- It is recommended to counsel patients with elevated antimüllerian hormone levels, polycystic ovary syndrome (PCOS), and anticipated high oocyte yields that they are at increased risk for ovarian hyperstimulation syndrome (OHSS). Interventions to reduce OHSS risk should be focused on this patient population. (Strength of evidence: A; strength of recommendation: strong)
- It is recommended to employ ovarian stimulation protocols using gonadotropin-releasing hormone (GnRH) antagonists over protocols using GnRH agonists when there is concern for OHSS. (Strength of evidence: A; strength of recommendation: strong)
- It is recommended to dose gonadotropins based on individualized ovarian reserve testing to decrease the risk of OHSS. (Strength of evidence: B; strength of recommendation: moderate)
- It is recommended to consider lowering the starting dose of gonadotropins and/or supplementing with oral ovulation-inducing medications (clomiphene citrate and/or letrozole) to decrease the risk of OHSS. (Strength of evidence: B; strength of recommendation: moderate)
- Coasting is generally not recommended as a primary strategy to reduce the risk of moderate-to-severe OHSS. However, when other more effective strategies are not available to reduce the risk of OHSS, coasting in combination with cabergoline and a freeze-only strategy may mitigate the risk. (Strength of evidence: C; strength of recommendation: weak)
- It is recommended to use a GnRH agonist to trigger oocyte maturation as a first-line strategy to reduce the risk of moderate-to-severe OHSS. (Strength of evidence: A; strength of recommendation: strong)
- It is recommended to add adequate luteal support when using a GnRH agonist as a trigger and planning a fresh embryo transfer. (Strength of evidence: A; strength of recommendation: strong)
- It is not recommended to use a lower dose for the human chorionic gonadotropin (hCG)-only trigger as a strategy to reduce the risk of moderate-to-severe OHSS. (Strength of evidence: C; strength of recommendation: weak).
- In patients at risk for moderate-to-severe OHSS, it is recommended to start a dopamine agonist such as cabergoline on the day of the hCG trigger or soon thereafter and continue for several days. (Strength of evidence: A; strength of recommendation: strong)
- It is not recommended to administer letrozole as an intervention to reduce rates of moderate-to-severe OHSS. (Strength of evidence: B; strength of recommendation: moderate)
- It is not recommended to administer a luteal GnRH antagonist alone to reduce rates of moderate-to-severe OHSS. Most studies report no reduction in rates of moderate-to-severe OHSS or signs or symptoms associated with OHSS. Some low-quality evidence suggests modest symptomatic improvement in women with OHSS who received

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a GnRH antagonist after the hCG trigger. (Strength of evidence: C; strength of recommendation: weak)

- It is not recommended to use aspirin as a primary strategy to reduce the incidence of OHSS. (Strength of evidence: C; strength of recommendation: weak)
- It is not recommended to administer metformin for the sole purpose of reducing the incidence of OHSS in GnRH antagonist cycles because most studies do not report a significant reduction in rates of OHSS in women with PCOS who were given metformin. Metformin may, however, be considered for OHSS risk reduction among women with PCOS using a GnRH-agonist protocol. (Strength of evidence: B; strength of recommendation: moderate)
- It is not recommended to administer medications such as mifepristone, myoinositol, D-chiro-inositol, or glucocorticoids to reduce rates of OHSS because studies have shown these interventions to be ineffective. (Strength of evidence: C; strength of recommendation: weak)
- It is recommended to consider a freeze-only cycle and subsequent frozen embryo transfer in patients at risk for OHSS on the basis of a high ovarian response or elevated serum estradiol levels. Multiple high-quality studies have reported a significant reduction in rates of moderate or severe OHSS when this strategy is employed. (Strength of evidence: A; strength of recommendation: strong)
- It is not recommended to use volume expanders such as albumin, hydroxyethyl starch, or mannitol in patients who are at high risk of developing moderate or severe OHSS. (Strength of evidence: C; strength of recommendation: weak)

Ovarian hyperstimulation syndrome (OHSS) is an uncommon but serious complication associated with controlled ovarian stimulation during assisted reproductive technology (ART). Historically, moderate-to-severe OHSS has been reported to occur in approximately 1%–5% of in vitro fertilization (IVF) 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 symptoms, including abdominal distention and discomfort, dyspnea, and findings such as ovarian enlargement, ascites, hemoconcentration, hypercoagulability, and electrolyte imbalances.

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 intravascular volume depletion and hyponatremia. Vascular

TABLE 1

Classification of ovarian hyperstimulation syndrome (OHSS) symptoms.

OHSS stage	Clinical features	Laboratory features
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 >45%) 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

Cr = creatinine; CrCL= creatinine clearance; Hct = hematocrit; K+ = potassium; Na+ = sodium; WBC = white blood cell.
Adapted from: Navot D, Bergh PA, Laufer N. Ovarian hyperstimulation syndrome in novel reproductive technologies: prevention and treatment. Fertil Steril 1992;58:249–61.

Hayes. OHSS. Fertil Steril 2024.

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 the severity of the disease (10–12).

Ovarian hyperstimulation syndrome is staged (mild, moderate, severe, or critical) by the severity of symptoms and laboratory findings. Ovarian hyperstimulation syndrome is further classified by the timing of onset (early or late) (Table 1). Early-onset OHSS occurs after controlled ovarian hyperstimulation and an ovulatory dose of hCG. Symptoms begin in the 4–7 days after the hCG trigger and usually resolve with menses. Late-onset OHSS typically begins at least 9 days after the hCG trigger in response to the rising hCG of pregnancy, is more severe, and significantly lengthens the course of OHSS. Severe OHSS can lead to life-threatening complications, including pleural effusion, acute renal insufficiency, and venous thromboembolism.

A systematic search of the literature was performed to answer 3 questions about OHSS: who is at high risk, how can it be prevented, and what is the treatment for it? 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 followed a methodological protocol established by the American Society for Reproductive Medicine (ASRM) staff and executive leadership, the ASRM Practice Committee, and an independent consulting epidemiologist. The ASRM Practice Committee identified the necessity to update the previously published guidelines on the prevention of moderate and severe OHSS and empaneled a task force of experts to engage in its development (2016). Members of the task force applied the Population, Interventions, Comparisons, and Outcomes framework to formulate focused questions related to clinical practice and evidence-based treatments for OHSS, as well as inclusion and exclusion criteria.

