Preventing ovarian hyperstimulation syndrome: guidance for the clinician

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Objective: To reevaluate ovarian hyperstimulation syndrome (OHSS) prevention techniques and provide a classification system for grading OHSS and evidence-based treatment strategies for preventing OHSS.

Design: A literature search was conducted in PubMed for articles published in the last 5 years using the keywords “controlled ovarian stimulation,” “controlled ovarian hyperstimulation,” “ovarian hyperstimulation syndrome,” “OHSS,” “prevention,” “chorionic gonadotropin,” “hCG,” “GnRH agonist,” “GnRH antagonist,” “coasting,” and “cryopreservation.” We reviewed randomized controlled trials (RCTs), retrospective studies, pilot studies, case studies, reviews, and meta-analyses.

Result(s): There is a shortage of large, prospective RCTs reporting OHSS prediction and prevention strategies. Our review showed that risk factors such as antral follicle count and baseline anti-Müllerian hormone level may identify women at high OHSS risk. Preventative strategies that appear highly effective at reducing or preventing OHSS include GnRH antagonist protocols and the use of GnRH agonists to trigger final oocyte maturation. Moreover, alternative therapies, such as dopamine receptor agonists (Cabergoline), have also emerged as potential new treatment modalities in the management of this disease.

Conclusion(s): These findings suggest that current treatment guidelines should be updated to incorporate findings from recent literature that show that GnRH antagonist protocols consistently reduce OHSS and that GnRH agonist triggering has considerable promise in preventing OHSS, although further RCTs will be needed to confirm this.

Key Words: OHSS, prevention, grading, IVF, controlled ovarian stimulation, GnRH agonist, GnRH antagonist

All ovarian stimulation protocols result in some degree of hyperstimulation, usually with no adverse consequences to the patient (1). In contrast, ovarian hyperstimulation syndrome (OHSS) is a iatrogenic complication of ovulation induction (OI) and ovarian stimulation for assisted reproductive technology (ART) and is characterized by cystic enlargement of the ovaries and rapid fluid shifts from the intravascular compartment to the third space. It is a potentially life-threatening condition in its severe form, resulting in hospitalization in 1.9% of cases (2), and hCG, either exogenous or endogenous, is the triggering factor of the syndrome. The relationship between hCG and OHSS is thought to be mediated via the production of the angiogenic molecule vascular endothelial growth factor (VEGF; Fig. 1).

Current guidelines for the prevention of OHSS differ in their recommendations and do not encompass the most recent advances described in the literature. The purpose of this paper is to review the most recent evidence supporting different OHSS reduction strategies. A literature search was conducted by searching PubMed for articles published in the last 5 years using the terms “controlled ovarian stimulation,” “controlled ovarian hyperstimulation,” “ovarian hyperstimulation syndrome,” “OHSS,” “prevention,” “chorionic gonadotropin,” “hCG,” “GnRH agonist,” “GnRH antagonist,” “coasting,” and “cryopreservation.” As there is a shortage of prospective, controlled, randomized trials investigating the efficacy of many of the proposed prevention methods for OHSS, a range of literature was included in the search to gain the widest understanding of current empirical and clinical experience, including randomized controlled trials, retrospective studies, pilot studies, case studies, meta-analyses, and reviews.

CLASSIFICATION OF OHSS

Two main clinical forms of OHSS, early OHSS and late OHSS, distinguished by their time of onset, are described in the literature. Early OHSS is correlated to ovarian response to stimulation (3, 4) and is an acute effect of exogenous hCG administration, usually occurring within 9 days after oocyte retrieval (3, 4). In contrast, late OHSS occurs after the initial 10-day period and is only poorly correlated to the ovarian response and is rather more correlated to the endogenous hCG produced by an implanting embryo (4, 5) or to the administration of hCG for luteal phase support (LPS).
We propose here a new OHSS severity classification scheme incorporating vaginal ultrasound and laboratory parameters that is more objectively related to symptoms than previous classifications (Table 1). Mild, moderate, and severe forms are distinguished by the extent of fluid shift into body cavities. Although subjective, moderate OHSS involves fluid shifts of less than 500 mL. In the severe form, hemoconcentration and hypovolemia are reflected in laboratory signs of hepatorenal dysfunction. The more subjective signs and symptoms encountered in OHSS, such as discomfort, pain, nausea, and vomiting, may vary in individual cases and cannot be assigned to a particular grade of OHSS. Therefore, in this classification system we suggest practical management guidelines that can be applied on a case-by-case basis.

**CLINICAL PRESENTATION AND MANAGEMENT**

Mild OHSS is relatively common in stimulated cycles, with symptoms including lower abdominal pain and discomfort, mild weight gain, nausea, vomiting, or diarrhea. Ovarian enlargement discernible on ultrasound is a key indicator of the severity of the condition after OI but is less indicative in IVF, as follicular aspiration may result in relatively small ovarian size, even in the presence of other indicators of severe OHSS (6). Moderate OHSS is characterized by the presence of ascites on ultrasound examination, moderate hemoconcentration, and elevated leukocytes. Symptoms include rapid weight gain (>1 kg/day), abdominal distension, nausea, and vomiting. In severe OHSS, increased fluid shifts into the peritoneal (around the intestinal loops) and possibly into the pleural and pericardial cavities, leading to hypovolemia and severe hemoconcentration. Life-threatening complications of severe OHSS include hepatorenal failure, acute respiratory distress syndrome, hemorrhage from ovarian rupture, and thromboembolism (7).

Most OHSS can be managed on an outpatient basis, with oral analgesics and patient education regarding indicators of worsening illness that may require more aggressive intervention. Symptomatic relief of moderate OHSS with antiemetics and stronger analgesics should be accompanied by careful monitoring, including physical examination, ultrasound, weight measurement, and laboratory determination of hematocrit, electrolytes, and serum creatinine, ideally on a daily basis. In nonconception cycles, mild or moderate OHSS is likely to resolve spontaneously after menstruation. However, in patients who become pregnant, rising serum levels of endogenous hCG significantly increase the risk of developing severe OHSS, which generally requires hospitalization, IV fluid management, ascites puncture via culdoscopy, and prophylactic measures to prevent thromboembolism.

**PREDICTING OHSS: IDENTIFYING THE AT-RISK PATIENT**

Identifying at-risk patients is critical in the prevention of OHSS as it enables changes to be made to the ovarian stimulation regimen and/or other preventative measures. Predictive factors for OHSS can be divided into primary risk factors, which confer an increased risk of OHSS on patients, and secondary risk factors, which become apparent during ovarian stimulation when patients with no known predisposing factors experience an excessive response to treatment. A summary of primary and secondary risk factors is given in Table 2.

**Primary Risk Factors**

Existing factors likely to magnify response to ovarian stimulation include young age, a history of elevated response to gonadotropins, previous OHSS, polycystic ovary syndrome (PCOS), or isolated PCOS characteristics (8, 9).
Women with PCOS have a higher incidence of OHSS after gonadotropin therapy than women with other causes of anovulatory infertility owing to the high number of follicles recruited (10, 13). The association between increased ovarian response and elevated OHSS risk means that prior warning regarding the level of response to ovarian stimulation could predict the likelihood of OHSS. Hormonal markers are, therefore, being investigated as potential predictors of ovarian response, with anti-Müllerian hormone (AMH) being a promising candidate. AMH is expressed in granulosa cells from preantral and small antral follicles (14) and is a measure of ovarian reserve. Initial studies suggest that AMH is a reliable predictor of ovarian response (15, 16), able to differentiate normal (more than 4 oocytes) responders (using a cut-off level of 1.26 ng/mL AMH) to ovarian stimulation with a success rate of 70% (15, 16), although cut-off values for predicting OHSS depend on the assay used (21). Adoption of an international standard for AMH would therefore facilitate its wider clinical applicability.

Another primary risk factor predictive of OHSS is ultrasound visualization of an ovary with ⩾ 12 antral follicles 2–8 mm in diameter typically located around the periphery of the ovary (the “necklace” sign; see Delvigne and Rozenberg [22] for a review). A study analyzing the antral follicle count (AFC) alone compared with multivariate models for predicting ovarian response found that the two measures were comparable (23); the authors, therefore, suggested that future models of ovarian response should incorporate the AFC. An AFC of > 14 may predict hyperresponse to IVF treatment with a sensitivity of 0.82 and a specificity of 0.89 (24).

### Secondary Risk Factors

A number of ovarian response parameters have been evaluated for their ability to predict the development of OHSS (reviewed in Delvigne and Rozenberg [22]), including absolute levels or rate of increase of serum E2, follicular size and number, and number of oocytes collected. None of these measures have been shown to be independently predictive of OHSS.

Several investigators have attempted to improve the predictive power of ovarian response parameters by combining E2 levels and follicle number/number of oocytes retrieved (3, 5–28), but with limited success. Research efforts are underway to identify better predictive factors and evaluate their usefulness, and a number of promising candidates, including VEGF, interleukins, and inhibin-B, have emerged. Of these factors, inhibin-B has shown potential as increased inhibin-B production may prime the follicle to overrespond to hCG; however, the mechanism for such a response is unknown.

Regarding the use of VEGF levels to predict the development of OHSS, conflicting results have been reported.

### Preventing OHSS: Better Than Cure

Complete prevention of OHSS is still not possible, but with early identification of potential risk factors and careful clinical management of all patients undergoing ovarian stimulation regimens, the incidence of OHSS can be significantly reduced.

Prevention strategies can be divided into two types—primary and secondary. In primary prevention, the stimulation protocol is personalized to suit the individual patient after an assessment of primary risk factors to classify patients as poor, normal, or high responders. Low responders then undergo treatment regimens that are associated with the recruitment of a larger follicular cohort. Conversely, high responders would receive treatment regimens associated with a lower ovarian response.

Secondary prevention methods are used in the presence of risk factors arising from an excessive response to ovarian stimulation and involve the withdrawal, delay, or modification of elements of the stimulation protocol treatment with the aim of averting OHSS in patients who have progressed to high risk during the treatment cycle.

Primary and secondary OHSS prevention strategies are described below. A summary of current clinical guidelines on OHSS prevention, and the most recent evidence for OHSS prevention strategies, is given in Table 3.

### Primary Prevention

1. **Reducing Exposure to Gonadotropins**

   **a. Reducing the Dose—IVF Cycles.** As PCOS is a known risk factor for OHSS, a number of low-dose gonadotropin protocols have been
implemented to reduce the risks of fertility treatment in this population. The aim of these protocols is to stimulate the ovaries without exceeding the FSH threshold, thus facilitating the development of a single dominant follicle rather than multiple follicles.

A variety of stepwise protocols have been used (29). These include chronic low-dose step-up protocols, whereby a low starting dose of FSH (usually 75 IU) is administered for 14 days, followed by small incremental increases (e.g., 37.5 IU) at intervals of 7 days until follicular development is initiated. This dose is then continued until the criteria for triggering ovulation are met (30).