This clinical practice guideline was on the basis of a systematic review of the literature performed in the electronic database MEDLINE through PubMed, with a filter for human subjects and English research, on June 12, 2020. This electronic search and examination of reference lists from primary and review articles yielded 427 studies, of which 74 were included. A recent search was conducted on September 22, 2023, adding 53 results to be examined; none 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*. Per inclusion and exclusion criteria that the task force agreed on (Table 2), studies included for assessment were randomized controlled trials (RCTs), systematic reviews or meta-analyses of RCTs, systematic reviews or meta-analyses of a combination of RCTs, controlled trials without randomization, and cohort studies; controlled trials without randomization; cohort studies; and case-control studies. Descriptive studies, case series, case reports, letters, nonsystematic reviews, opinions on the basis of clinical experience, and reports of expert committees were excluded from this guideline. Titles and abstracts of potentially relevant articles were screened and reviewed initially according to preliminary inclusion and exclusion criteria determined by members of the task force. All members of the task force reviewed the articles of all citations that potentially matched the predefined selection criteria. Final inclusion or exclusion decisions were made on examination of the articles in full. Disagreements about inclusion were discussed and resolved by consensus or arbitration after consultation with an independent reviewer and epidemiologist. This electronic search and examination of reference lists from primary and review articles yielded 427 studies, of which 74 were included.

Quality of evidence

A methodological specialist extracted data from the included studies into an evidence table for outcomes identified by the task force. Nonconflicted members of the task force critically assessed the strengths and limitations of available evidence to rate the quality of each study and assign a quality grade on the basis of the rating scale depicted in Table 3, which was recorded in the evidence table (Supplemental Table 1, available online).

The task force chair reviewed grades of quality assigned by members of the task force and provided oversight throughout the entire development process. When no grade was assigned, the task force chair determined a grade of quality on the basis of a study's strengths and limitations. The study design was evaluated, and the quality of the methodology was assessed on the basis of components, including blinding, allocation concealment, appropriate control groups, intention-to-treat analysis, generalizability, and risk of bias.

The task force summarized data from the evidence table in narrative form to include the characteristics, quality, benefit, and conclusions of studies relevant to answering each treatment related to the question. The expert task force

TABLE 2

Summary of inclusion and exclusion criteria.

Include:	Exclude:
➢ Human studies	➢ Series, case reports, reviews, opinions, and off-topic
➢ English	➢ Animal studies
➢ Studies with a comparison group	➢ Non-English
➢ IVF studies	➢ Studies without a comparison group
➢ ≥10 OHSS events (observational); any OHSS events (RCTs)	➢ non-IVF studies; IUI studies; IVM studies
➢ Studies that address clinical risk factors	➢ <10 OHSS events (observational)
➢ Moderate-to-severe OHSS	

IUI = intrauterine insemination; IVF = in vitro fertilization; IVM = in vitro maturation; OHSS = Ovarian hyperstimulation syndrome; RCTs = randomized controlled trials.

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TABLE 3

Rating for quality of evidence.

Quality of Evidence	Definition
High quality	✓ The target population clearly identified ✓ Sufficient sample size for the study design ✓ Clear description of study design ✓ Appropriate control(s) ✓ Generalizable results ✓ Definitive conclusions ✓ Minimal risk of bias ✓ Limitations do not invalidate conclusions ✓ Evidence primarily on the basis of well-designed systematic reviews or meta-analyses of RCTs
Intermediate quality	✓ Target population ✓ Sufficient sample size for the study design but could benefit from larger studies ✓ Control group identified ✓ Reasonably consistent results whose limitations do not invalidate ✓ Fairly definitive conclusions ✓ Low risk of bias ✓ Evidence primarily on the basis of small RCTs; systematic reviews or meta-analyses of a combination of RCTs, controlled trials without randomization, and cohort studies; controlled trials without randomization; and/or well-designed observational studies
Low quality	✓ Insufficient sample size for the study design ✓ Discrepancies among reported data ✓ Errors in study design or analysis ✓ Missing significant information ✓ Unclear or inconsistent results ✓ High risk of bias because of multiple flaws so that conclusions cannot be drawn ✓ High uncertainty about the validity of conclusions

RCTs = randomized controlled trials.

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convened via e-mail to review the literature and summarize findings. The chair of the task force presented these summaries of evidence and draft conclusions to the ASRM Practice Committee for deliberation of the strength of the evidence and the strength of the recommendations and approval of summary statements and recommendations. The quality of the evidence-informed the strength of the guideline's evidence (Table 4). The strengths of recommendations in this guideline were on the basis of both the quality and strength (confidence and certainty) of evidence, risks, and benefits, as well as the expert judgment of the Practice Committee and task force. Patient perspective and feedback were elicited during the review and before publication of the guidelines.

WHO IS AT HIGH RISK FOR MODERATE AND SEVERE OHSS?

Ovarian hyperstimulation syndrome 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. Suggested thresholds to identify risk factors for OHSS on the basis of conservative estimates from the literature are presented in Table 5. It is important to identify individuals at increased risk for OHSS to facilitate the implementation of strategies to mitigate or eliminate its incidence. Furthermore, through early identification, patients can be targeted for appropriate counseling in advance regarding risk.

Demographics, baseline characteristics

Baseline patient characteristics are helpful when assessing risk for OHSS and may allow for early counseling and risk mitigation before treatment. A Society for Assisted Reproductive Technology database study of >210,000 IVF cycles investigated risk factors for OHSS. This analysis revealed that younger age, Black race, and infertility because of disorders of ovulation, tubal factor, or unexplained infertility were associated with increased risk for OHSS (2). Compared with white women, the risk of developing OHSS was increased for Black women (any OHSS, 1.88; severe OHSS, 2.93) and decreased for Hispanic women (any OHSS, 0.79) (2). Although younger age has been associated with an increased risk of OHSS (13–20), among individuals hospitalized with severe OHSS, age >40 years has been associated with an increased risk for life-threatening complications (21).

Ovulation disorders, including polycystic ovary syndrome (PCOS), have been consistently associated with a higher incidence of OHSS (2, 3, 15, 16, 22, 23). Among women with PCOS, those with metabolic syndrome appear to be at lower OHSS risk than those without (24). Data are mixed regarding body mass index (BMI), with some studies revealing an inverse association between BMI and OHSS risk (17, 25, 26), whereas others have failed to demonstrate a relationship (13, 15, 22, 27, 19). Finally, genetic predictors of OHSS risk have been explored recently with the follicle-stimulating hormone (FSH) receptor N680S variant associated with increased odds of developing OHSS (odds ratio [OR] 1.7, 95% confidence interval [CI] 1.025–2.839) in a small case-control study (28). Additionally, a case series of 4 individuals with OHSS who underwent whole exome sequencing reported a novel association between variants in the *FLT4* gene (which encodes a tyrosine kinase receptor for VEGF) and OHSS (29).

Markers of ovarian reserve

Although demographics may provide preliminary data for risk stratification, markers of ovarian reserve have consistently proven to be better predictors of OHSS risk (30). Before treatment antimüllerian hormone (AMH) levels and antral follicle count (AFC) have been studied as markers of response to ovarian stimulation, with various thresholds suggesting an elevated risk for OHSS.

An elevated AMH level has consistently predicted risk for OHSS (27, 30–33). In one study, AMH levels in women who developed OHSS were sixfold higher than in age- and weight-matched controls (31). Another study demonstrated that an AMH level of >10 ng/mL was associated with a >three-fold risk for OHSS compared with women whose AMH levels were elevated to a lesser extent at >5 ng/mL (32). In a separate investigation, a receiver operating characteristic

curve analysis revealed an AMH level cutoff of 6.95 ng/mL predicted OHSS with 75% sensitivity and 84% specificity (30). Finally, in a prospective study of women undergoing stimulation for IVF, an AMH level cutoff of 3.36 ng/mL predicted OHSS better than age and BMI, with a sensitivity of 90.5% and a specificity of 81.3% (27). As evidenced by the findings from these studies, thresholds for AMH levels are difficult to determine and should be interpreted with caution given the evolution and variety of clinical assays.

Antral follicle count is closely related to AMH levels as a marker of ovarian reserve and has been demonstrated to have a similar relationship with OHSS risk (3, 13, 34). In a prospective cohort of 1,012 women undergoing their first IVF cycle, an AFC >24 was associated with an 8.6% risk of OHSS compared with 2.2% in women with an AFC <24 (3).

Stimulation-related factors

Although before treatment identification of individuals at increased risk for OHSS is most desirable, stimulation-related factors may reveal those at risk of impending OHSS. A greater number of mature range follicles at the ovulatory trigger, elevated peak estradiol, or a heightened number of oocytes retrieved have all been demonstrated to increase the risk for OHSS. Multiple studies have supported a positive correlation between the number of oocytes retrieved and the development of OHSS (1, 13–17, 22, 26). Recent studies have demonstrated a greater risk for OHSS when at least 15–18 oocytes were retrieved (35–37). Additionally, an ART registry study demonstrated an increased risk of OHSS without an improvement in live birth rates per cycle when >15 oocytes were retrieved (of note, cumulative live birth rates were not calculated) (1).

As a corollary to the number of oocytes retrieved, an increased total number of large follicles has been consistently predictive of OHSS risk (5, 18, 26, 38–40). Total follicle number >17 was an independent risk factor for OHSS in a multivariate model conducted in a retrospective case-control study with a sensitivity of 85% and a specificity of 77% (18). The total number of follicles of ≥19 measuring ≥11 mm was associated with heightened risk for moderate-to-severe OHSS (39), although a cutoff of 15 or greater follicles ≥10 mm was associated with OHSS risk in another retrospective cohort (40). Yet another study focused on the proportion of dominant follicles in patients with PCOS and found an increased risk for OHSS when this variable increased (41).

In a similar fashion, a higher serum estradiol concentration at the time of the ovulatory trigger has been associated with OHSS risk (22, 27, 42, 43). In a case-control study evaluating risk factors for OHSS after IVF, higher serum estradiol was associated with an IRR of 1.43 (1.31–1.57) for OHSS (19). Elevated estradiol is variably defined across studies but generally ranges from 3,500–5,000 pg/mL.

TABLE 4

Rating for strength of evidence.

Strength of evidence	Definition
Grade A	High confidence in the evidence. A larger or further study was very unlikely to change the reported effect. Most evidence is supported by well-constructed RCTs or extremely strong and consistent observational studies with generalizable results, sufficient sample sizes for the study design, adequate controls, definitive conclusions, and minimal risk of bias.
Grade B	Moderate confidence in evidence. Larger or further studies are not likely to change the reported effect but may more precisely identify the magnitude of the effect. Most evidence comprised of RCTs with potential weaknesses, including small sample size or generalizability or moderately strong and consistent observational studies with reasonably consistent results, sufficient sample sizes for the study designs, identified appropriate controls, fairly definitive conclusions, and low risk of bias.
Grade C	Low confidence in the evidence. Evidence lacking to support on the basis of the reported effect. Evidence comprised of observational studies with significant methodological flaws and/or inconsistent findings on the basis of poor evidence, inconsistent results, insufficient sample size for study design, conclusions that cannot be drawn, and/or high risk of bias.

RCTs = randomized controlled trial.

Hayes. OHSS. Fertil Steril 2024.

Summary statements.

- There is strong evidence that factors associated with a robust response to ovarian stimulation predispose to OHSS. This includes baseline characteristics such as younger age and the diagnosis of PCOS, in addition to elevated ovarian reserve markers, including AFC (>24) and AMH levels (>3.4 ng/mL). (Grade A)
- There is strong evidence associating OHSS with stimulation-related factors such as a heightened number of mature range follicles at the trigger (>17–19), elevated estradiol at the trigger (>3,500–5,000 pg/mL), and an increased number of oocytes retrieved (>15–18). (Grade A)
- There is insufficient evidence that a genetic predisposition may play a role in the propensity for OHSS. (Grade C)

Recommendation.

- It is recommended to counsel patients with elevated AMH levels, PCOS, and anticipated high oocyte yields that they are at increased risk for OHSS. Strategies to reduce OHSS risk should be implemented in this patient population (Strength of evidence: A; strength of recommendation: strong)

PREVENTION OF OHSS

Does the type of stimulation protocol influence the risk of OHSS?