### TABLE 2

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Threshold of risk</th>
<th>Intervention/ detection possible?</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary risk factors (patient related)</strong></td>
<td></td>
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</tr>
<tr>
<td>High basal AMH</td>
<td>Cut-off level of 3.36 ng/mL has a sensitivity of 90.5% and specificity of 80% in predicting OHSS (8)</td>
<td>Can be assessed on any day of the menstrual cycle (37)</td>
<td>Regression analysis has proven that receiver operating characteristic curve is superior to age, number of follicles (8)</td>
</tr>
<tr>
<td>High AFC</td>
<td>AFC &gt;14 may predict hyperresponse (48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Less than 33 y (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous OHSS</td>
<td>Moderate or severe cases especially when hospitalization required</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCOS/isolated PCOS characteristics</td>
<td>≥12 antral follicles 2–8 mm in diameter is predictive (46)</td>
<td>Yes</td>
<td>10%–12% incidence of moderate or severe OHSS in PCOS population compared with 0%–3% in women with normal ovaries</td>
</tr>
<tr>
<td><strong>Secondary risk factors (ovarian response related)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of follicles on the day of hCG</td>
<td>&gt;14 follicles diameter of 11 mm (5); &gt;11 follicles with diameter of 10 mm (8)</td>
<td></td>
<td>Practical difficulties in correct measurement of follicle size, particularly with increasing follicle number associated with hyperstimulation (50)</td>
</tr>
<tr>
<td>Absolute level or rate of increase of serum E2</td>
<td>Poorly predictive for OHSS; however, the combination of E2-related higher specificity and follicle-related better sensitivity produces a criterion (≥18 follicles and/or E2 of 5,000 ng/L) with a significant positive-likelihood ratio (LR = 5.19) that can predict 83% of the severe OHSS cases, including both early and late cases, with an acceptable specificity of 84% (5)</td>
<td></td>
<td>Reasons for poor predictive power of these variables: arbitrary nature of cut-off points used by different investigators (46), high degree of variability between patients, modest sensitivity, high false-positive rates (49)</td>
</tr>
<tr>
<td>VEGF levels</td>
<td>Not applicable</td>
<td>Serum or follicular fluid</td>
<td>Conflicting results obtained, however, Pau et al. (124) found significantly higher total VEGF and free VEGF due to lower secretion of sVEGFR-1, concluding that in early and late OHSS, the ability to secrete sVEGFR-1 and bind VEGF seems to be the determinant factor in OHSS</td>
</tr>
<tr>
<td>Elevated inhibin-B levels</td>
<td>Elevated levels on day 5 of gonadotropin stimulation, at OPU, and 3 days before OPU appear to correlate with development of OHSS</td>
<td></td>
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</tbody>
</table>

Note: NA = not applicable.

of monofollicular ovulation and fewer cycle cancellations (33). “Limited ovarian stimulation,” which involves stimulating the leading Graafian follicle to a size of just 12 mm (35), has also been shown to prevent the recurrence of severe OHSS in high-risk patients with a previous history of the condition (34, 35).

b. Reducing Duration of FSH Exposure—IVF/intracytoplasmic sperm injection (ICSI) Cycles. Little consensus exists on the appropriate duration of FSH treatment, partly because of the wide variation in individual responses to gonadotropin therapy. However, there is also great variability in the criteria used to determine when to stop gonadotropin therapy and trigger final oocyte maturation. Investigators have used different follicle sizes, with or without predetermined serum E2 level requirements (36), but few studies have actively investigated the impact of these criteria on outcome and OHSS incidence.

Another issue is whether FSH should be given on the day of hCG administration, a practice that is still quite widespread. To our knowledge, there have been no studies directly investigating this. However, it is not unreasonable to assume that this could increase the risk of developing OHSS and should thus be avoided. Further supporting this position, a prospective, randomized controlled trial in 413 IVF patients cotreated with a GnRHa antagonist reported that delaying triggering and continuing FSH administration for 2 days after the criteria for hCG administration were reached had a negative impact on pregnancy rates (37). Although no mention was made of OHSS occurrence, this study suggests that once the primary follicles reach the criteria for triggering ovulation, additional FSH is not clinically necessary and may be detrimental to outcome, possibly owing to a negative impact on endometrial receptivity.

Reducing exposure to gonadotropins can also be achieved via the use of “mild stimulation” protocols, where administration of FSH is delayed until the mid to late follicular phase. Although early attempts at natural cycle or minimal stimulation protocols resulted in a high

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**TABLE 3**

Current clinical guidelines and summary of the most recent evidence for OHSS prevention strategies.