Gonadotropin-releasing hormone (GnRH) agonist vs. GnRH antagonist protocols. There are multiple studies demonstrating that stimulation protocols using GnRH

antagonists for ovulation suppression reduce the incidence of OHSS compared with protocols that use a GnRH agonist, independent of trigger type. A large RCT enrolling 1,050 women for their first IVF cycle to either the GnRH antagonist vs. GnRH agonist protocol demonstrated a significant reduction in severe (5.1% vs. 8.9%, $P=.02$) and moderate OHSS (10.2% vs. 15.6%, $P=.01$) with the use of the GnRH antagonist protocol with no significant differences in live birth rates (22.8% vs. 23.8%, respectively, $P=.7$) (44). The trigger used for oocyte maturation was hCG in all but 3 of the antagonist protocol cases. The largest Cochrane systemic review and meta-analysis, including 73 RCTs with 12,212 participants, demonstrated a statistically significant reduction in the incidence of any grade of OHSS (OR 0.61, 95% CI 0.51–0.72) with the use of GnRH antagonists vs. GnRH agonists with no significant differences in live birth and miscarriage rates (45). An RCT of 194 patients evaluating early-onset moderate and severe OHSS comparing GnRH antagonists administered twice in the day before hCG trigger vs. once in the day before hCG trigger revealed a significant reduction in early-onset moderate and severe OHSS in the arm administered GnRH antagonists twice in the day before retrieval (0 vs. 12.37%, $P<.001$) with no difference in pregnancy rates (46).

Individualized gonadotropin dosing on the basis of ovarian reserve testing vs. Fixed Gonadotropin dosing. A randomized, controlled, assessor-blind, international, multicenter trial over 37 sites in 11 countries compared fixed, individualized dosing with follitropin delta with standard dosing using follitropin alpha (47, 48). Patients in the follitropin delta arm were dosed in a fixed dose (up to 12 μg per day) on the basis of their serum AMH levels and BMI, whereas women in the follitropin alpha arm were administered 150 units for the first 5 days and then adjusted by 75 units daily on and after day 6 on the basis of ovarian response. The individualized, fixed-dose follitropin delta arm demonstrated a 50% lower incidence of moderate and severe OHSS vs. the conventional follitropin alpha arm (OR 0.50, 95% CI 0.26–0.97, $P=.036$), with no significant difference in live birth rates. The proportion of patients experiencing moderate and severe OHSS and/or preventive interventions over 3 cycles was 5.0% in the individualized follitropin delta arm vs. 8.2% in the conventional follitropin alpha arm (OR of 0.59, 95% CI 0.38–0.92, $P=.018$). It is not entirely clear whether differences in the incidence of OHSS were related to individualization, a fixed dose, or inheriting differences in follitropin delta and alpha. In another multicentered RCT of women with regular menstrual cycles, no PCOS, and an AFC >15, the participants were randomized to a fixed low FSH dose of 100 IU per day or a standard FSH dose of 150 IU per day (49). In both groups, dose adjustment was allowed in subsequent cycles (a maximum of 25 IU in the reduced group and 50 IU in the standard group). The occurrence of any grade of OHSS was lower after a lower FSH dose (5.2% vs. 11.8%, risk ratio [RR] 0.44, {95% CI 0.28–0.71}, $P=.001$), but the occurrence of severe OHSS did not differ (1.3% vs. 1.1%, RR 1.25, [95% CI, 0.38–4.07], $P=.728$). Furthermore, there was no significant difference in the cumulative live birth rates between the low dose (66.3%) and standard dose (69.5%) groups (RR 0.95, 95% CI 0.85–1.07). A recent systematic review evaluating 20 RCTs comparing individualized gonadotropin dosing on the basis of ovarian reserve testing (ORT) vs. uniform gonadotropin dosing found that lower gonadotropin dosing on the basis of ORT decreased the incidence of moderate or severe OHSS (OR 0.58, CI 0.34–1.0) (50) with no significant differences in live birth rates. Significant heterogeneity in ORT algorithms and study design limits its applicability.

TABLE 5

Risk factors for ovarian hyperstimulation syndrome (OHSS).

Risk factors at baseline	Risk factors during ovarian stimulation
PCOS	>17 follicles over 10 mm at the trigger
Previous OHSS	Elevated estradiol at trigger (>3,500 pg/mL)
AFC >24	>15 oocytes retrieved
AMH level >3.4 ng/mL	

AFC = antral follicle count; AMH = antimüllerian hormone; PCOS = polycystic ovary syndrome.

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Lowering the dose of gonadotropins and/or supplementing with oral ovulation-inducing agents. A retrospective cohort study comparing 2 GnRH antagonist protocol ovarian stimulation groups in which one received a fixed dose of 225 IU of FSH daily until trigger, whereas the other received FSH 225 IU from stimulation days 1–3, followed by 150 IU from days 4–6, followed by 75 IU from days 7–8, alongside 200 IU of low-dose hCG, which was continued until trigger revealed lower rates of OHSS in the group in which the FSH dose was reduced. (1.3% vs. 6.7%, $P=.025$) (51). Of note, live birth rates were not reported. A Cochrane meta-analysis, including 5 studies comparing oral ovulation-inducing medications including letrozole and/or clomiphene citrate with or without gonadotropins compared with gonadotropins alone, revealed a significant decrease in the incidence of OHSS with oral ovulation-inducing medications (OR 0.21, 95% CI 0.11–0.41), without a significant difference in live birth rates (52). The limitation of this meta-analysis was that 4 of the 5 studies included compared oral ovulation stimulation agents alongside gonadotropins in GnRH antagonist cycles, whereas the gonadotropin-only cycles were in GnRH agonist cycles. Additionally, the studies included differing doses of gonadotropins between the oral ovulation stimulation groups compared with the gonadotropin-only groups.

Summary statements.

- There is strong evidence to support the use of GnRH antagonist cycles over GnRH agonist cycles in controlled ovarian stimulation protocols to decrease the risk of OHSS. (Grade A)
- There is moderate evidence to support individualized gonadotropin dosing on the basis of ORT compared with standardized dosing to decrease the risk of OHSS. (Grade B)
- There is moderate evidence that lowering the starting dose of gonadotropins and/or supplementing with oral

ovulation-inducing medications (clomiphene citrate and/or letrozole) may decrease the risk of OHSS. (Grade B)

Recommendations.

- It is recommended to employ ovarian stimulation protocols using GnRH antagonists over protocols using GnRH agonists when there is concern for OHSS. (Strength of evidence: A; strength of recommendation: strong).
- It is recommended to dose gonadotropins on the basis of individualized ORT to decrease the risk of OHSS. (Strength of evidence: B; strength of recommendation: moderate).
- It is recommended to consider lowering the starting dose of gonadotropins and/or supplementing with oral ovulation-inducing medications (clomiphene citrate and/or letrozole) to decrease the risk of OHSS. (Strength of evidence: B; strength of recommendation: moderate)

CAN COASTING REDUCE THE RISK OF OHSS?

"Coasting" is used when there is a high risk of OHSS on the basis of estrogen levels and the number of follicles. Coasting involves withholding gonadotropins until estradiol levels and follicle sizes are appropriate for the trigger for the final maturation of oocytes.

The optimal length of coasting has not been determined, with limited cohort studies suggesting that coasting ≥ 4 days decreases implantation rates (53). One RCT of 300 women compared coasting up to 3 days vs. cabergoline 0.25 mg for 8 days posttrigger vs. a combination of coasting 1 day plus cabergoline 0.25 mg for 8 days and found a statistically significant reduction in the incidence of early moderate-to-severe OHSS with the combination approach (54).

Early cohort studies on coasting found a reduction in OHSS without compromising the pregnancy rate (55, 56). Other cohort studies showed that coasting had comparable reductions in OHSS to cryopreservation (57), albumin (58), or, in one RCT, early unilateral follicular aspiration (59). A recent systematic review of 8 RCTs concluded that coasting reduced rates of moderate or severe OHSS more than no coasting on the basis of only 2 RCTs (OR 0.11, 95% CI 0.05–0.24) (60). The quality of the evidence was low, and there were too few data points to determine whether there was a difference between the groups in rates of live births. There was also no high-quality evidence to suggest that coasting was more beneficial than other interventions.

Summary statement

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

Recommendation

- Coasting is generally not recommended as a primary strategy to reduce the risk of moderate-to-severe OHSS. However, when other more effective strategies are not available to reduce the risk of OHSS, coasting in combination with cabergoline and a freeze-only strategy may mitigate risk. (Strength of evidence: C; strength of recommendation: weak)

CHOICE OF TRIGGER FOR FINAL OOCYTE MATURATION BEFORE RETRIEVAL

The "trigger" is the activation of the luteinizing hormone (LH) receptor over a 24- to 36-hour window, mimicking the LH surge, to induce final oocyte maturation before egg retrieval. A single hCG injection adequately activates the LH receptor. Human chorionic gonadotropin administration was the standard of care for decades until the use of GnRH agonists to induce an endogenous LH surge was introduced. Human chorionic gonadotropin has a longer half-life than LH, leading to sustained stimulation of the LH receptor even after postretrieval. Reduction in dosages of hCG and administration of GnRH agonists alone or in combination with hCG have been widely investigated as methods to reduce OHSS.

The dose reduction of the hCG-only trigger down to 4,000 IU compared with 6,000 IU or 10,000 IU has been examined in RCTs without finding consistent or statistically significant differences in the rate of OHSS (61, 62). A retrospective review of 10,427 cycles at one academic practice >7 years where they applied a sliding scale for hCG dosage on the basis of peak estradiol level (10,000 IU down to 3,300 IU) found no difference in fertilization, clinical pregnancy, or live birth rates across all hCG doses (63). Notably, of all the moderate-severe OHSS cases over the 7 years, 14% were in the 10,000 IU group, 36% in the 5,000 IU, 29% in the 4,000 IU, and 21% in the 3,300 IU hCG group. Another retrospective study in patients at high risk of OHSS (peak estradiol >5,000 pg/mL) compared an hCG dose of 1,500 IU together with FSH 450 IU for trigger to hCG 3,300 IU alone and found a trend toward lower OHSS incidence, whereas maintaining similar oocyte maturation, fertilization, and blastocyst formation rates. However, the cohort receiving the hCG 1,500 IU and FSH 450 IU was underpowered with only 39 participants (25).

There are many studies that assess the development of OHSS in women who receive the GnRH agonist trigger compared with the hCG trigger for final oocyte maturation. This includes several RCTs providing strong evidence that the use of a GnRH agonist trigger results in a significant reduction in the development of OHSS. Most of these studies were conducted on 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 (64). Subsequently, 3 separate RCTs were performed in an oocyte donor population at high risk for OHSS and found that the GnRH agonist trigger eliminated the development of OHSS in these women (0 risk of OHSS with GnRH agonist vs. 7%–16% with hCG trigger) (65–67). One of the largest studies assessed a cohort of oocyte donors over 4,052 stimulation cycles in which hCG or GnRH agonists were administered on the basis of physician discretion (68). Consistent with other reports, the incidence of moderate and 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) (68). Multiple other cohort studies in the literature corroborate the reduction in OHSS after GnRH agonists compared with hCG triggers (69–73). In addition to the risk of OHSS, a retrospective cohort analysis of 15,577 cycles found a statistically significant lower risk of ovarian torsion in the GnRH agonist trigger cohort compared with the hCG trigger cohort in antagonist freeze-all cycles over 16 years (74).

A 2014 Cochrane review summarized the results of 17 RCTs that assessed GnRH agonists compared with hCG triggers (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; 8 RCTs, 989 women) as well as in oocyte donor-recipient cycles (OR 0.05, 95% CI 0.01–0.28; 3 RCTs, 374 women) (75). The investigators 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) in fresh autologous cycles (75). This lower birth rate is hypothesized to be because of the rapid luteolysis caused by the insufficient duration of LH receptor activation of the corpora luteal cysts. The observation that the fresh transfer of oocyte donor-derived embryos resulting from the GnRH agonist-only trigger compared with the hCG trigger did not have lower implantation and pregnancy rates supports this hypothesis of premature luteolysis leading to insufficient endometrial receptivity (64).

Multiple studies investigated further modifications to reduce OHSS risk while not compromising the live birth rate in fresh autologous cycles by more aggressive luteal support with GnRH agonist trigger or use of dual trigger (low-dose hCG and GnRH agonist trigger) (72, 76–79). An RCT of 190 women at high risk for OHSS (>18 follicles over 11 mm) undergoing GnRH antagonist stimulation cycles compared GnRH agonist trigger (triptorelin 0.4 mg) with additional luteal support (1,500 IU hCG 35 hours after trigger, 100 mg progesterone intramuscularly daily, and 6 mg estradiol valerate daily) vs. hCG trigger (5,000 IU) with luteal support (100 mg vaginal progesterone 3 times a day and 6 mg estradiol valerate daily) found comparable pregnancy rates (51.6% vs. 52.6%; $P=.88$) along with a significant reduction in OHSS (5% vs. 14%; $P=.047$)) (78). A retrospective cohort study analyzed the use of dual trigger (0.2 mg treptorelin and 500 to 1,000 IU hCG) and possible adjuvant hCG depending on estradiol level on the day of blastocyst transfer compared with GnRH agonist alone in antagonist cycles or hCG 10,000 IU alone in antagonist or down-regulated cycles. The incidence of moderate-to-severe OHSS was significantly reduced in both GnRH agonist trigger groups compared with the hCG trigger group, but the dual trigger group had a trend toward a higher pregnancy rate (48.5% vs. 17.4%) and lower miscarriage rate (16.7% vs. 50%) (76). An RCT of 89 patients comparing dual trigger (addition of 1,000 IU hCG) at the time of GnRH agonist trigger (leuprolide acetate 1 mg) to adjuvant 1,500 IU hCG at the time of oocyte retrieval after the GnRH agonist trigger (leuprolide acetate 1 mg) found no significant differences between the 2 groups in mild and moderate OHSS (3.8% vs. 9.7%), miscarriage rates (26.3% vs. 24.0%), and live birth rates (53.8% vs. 61.3%) (80).