<table>
<thead>
<tr>
<th>OHSS prevention strategy</th>
<th>Findings based on current evidence</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreasing exposure to gonadotropins</td>
<td>Chronic low dose (OI); limited ovarian stimulation (OI); mild stimulation protocol (IVF); no FSH on day of hCG</td>
<td>1b, 2a, 2b, 4</td>
</tr>
<tr>
<td>GnRH antagonist</td>
<td>Decreases risk of severe OHSS, reduces incidence of OHSS hospital admissions, reduces the need for secondary interventions such as coasting or cycle cancellation</td>
<td>1a</td>
</tr>
<tr>
<td>Reduced dose hCG for triggering ovulation</td>
<td>Appears to reduce risk of severe OHSS but large RCTs needed</td>
<td>2a</td>
</tr>
<tr>
<td>Avoiding hCG for LPS</td>
<td>Approximately half the risk of OHSS with P for LPS vs. hCG</td>
<td>1a</td>
</tr>
<tr>
<td>IVM</td>
<td>Promising, but no data on OHSS prevention available</td>
<td>—</td>
</tr>
<tr>
<td>Insulin-sensitizing agents</td>
<td>Reduces risk of OHSS in women with PCOS undergoing OI or IVF; may reduce risk of moderate/severe OHSS in normal responders</td>
<td>1a, 2a</td>
</tr>
<tr>
<td>Cycle cancellation</td>
<td>Almost eliminates risk of OHSS; in nonsuppressed cycles, ovulation may still occur and ensuing pregnancy could lead to the development of late OHSS</td>
<td>4</td>
</tr>
<tr>
<td>Coasting</td>
<td>Appears to reduce, but not eliminate, the incidence of severe OHSS in high-risk patients compared with expected values; no placebo-controlled RCTs; optimal criteria and protocols remain to be determined</td>
<td>1a</td>
</tr>
<tr>
<td>Alternative agents for triggering ovulation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GnRHa</td>
<td>Very significant reductions in incidence of OHSS in high-risk patients compared with hCG</td>
<td>1b</td>
</tr>
<tr>
<td>Recombinant human LH</td>
<td>Appears to be effective in reducing the incidence of OHSS, but associated with poor outcomes and high costs; not commercially available</td>
<td>1b</td>
</tr>
<tr>
<td>Cryopreservation of all embryos</td>
<td>Insufficient evidence available</td>
<td>1a</td>
</tr>
<tr>
<td>Antagonist salvage</td>
<td>Appears to halt the development of severe OHSS; as effective as coasting</td>
<td>1b</td>
</tr>
<tr>
<td>Albumin</td>
<td>Does not appear to be effective</td>
<td>1a</td>
</tr>
<tr>
<td>Hydroxyethyl starch</td>
<td>Appears to reduce the risk of moderate and severe OHSS</td>
<td>1b</td>
</tr>
<tr>
<td>Follicular aspiration</td>
<td>Results are variable and negative drawbacks of this approach not trivial; cannot recommend</td>
<td>1a</td>
</tr>
<tr>
<td>Aromatase inhibitors</td>
<td>No literature on the effects of aromatase inhibitors on incidence or severity of OHSS</td>
<td>—</td>
</tr>
<tr>
<td>Dopamine agonists</td>
<td>Superior to placebo at reducing incidence of OHSS in high-risk patients but does not eliminate the risk</td>
<td>1b</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Conflicting results; may be effective when used at an early stage of ovarian stimulation</td>
<td>2a</td>
</tr>
</tbody>
</table>

Note: RCT = randomized controlled trial. Hierarchy of evidence: 1a = systematic review and meta-analysis of RCTs; 1b = at least one RCT; 2a = at least one well-designed controlled study without randomization; 2b = at least one other type of well-designed quasi-experimental study; 3 = well-designed nonexperimental descriptive studies, e.g., comparative studies, correlation studies, case studies; 4 = expert commentary reports or opinions and/or clinical experience of respected authorities.

rate of cycle cancellation owing to premature luteinization (38), the introduction of GnRH antagonists for late-cycle suppression of pituitary gonadotropin release has improved clinical outcomes with mild stimulation protocols, making these an appealing treatment choice for prevention of OHSS (39, 40). A parallel group, open-label, randomized, noninferiority trial compared a mild stimulation protocol with single ET with the traditional long agonist protocol with double ET in 404 expected normoresponder patients (41, 42). The mild treatment protocol involved FSH administration from cycle day 5 and GnRH antagonist cotreatment when at least one follicle ≥14 mm was observed on ultrasound. A total of 769 IVF cycles were performed, with six in 444 (1.4%) mild treatment cycles resulting in OHSS of any severity compared with 12 in 325 (3.7%) long agonist treatment cycles (P = .04). Cumulative live births after 1 year were similar for both groups (43.4% vs. 44.7% in the mild and standard treatment arms, respectively), but there were fewer multiple pregnancies with mild stimulation (0.5% vs. 13.1%; P < .0001). As higher order pregnancies are a significant risk factor for OHSS (3, 43), this may also contribute to reduced OHSS risk with mild stimulation. A further benefit of mild stimulation treatment protocols is the significant cost reduction compared with standard treatments. So, although studies have been conducted only in women expected to have a normal response, mild stimulation may offer significant advantages in high-risk populations, and prospective, controlled, randomized trials should be carried out in these patients.

2. GnRH Antagonist Protocols The addition of GnRH agonists (GnRHa) to gonadotropin therapy in the late 1980s led to a large increase in the incidence of OHSS (44). One possible explanation is that pretreatment blockade of endogenous gonadotropins necessitates an increased dose of exogenous FSH for adequate ovarian stimulation. It is also possible that pituitary downregulation interferes with natural cohort selection and prevents smaller antral follicles from becoming atretic (45).

In contrast to the extended pretreatment phase with GnRHa, the rapid competitive blockade of pituitary GnRH receptors by antagonists means that they do not need to be administered until just before the expected rise in endogenous LH, usually at a follicle size of 12–14 mm. As natural cohort selection occurs at the start of the cycle, a smaller number of midsized follicles are produced. The lack of suppression of natural endogenous FSH during the early follicular development phase means that a reduced dose of exogenous FSH is required for ovarian stimulation with antagonists (46–48).

The differential action of GnRH antagonists at both pituitary and ovarian receptors suggests that antagonist-suppressed cycles might result in a lower incidence of OHSS compared with agonist cycles, and this hypothesis has been supported by two recent meta-analyses. A Cochrane review (49) demonstrated that the incidence of severe OHSS was significantly lower in an antagonist protocol than in an agonist protocol (relative risk [RR], 0.61; 95% confidence interval [CI], 0.42–0.89; P = .01) and that secondary intervention methods such as coating and cycle cancellation were administered more frequently in agonist-suppressed cycles (OR, 0.44; 95% CI 0.21–0.93; P = .03 [49]). A second meta-analysis (50) found that the incidence of hospital admissions for OHSS was significantly lower in antagonist cycles than in agonist cycles (OR, 0.46; 95% CI, 0.26–0.82; P = .01).

There are clear advantages with GnRH antagonists, including lack of flare effect, no accompanying menopausal-like symptoms, no refractory period, reduced risk of ovarian cyst formation, shorter treatment cycle, and reduced FSH consumption. However, results from initial comparative trials have led to uncertainty regarding the efficacy of antagonists, which were shown to result in a lower probability of clinical pregnancy than GnRHa, despite there being no accompanying significant difference in live-birth rate (51). Two subsequent meta-analyses investigating GnRH analogs in IVF (49, 50) produced conflicting results: Kolibianakis et al. (50) observed that there was no difference in live-birth rate between the two analogs, whereas Al-Inany et al. (49) showed that the clinical pregnancy rate was slightly lower with antagonists compared with agonists. However, the two studies both found favorable clinical outcomes with each of the GnRH analogs, and the different overall conclusions can be attributed to differences in the meta-analysis methodologies applied. A wider awareness of clinical equivalence between the GnRH analogs is needed, and the use of antagonist regimens in normal and predicted high responders should be considered.

3. Avoidance of hCG for LPS The supraphysiological steroid levels (E2 and P) obtained in the luteal phase after controlled ovarian hyperstimulation cause an impairment of the luteal phase owing to negative feedback on the pituitary (52, 53), resulting in low endogenous LH levels and leading to reduced implantation and pregnancy rates and increased early pregnancy loss rates (54). As a result of this impairment, LPS is required. The use of hCG in LPS has been shown to confer significant benefits over placebo in agonist suppressed cycles; however, hCG is also known to increase the risk of OHSS (55). The use of P appears to halve this risk, while demonstrating similar improvements in pregnancy and miscarriage rates (55). Evidence for the efficacy and safety of P in LPS has been further strengthened by a large, prospective, multicenter, randomized controlled trial of 1,211 patients undergoing IVF (56) in which patients receiving P for LPS experienced high birth rates (35%–38%) and a low incidence of OHSS (6%–7%).

As an alternative to P, it has been suggested that repeated intranasal administration of a GnRHa could be used for LPS (57); however, larger studies are required to support this. Based on currently available evidence, it is recommended that LPS in GnRH analog–suppressed cycles be provided in the form of P, with or without supplemental E2, rather than in the form of hCG.

4. In Vitro Maturation In patients with PCOS and in normo-ovulatory patients at high risk of developing OHSS, in vitro maturation (IVM) of oocytes offers great potential for OHSS prevention. Despite safety advantages, IVM is not yet widely used owing to a reduced live-birth rate in comparison with standard IVF. However, clinical outcomes have improved in recent years, and pregnancy rates of between 20% and 54% have been reported (58). Cryopreservation of oocytes can further improve the likelihood of pregnancy per treatment cycle, despite a relatively low post-thaw survival rate (59).

5. Insulin-Sensitizing Agents Insulin resistance with compensatory hyperinsulinemia is thought to play a pathophysiological role in the ovarian dysfunction (60, 61) and hyperandrogenism (62, 63) associated with PCOS. Thiazolidinediones, a class of insulin-sensitizing agents, are associated with increased cardiac morbidity that may contraindicate their use in otherwise healthy women with PCOS (64). However, metformin is a cheap, effective insulin-sensitizing agent with a good safety profile that has been widely used in OI as monotherapy or in combination with other OI drugs and also as pretreatment before IUI or IVF/ICSI in women with PCOS. A 2006 meta-analysis of eight randomized controlled trials of metformin coadministration during gonadotropin-stimulated OI or IVF in women with PCOS found little benefit of metformin treatment in terms of improved ovulation or clinical outcome in this
population but did note a significant positive effect on the incidence of OHSS (OR, 0.21; 95% CI, 0.11–0.41; \(P<.00001\)) across the five trials that listed OHSS as an outcome measure (n = 426) (65).

Secondary Prevention Strategies

1. Coasting Coasting involves withholding further gonadotropin stimulation and delaying hCG administration until \(E_2\) levels plateau or decrease significantly (66, 67). A 2002 systematic review of 493 patients in 12 studies found that coasting does not eliminate the risk of OHSS in high-risk patients but may reduce the incidence and severity of the condition (68). A Cochrane review in the same year identified 13 studies examining the effects of coasting, but only one met their inclusion criteria (69). The authors concluded that there was insufficient evidence to determine whether coasting was an effective strategy for preventing OHSS.

Nevertheless, coasting has been widely adopted as the first-line intervention of choice for reducing the risk and severity of OHSS in patients with excessive follicular response to ovarian stimulation (70). Yet, despite its popularity, the scientific evidence base supporting the use of coasting to prevent OHSS is not strong. The majority of the reports on coasting in the literature are retrospective analyses, and there is a need for large prospective, randomized controlled trials to identify optimal coasting guidelines and to evaluate the safety and efficacy of coasting compared with other prevention methods.