The addition of supplemental hCG at the trigger may, however, increase the risk of OHSS, as reported in a retrospective study of 174 cycles with GnRH-agonist-only trigger (leuprolide acetate 4 mg) (n = 108) vs. dual trigger (leuprolide acetate 4 mg and hCG 1,000 IU) (n = 66) (moderate-to-severe OHSS of 0 vs. 8%), but the oocyte yield both in number and maturity was modestly increased in the dual trigger group (77). The study, however, did not address pregnancy rates.

It should be noted that certain subgroups of patients exhibit a poor response to GnRH agonists for final oocyte maturation. A retrospective cohort analysis of 500 cycles attempted to identify patients at risk for suboptimal LH surge (LH <15) after triggering with GnRH agonist alone (n = 73) or in combination with low-dose hCG (n = 427) (79). The investigators reported a 5.2% rate of suboptimal response overall and found it was correlated with lower FSH and LH levels at baseline as well as lower LH levels on the day of the GnRH agonist trigger. Specifically, they reported a 25% chance of suboptimal response when the LH level was undetectable on the day of the trigger. In addition, irregular menses and prolonged oral contraceptive pill use were also reported to be associated with a suboptimal response to a GnRH agonist trigger or cotrigger. As such, patients who exhibit signs of significant suppression of the hypothalamic-pituitary axis may not be good candidates for GnRH agonists for final maturation; this strategy should be avoided or used with caution in this patient population.

Summary statements

- There is strong evidence to recommend the use of a GnRH agonist to trigger oocyte maturation before oocyte retrieval to reduce the risk of OHSS. (Grade A)
- There is strong evidence that live birth rates are lower in fresh autologous cycles after GnRH-only triggers but not donor-recipient cycles. (Grade A)
- There is moderate evidence that pregnancy rates in fresh autologous transfer cycles are not compromised when a GnRH agonist trigger is used in combination with low-dose hCG at the time of trigger (dual trigger), at the time of egg retrieval, or during the luteal phase, compared with a traditional hCG-only trigger. (Grade B)
- There is weak evidence that repeated luteal hCG supplementation in autologous fresh transfer cycles improves pregnancy rates but increases the rate of OHSS. (Grade C)
- There is insufficient evidence to recommend a lower dose of hCG administration alone to trigger oocyte maturation before oocyte retrieval to reduce the risk of OHSS. (Grade C)

Recommendations

- It is recommended to use a GnRH agonist to trigger oocyte maturation as a first-line strategy to reduce the risk of moderate-to-severe OHSS. (Strength of evidence: A; strength of recommendation: strong).

- It is recommended to add adequate luteal support if using a GnRH agonist for trigger and planning a fresh embryo transfer. (Strength of evidence: A; strength of recommendation: strong).
- It is not recommended to use a lower dose for the hCG-only trigger as a strategy to reduce the risk of moderate-to-severe OHSS. (Strength of evidence: C; strength of recommendation: weak).

ROLE OF MEDICATIONS OR FREEZE-ALL CYCLES TO PREVENT OHSS

Dopamine agonist

The pathophysiology of 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 substantial body of evidence evaluating the administration of dopamine agonists such as cabergoline to reduce the severity and incidence of OHSS. This includes 10 randomized controlled studies (62, 81–89). A prospective, randomized, double-blind study assessed oocyte donors who were receiving cabergoline 0.5 mg/d (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 investigators also assessed ascites as an endpoint and found a lower rate of a fluid pocket >9 cm^2 in women treated with cabergoline (25.7%) compared with those who did not receive treatment (59.4%, P=.005) (84). 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 reduced also in the cabergoline-treated group vs. controls, 15% vs. 50%, respectively (P=.04), with the incidence of severe OHSS not significantly different between the treated and control groups (0 and 10%, respectively) (85). Numerous systematic reviews have assessed cabergoline compared with placebo and other risk-reducing strategies. A review of 7 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, 4 studies, 561 women) (90).

Summary statement.

- There is strong evidence that dopamine agonist administration near the time of the hCG trigger reduces the incidence of moderate-to-severe OHSS. (Grade A)

Recommendation.

- In patients at risk for moderate-to-severe OHSS, it is recommended to start a dopamine agonist such as cabergoline on the day of the hCG trigger or soon thereafter and continue for several days. Studies reported a reduction in OHSS incidence when a dopamine agonist is administered alone or in combination with other risk-reducing strategies. (Strength of evidence: A; strength of recommendation: strong)

Letrozole (aromatase inhibitor)

Elevated serum estradiol levels, typically observed in the setting of a robust response to ovarian stimulation, are strongly associated with an increased risk of developing moderate to severe OHSS. High serum estradiol suppresses the expression of the KISS1 receptor and increases both VEGF and nitric oxide secretion via estrogen receptor modulation (91). Because of the relationship between estradiol and VEGF secretion, it has been proposed that the administration of an aromatase inhibitor such as letrozole after the administration of the hCG trigger injection will decrease serum estradiol levels and may reduce the incidence of OHSS. In a prospective, randomized trial, 238 women at high risk for OHSS (≥25 oocytes retrieved; estradiol ≥5,000 pg/mL) received either letrozole or aspirin after the hCG trigger injection. This study demonstrated that the incidence of moderate or severe OHSS was reduced in the letrozole group (25.0%) compared with the aspirin group (45.1%) (P=.002) (43). However, a retrospective cohort study involving 181 women with PCOS at high risk for OHSS who received either letrozole (n = 78) or no treatment (n = 103) demonstrated no significant reduction in the incidence of OHSS (92). A prospective cohort study evaluating 281 women at high risk for OHSS (≥20 oocytes retrieved; estradiol ≥8,000 pg/mL; or ≥20 follicles with diameter ≥14 mm) similarly demonstrated no statistically significant difference in the rates of severe OHSS in patients who received luteal phase preventive treatment with letrozole (16.3%) compared with controls (18.3%) (P<.05) (93).