2. Reduced Dose of hCG As hCG is known to be a risk factor for OHSS, a number of investigators have assessed the value of using lower doses for triggering ovulation. Compared with the standard dose of 10,000 IU, doses of 5,000 IU have been used successfully to trigger ovulation without impairing clinical outcome (71, 72). Promising results have also been reported from the Cornell low-dose protocol, which determines hCG dosage according to serum \(E_2\) levels on the day of hCG administration. A sliding scale is used, with between 5,000 and 3,300 IU of hCG administered to women with \(E_2\) levels of 2,000–3,000 pg/mL (73). Women with \(E_2\) levels >3,000 pg/mL undergo coasting until \(E_2\) falls below 3,000 pg/mL. One university-based IVF program reported similar pregnancy rates but significant reductions in early OHSS (occurring before ET; \(P<.001\)) and severe OHSS (post-ET, requiring hospitalization, thrombophlebitis, and removal of ascitic fluid; \(P<.05\)) in 792 cycles in the 1.5 years after the introduction of this low-dose hCG protocol, compared with 1,789 cycles in women treated in the 3.5 years before the introduction of this protocol (74). Unfortunately, a proposed multicenter, randomized controlled trial was not initiated, as the positive effect of the low-dose hCG protocol was deemed to be sufficiently high that it would be unethical to randomize patients to the control arm.

These positive findings for the benefits of low-dose hCG have not been duplicated in other reports. One retrospective review of 94 IVF high-responder cycles evaluated the effect of triggering ovulation with either 5,000 IU hCG in women with \(E_2\) levels ≥2,500 pg/mL but <4,000 pg/mL or 3,300 IU hCG for levels between 4,000 and 5,500 pg/mL, and reported rates of mild OHSS of 8.5% and 6.3%, moderate OHSS of 2.1% and 10.6%, and severe OHSS of 0% and 4.2% in the two groups, respectively (71). The authors concluded that low-dose hCG does not eliminate the risk of OHSS in high-risk patients, although the absence of a standard-dose control arm means that the effect of lower doses of hCG on the incidence or severity of OHSS cannot be gauged.

One possible drawback of low-dose hCG protocols is a potentially increased cycle cancellation rate (72, 75). This effect warrants further study before very low doses of hCG can be recommended.

In addition, it should be noted that the majority of data on the effectiveness of this strategy on reducing OHSS rates come from small, uncontrolled, and/or retrospective studies. The evidence to suggest that the risk of OHSS is lower after a reduced-dose hCG trigger will require further support from large prospective randomized controlled trials.

3. Cryopreservation of All Embryos Another alternative is the normal progression of IVF until oocyte pickup (OPU), followed by cryopreservation of embryos to be thawed and reimplanted at a later date when the patient’s serum hormone levels are not elevated. Although early OHSS associated with hCG administration may still occur (76–79), it is the increase in endogenous hCG associated with pregnancy that is responsible for secondary exacerbation of early OHSS or the development of late OHSS, and these more serious forms of the condition can thus be avoided (77, 80, 81). Where OHSS does occur after cryopreservation, the severity and duration of the condition appear to be reduced (82).

The major disadvantage of this technique is that the success rate of establishing a pregnancy using frozen/thawed embryos is generally lower than using fresh embryos (83). Although the introduction of vitrification, which reduces damage to the embryo by eliminating ice crystal formation within the tissue, may improve the chances of success, further large-scale studies are still required. To date, the evidence for the efficacy of cryopreservation in OHSS prevention has been conflicting (reviewed in Delvigne and Rozenberg [22]). This may be partly explained by different trial designs, patient populations, and cryopreservation techniques. The majority of elective cryopreservation studies reported in the literature have been retrospective and/or observational in design. One of the few prospective randomized controlled trials comparing elective cryopreservation with transfer of fresh embryos in 125 at-risk patients reported that four of 67 patients developed severe OHSS requiring hospitalization after fresh ET, compared with none of 58 after frozen ET; these differences were not statistically significant (37). One possible confounding factor in this study was that patients in both treatment arms received 20 g human albumin IV on the day of oocyte recovery, which may have had an impact on the results. In addition, the criteria used for defining the at-risk population—\(E_2\) ≥1,500 pg/mL on the day of hCG administration and ≥15 oocytes retrieved—were rather more conservative than those used by other investigators (84).

Further large randomized controlled trials of embryo or two pronuclei oocyte cryopreservation, sufficiently powered to identify any significant reductions in OHSS, are urgently needed, particularly as this technology will be critical for the success of the new, milder stimulation regimens and limited ET policies that are gaining increasing popularity. However, the true value of cryopreservation for the prevention of OHSS during IVF may be as an adjunct intervention in support of other more effective rescue techniques rather than as a stand-alone option.

4. Cycle Cancellation Cycle cancellation and withholding of hCG is the only guaranteed method for prevention of early OHSS (85). It should be noted that, in OI cycles without GnRH analog use, a natural LH surge may still result in ovulation and natural conception in some cases, resulting in the possibility of late OHSS. Thus, suitable contraceptive methods should be used to avoid this in high-risk cases.