Summary statement.

- There is weak evidence that the use of an aromatase inhibitor such as letrozole does not prevent OHSS on the basis of a few studies with contradictory findings. The studies with an appropriate control group report no reduction in the incidence of moderate-to-severe OHSS after letrozole administration. (Grade C)

Recommendation.

- It is not recommended to administer letrozole as an intervention to reduce rates of moderate-to-severe OHSS. (Strength of Evidence: C; strength of recommendation: weak)

Gonadotropin-releasing hormone antagonist after retrieval

After the hCG trigger injection, administration of a GnRH antagonist during the luteal phase has been proposed as a potential intervention to accelerate luteolysis, reduce ovarian VEGF secretion, and promote regression of symptoms associated with OHSS. A prospective cohort study investigating 105 patients at high risk for OHSS undergoing cryopreservation of all embryos demonstrated that the incidence of moderate and severe OHSS was significantly lower in patients receiving

luteal GnRH antagonists (18.03%) compared with controls (37.14%) ($P=.025$) (94). One small randomized controlled trial evaluating 48 women at high risk for OHSS (≥20 oocytes retrieved; ≥18 follicles >16 mm in diameter; estradiol ≥3,500 pg/mL; or ovarian diameter >10 cm) demonstrated that administration of a GnRH antagonist for 3 days starting after oocyte retrieval reduced serum estradiol levels, pain scores, gastrointestinal symptoms, and severity of ascites, although not all outcomes met statistical significance (95). A prospective cohort study evaluating 39 patients at high risk for OHSS who received GnRH antagonists for 5 days in the luteal phase compared with 120 controls, respectively, found no significant differences in rates of moderate OHSS (33.3% vs. 27.5%) or severe OHSS (18.0% vs. 18.3%) ($P<.05$) (93). Overall, data are limited, and many small or low-quality studies are conflicting regarding the effectiveness of GnRH antagonist administration in the luteal phase to reduce rates of OHSS.

Summary statement.

- There is insufficient evidence that the administration of a GnRH antagonist after the hCG trigger leads to a statistically significant reduction in rates of moderate to severe OHSS. (Grade C)

Recommendation.

- It is not recommended to administer a luteal GnRH antagonist alone to reduce rates of moderate-to-severe OHSS. Most studies report no reduction in rates of moderate-to-severe OHSS or in signs or symptoms associated with OHSS. Some low-quality evidence suggests modest symptomatic improvement in women with OHSS who received a GnRH antagonist after the hCG trigger. (Strength of evidence: C; strength of recommendation: weak)

Aspirin

Increased platelet activation because of VEGF levels may lead to the release of substances such as histamine, serotonin, platelet-derived growth factor, or lysophosphatidic acid that can further potentiate the physiologic cascade of OHSS. On the basis of this theory, aspirin has been considered for the risk reduction of OHSS (96). There are 3 randomized trials on the use of aspirin for OHSS prevention. In one study, patients were randomized to receive low-dose aspirin and prednisolone (n = 97) or no treatment (n = 298), in addition to standard IVF stimulation 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 (10–30 mg) during the same time frame. Patients who received the combination of aspirin and prednisolone had a lower incidence of severe OHSS (1.7% vs. 6.5%) compared with controls (97). In a second trial, women at high risk for OHSS who were given 100 mg of aspirin daily were found to have lower rates of severe OHSS requiring hospitalization compared with controls (0.25% vs. 8.4%, respectively) ($P<.001$) (96). However, a recent double-blinded, placebo-controlled RCT performed on 232 patients with PCOS undergoing IVF stimulation demonstrated no significant reduction in rates of moderate-to-severe OHSS compared with women who received low-dose aspirin (34.9%) to those who received placebo (30.5%) ($P<.001$) (98).

Summary statement.

- There is weak evidence that aspirin reduces the incidence of OHSS on the basis of a limited number of mixed studies. (Grade C)

Recommendation.

- It is not recommended to use aspirin as a primary strategy to reduce the incidence of OHSS. (Strength of evidence: C; strength of recommendation: weak)

Metformin

Metformin is an insulin-sensitizing drug that is commonly used to treat type 2 diabetes and has been widely studied in patients with PCOS. It has been theorized that metformin can affect ovarian response by reducing the number of nonperiovulatory follicles and thereby reducing estradiol secretion. Studies have addressed whether metformin during ovarian stimulation for IVF in patients with PCOS can reduce OHSS in this high-risk group. The first RCT addressing this question in 2006 showed that metformin during ovarian stimulation in GnRH agonist down-regulation protocols decreased the incidence of OHSS in patients with PCOS (3.8% vs. 20.4%, $P=.023$) (99). Subsequent RCTs supported this finding (100, 101). A meta-analysis of 12 studies made up of 1,516 participants demonstrated that the risk of OHSS was significantly lower in patients with PCOS who were given metformin (RR 0.44, 95% CI 0.26–0.77) compared with controls (102). Recently, the use of metformin as a strategy to reduce the risk of OHSS in patients with PCOS has been evaluated in the setting of GnRH antagonist stimulation protocols. A recent randomized, placebo-controlled trial evaluated 153 patients with PCOS undergoing IVF stimulation with a GnRH antagonist protocol and determined that metformin did not lead to a significant reduction in the incidence of moderate-to-severe OHSS (16.0%) compared with placebo (12.2%) ($P=.66$). Similarly, a large retrospective study assessing 496 patients with PCOS demonstrated no significant reduction in the incidence of OHSS after IVF stimulation with a GnRH antagonist protocol when metformin was given (3.6%) compared with controls (7.5%) ($P=.421$) (103).

Summary Statement.

- There is moderate evidence that metformin reduces the incidence of OHSS in patients with PCOS who are at high risk for OHSS in the setting of GnRH agonists but not antagonist stimulation protocols. (Grade B)

Recommendation:.

- It is not recommended to administer metformin for the sole purpose of reducing the incidence of OHSS in GnRH antagonist cycles because most studies do not report a significant reduction in rates of OHSS in women with PCOS who were given metformin. Metformin may, however, be considered

for OHSS risk reduction among women with PCOS using a GnRH-agonist protocol. (Strength of evidence: B; strength of recommendation: moderate)

Additional strategies to prevent OHSS (mifepristone, myoinositol, D-chiro-inositol, and glucocorticoids)

Miscellaneous treatments such as the administration of mifepristone, myoinositol, D-chiro-inositol, and glucocorticoids have been proposed as potential interventions to reduce the risk of OHSS. The mechanisms of action underlying these potential treatment modalities have varying degrees of supporting evidence. A prospective cohort study evaluating 51 patients who received mifepristone in the luteal phase after the hCG trigger injection demonstrated no significant differences in the rates of moderate or severe OHSS, respectively, in the mifepristone group (29.4% and 19.6%) compared with controls who received no intervention (27.5% and 18.3%) ($P>.05$) (93). The data surrounding myoinositol use and D-chiro-inositol use for the purpose of OHSS risk reduction is generally of low quality and limited. A single randomized controlled trial evaluating the use of methylprednisolone for the prevention of OHSS in women with PCOS compared with placebo failed to show a statistically significant reduction in the incidence of OHSS in the glucocorticoid group (19.4%) compared with placebo (16.5%) ($P=.61$) (104).

Summary Statement.

- There is insufficient evidence to determine whether additional strategies such as administration of mifepristone, myoinositol, D-chiro-inositol, or glucocorticoids reduce the incidence of moderate-to-severe OHSS. (Grade C)

Recommendation.

- It is not recommended to administer medications such as mifepristone, myoinositol, D-chiro-inositol, or glucocorticoids to reduce rates of OHSS. (Strength of evidence: C; strength of recommendation: weak)

Freeze-only Cycles

Elective cryopreservation of all embryos and their subsequent transfer in nonstimulated cycles can be used to avoid the endogenous hCG rise associated with a fresh transfer cycle, which can exacerbate late-onset OHSS symptoms and duration. Early small RCTs found that elective cryopreservation prevents late-onset OHSS (105, 106). One RCT of 125 patients showed that cryopreservation results in a lower incidence of OHSS than controls with fresh embryo transfers (0 events in the cryopreservation group vs. 4 events in the fresh transfer group) (107). This study showed that there were no differences in pregnancy rates (46% controls vs. 48% cryopreservation) or live birth rates (39% controls vs. 40% cryopreservation). A more recent large, multicenter RCT of 2,157 patients demonstrated that the live birth rate did not differ significantly between patients undergoing frozen embryo transfer (48.7%) and fresh embryo transfer (50.2%) ($P=.50$), but the risk of OHSS was significantly lower in patients undergoing cryopreservation of embryos (0.6%) compared with those undergoing fresh embryo transfer (2.0%) ($P=.005$) (108). A subsequent meta-analysis of 8 studies involving 4,712 patients similarly concluded that the risk of OHSS is reduced with a "freeze-only" strategy (OR 0.26, 95% CI 0.17–0.39) and there is likely no difference between a "freeze-only" and fresh transfer strategy in terms of cumulative ongoing pregnancy rate (OR 0.95, 95% CI 0.75–1.19; $I^2 = 31\%$) (109).

Summary Statement.

- There is strong evidence that avoiding a fresh embryo transfer and cryopreserving embryos (freeze-only cycle) significantly reduces the risk of moderate-to-severe OHSS compared with fresh embryo transfer cycles. (Grade A)

Recommendation.

- It is recommended to consider a freeze-only cycle and subsequent frozen embryo transfer in patients at risk for OHSS on the basis of high ovarian response or elevated serum estradiol levels. Multiple high-quality studies have reported a significant reduction in rates of moderate or severe OHSS when this strategy is employed. (Strength of evidence: A; strength of recommendation: strong)

Volume Expanders

Albumin has a low molecular weight and an average half-life of 20 days. Its binding and transport properties have been hypothesized to play a role in OHSS prevention. It is important to note that albumin is a blood-derived product and may lead to allergic reactions, anaphylaxis, and the transmission of viral or unidentified diseases. Because 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 (110–112). One such RCT randomized women at high risk for OHSS on the basis of a serum estradiol cutoff level of 3,000 pg/mL to albumin treatment or none after using 5,000 IU hCG as a trigger. In this study, 5 patients developed moderate or severe OHSS in the control group vs. none in the albumin group ($P=.028$) (110). However, further studies have not found albumin to be effective in decreasing the incidence of OHSS (112–114). Two systematic reviews concluded that albumin does not prevent OHSS (115, 116). In a Cochrane review of 9 RCTs, although albumin decreased the odds of OHSS compared with placebo (OR 0.67, 95% CI 0.47–0.95), the quality of the evidence was very low, and there was evidence of a detrimental effect on pregnancy rates (OR 0.72, 95% CI 0.55–0.94) (117). There was evidence of a beneficial effect of hydroxyethyl starch (HES) on OHSS (OR 0.27, 95% CI 0.12–0.59), but this was on the basis of 2 small studies totaling 272 women. There was evidence of a beneficial effect of mannitol on OHSS (OR 0.38, 95% CI 0.22–0.64),

but this was on the basis of only one study of 226 women with PCOS. None of the studies had data on live birth rates, and adverse events were poorly reported.

Summary Statement.

- There is weak evidence that the use of volume expanders such as albumin, HES, and mannitol can reduce rates of moderate-to-severe OHSS. (Grade C)

Recommendation.

- It is not recommended to use volume expanders such as albumin, HES, or mannitol in patients who are at high risk of developing moderate or severe OHSS. (Strength of Evidence: C; Strength of Recommendation: Weak)

CONCLUSIONS

Ovarian hyperstimulation syndrome is a known complication of controlled ovarian stimulation. Ideally, women at risk for this disorder should be identified before stimulation, and stimulation protocols should be selected that minimize the risk of OHSS. The use of GnRH antagonist protocols with a GnRH agonist to trigger final oocyte maturation is a particularly effective strategy and should be considered first-line for OHSS prevention. Other strategies that show some benefit include the use of cabergoline and cryopreservation of embryos rather than fresh transfer.

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Prevención del síndrome de hiperestimulación ovárica moderado y grave: una guía

El síndrome de hiperestimulación ovárica es una complicación grave asociada con la tecnología de la reproducción asistida. Esta revisión sistemática tiene como objetivo identificar quiénes tienen alto riesgo de desarrollar el síndrome de hiperestimulación ovárica, junto con estrategias basadas en la evidencia para prevenirlo y reemplaza el documento del mismo nombre publicado por última vez en 2016.