Despite the success of cycle cancellation in the prevention of OHSS, most physicians are reluctant to use this method, particularly in IVF, where the financial burden of treatment and the patient’s psychological distress may be significant.
5. Alternative Agents for Triggering Ovulation  HCG has been used successfully to trigger ovulation for over 60 years. However, the relatively long serum half-life of hCG (86) results in a prolonged luteotropic effect, multiple corpus luteum development, and raised serum levels of E2 and P throughout the luteal phase (87), which increases the risk of OHSS (88). This risk is similar for urinary-derived and recombinant hCG (rHCG) (89). To prevent OHSS, alternative agents for triggering final oocyte maturation and ovulation have been investigated.

a. GnRHα. Continual application of a GnRHα results in receptor down-regulation and desensitization. However, in gonadotropin-only or antagonist-stimulated cycles, administration of a bolus of GnRHα results in a surge (flare) of gonadotropins (LH and FSH) released by the pituitary, mimicking the natural midcycle surge of gonadotropins and effectively stimulating ovulation and final oocyte maturation (90, 87). However, the total amount of gonadotropins secreted by the pituitary after a bolus of GnRHα is significantly reduced compared with the midcycle surge of gonadotropins, owing to differences in the duration and profile of the surge (90, 87).

Evidence from small-scale trials in OHSS high-risk patient populations suggests that this approach significantly reduces, or even eliminates, the incidence of OHSS. In one study of 28 high-risk patients, four of 13 patients (30.8%) in whom ovulation was triggered with hCG developed moderate or severe OHSS, compared with none of 15 patients who received a GnRHα (P <.05) (91). A larger study of 66 high-risk patients produced similar results, with 10 of 32 patients (31.3%) in the hCG control group developing OHSS, of which five (15.6%) were classed as severe cases, whereas no cases of OHSS were reported in the GnRHa treatment arm (P <.01). Based on the 95% CI of the odds ratio, those who received hCG triggering were at a 3.79 times greater risk of developing any form of OHSS and a 1.35 times greater risk of developing moderate or severe OHSS than those who were triggered with a GnRH antagonist (92).

However, it is important to note that, despite the fact that patients received a similar intensive LPS, conflicting results regarding the reproductive outcome were seen in the above-mentioned studies. Thus, in one study (92), a normal reproductive outcome was reported, whereas in another study (91), a disappointingly low ongoing pregnancy rate of 6% and a high early pregnancy loss rate (80%) were reported.

The first reports from prospective randomized clinical trials exploring the reproductive outcome after GnRHa triggering supported the notion of a poor clinical outcome when GnRHa was used to trigger final oocyte maturation, as an extremely high early pregnancy loss rate was seen despite luteal phase supplementation with vaginal P and oral E2 (93, 94). The negative outcome was ascribed to a luteal phase insufficiency, due to too low circulating endogenous LH levels (93, 95, 96). This was supported by good live-birth rates in frozen-thawed embryo replacement cycles in which embryos were derived from GnRHa-triggered cycles (97). Furthermore, a follicular fluid study concluded that OI with GnRHa secures a proper preovulatory follicular maturation and release of mature oocytes (98).

Subsequently a pilot study, exploring the possibility of rescuing the luteal phase with a small bolus of LH activity in the form of 1,500 IU hCG after GnRH agonist triggering, showed that good clinical pregnancy rates could be obtained if a bolus of 1,500 IU hCG was administered 35 hours after the triggering dose of GnRH agonist, that is, after the OPU (95). The results were subsequently corroborated in a large randomized controlled trial that included a total of 302 patients and showed a nonsignificant difference in live-birth rates when GnRHa supplemented with 1,500 IU hCG 35 hours later was used to trigger final oocyte maturation, compared with 10,000 IU hCG (96). Furthermore the retrieval of more mature oocytes (4%) in the GnRHa-triggered group supported previous clinical findings of a possible beneficial effect of the midcycle FSH surge on oocyte maturity (93, 99). Interestingly, one-third of patients in both study groups had at least 14 follicles ≥11 mm on the day of OI, a cut-off level that has previously been suggested to predict 87% of severe OHSS cases (100). However, no OHSS case was seen in the group of patients who used GnRHa to trigger final oocyte maturation, compared with two cases in the hCG group (96).

When a GnRHa is used to trigger ovulation, additional LPS is particularly important (101–105). At present there is no consensus on what form this should take (95). Apart from one bolus of hCG, microdoses of hCG, repeated doses of GnRHa, and daily rLH administration during the luteal phase are presently under investigation.

In oocyte donation cycles, however, the concept of GnRHa triggering of final oocyte maturation has been widely adapted, as the luteal phase can be disregarded. All studies until now show a total elimination of OHSS. Thus, the largest study of 2,077 stimulated donor cycles in 1,171 egg donors and reported an incidence of 1.26% (13/1,031 patients) of moderate or severe OHSS in the rhCG group compared with no cases in the GnRHa group (104).

In conclusion, GnRHa triggering of ovulation appears to be a very promising approach for high-risk patients, in conjunction with GnRH antagonist-stimulated cycles, but larger randomized controlled trials are needed to confirm its efficacy, applicability to normal responders, and the optimal LPS required.

6. Other Possible Strategies for Preventing OHSS

a. GnRH Antagonist Salvage. An initial decrease or plateau in serum E2 levels has been reported in some women in the 24–48 hours after the initial administration of a GnRH antagonist in IVF cycles, with no apparent impact on treatment outcome (106). Thus, it is possible that administration of an antagonist to patients with elevated serum E2 at risk of developing OHSS may provide a means of interrupting the development or progression of the condition while salvaging the current treatment cycle.

b. Intravenous Albumin and Hydroxyethyl Starch. Albumin is a major plasma-binding protein that may bind to the vasoactive agents responsible for the development of OHSS and facilitate their removal from the circulation. Additionally, albumin administration could increase plasma osmotic pressure, helping to maintain the intravascular volume and attenuate the effects of hypovolemia, hemocoencentration, and ascites (107, 108).

However, the evidence supporting the use of IV albumin for the reduction of OHSS is not strong. Together with potential side effects (109–111), the potential for worsening OHSS (112), and the risk of pulmonary edema in patients with diminished cardiac reserve (113, 114), this intervention cannot be recommended.
Hydroxyethyl starch (HES) solution has been suggested as an alternative to albumin. Only a small number of studies evaluating the benefits of HES in the prevention of OHSS have been reported; however, it is thought that, as a cheaper, potentially safer alternative to albumin, HES should be the first-line treatment.

c. Dopamine Agonists. Evidence exists for a dopaminergic component in the control of LH release in PCOS patients, and pretreatment with the dopamine agonist cabergoline (Cb2) before OI reduces ovarian response to FSH (115), making this a potential primary OHSS prevention measure in this population. However, Cb2 also acts at the VEGF receptor implicated in vascular hyperpermeability during OHSS (116–118), and studies have suggested a role for Cb2 in secondary prevention after ovarian stimulation.

In studies conducted so far, Cb2 appears to be effective in reducing, but not eliminating, the incidence of moderate OHSS and does not appear to affect ART outcome. Larger prospective randomized controlled trials are thus needed to confirm the efficacy and safety of Cb2 for primary prevention of OHSS in OI and as a secondary prevention measure after ovarian stimulation before IVF (119).

d. Glucocorticoids. Glucocorticoids and their synthetic derivatives have an inhibitory effect on the VEGF gene expression in vascular smooth muscle cells (120). By inhibiting vasodilation and preventing increases in vascular permeability, these agents can dampen the inflammatory response and prevent edema formation (121), thus offering a potential therapeutic intervention in the case of early signs of developing OHSS.

The data collected so far suggest that an optimized corticosteroid protocol may offer a means of reducing the incidence of OHSS in hyperresponders without having to cancel the cycle or perform costly oocyte aspiration. This method does not eliminate the risk of OHSS entirely, however, and the nonspecificity of action may result in undesirable side effects. Further studies are needed to determine optimal protocols and the effects of antiangiogenic activity on normal endometrial development during pregnancy.

7. Nonrecommended Strategies

a. Follicular Aspiration. Aspiration of granulosa cells from one ovary has been proposed as a means of inducing intraovarian bleeding and limiting the production of OHSS mediators while allowing continued contralateral ovarian development (122).

Despite the success of this technique in the hands of some investigators, the drawbacks of follicular aspiration are not trivial and include cost, patient discomfort, and increased requirement for invasive procedures under anesthesia. For these reasons, and in the presence of viable alternatives with a greater weight of evidence to support them, this approach cannot be recommended.

b. Aromatase Inhibitors. The aromatase enzyme catalyzes the rate-limiting step in the production of estrogen (123). Aromatase inhibitors may therefore help to reduce excessive E2 synthesis during ovarian stimulation and thereby reduce the risk of OHSS. No large trials have been conducted to evaluate the impact of aromatase inhibitors on OHSS in women with anovulatory infertility associated with PCOS. Clinical trials of aromatase inhibitors for ovarian stimulation in IVF have concentrated on their ability to increase the response to FSH in poor responders (114). Thus, although the antiestrogenic effects of these agents appear promising for reducing the risk of OHSS, aromatase inhibitors cannot yet be recommended in a clinical setting.

SUMMARY

There is no doubt that high ovarian response is mandatory for OHSS disease to develop. Nevertheless, the occurrence of late OHSS is mainly dependent on the presence of an evolving pregnancy, thus rendering the prediction of the disease difficult. In addition, the genetic predisposition of some patients to a high vasoactive response complicates the accuracy of several prognostic factors tested to date.

Much of the literature on OHSS prevention comprises retrospective, uncontrolled, and/or small studies. There are a number of reasons for the shortage of large prospective, randomized controlled trials. First, owing to the relative rarity of OHSS, very large sample sizes are required to identify a meaningful change in occurrence of the condition. Many of the reports of OHSS incidence in the literature are secondary to trials investigating other aspects of clinical outcome and, as such, are underpowered to identify significant differences in OHSS incidence. A further complicating factor is the potential seriousness of the condition, which makes it unethical to randomize a patient at high risk of developing OHSS to a placebo group. Nevertheless, evidence-based medicine requires that the clinician consider the current best evidence in making decisions about the care of individual patients.

Currently available treatment guidelines for the prevention of OHSS, such as those from the National Institute of Clinical Excellence and the European Society for Human Reproduction and Embryology, were produced several years ago (2004), and the 2006 American Society for Reproductive Medicine guidelines did not provide additional advice compared with the 2004 publication. Hence, these guidelines do not take into account the latest available evidence from the literature (Table 3).

We have reviewed the scientific literature on a variety of potential OHSS prevention methods, concentrating on the most recently available evidence. A summary of our findings is presented in Table 3. The balance of new evidence in the last 5 years has identified two treatment strategies that appear to be highly effective at reducing, or even preventing, the occurrence of OHSS, namely, GnRH antagonist protocols and triggering of final oocyte maturation with GnRHa—two strategies that may confer even greater risk reduction when used in conjunction. Other strategies that appear promising for halting the progression of imminent OHSS include antagonist salvage of the cycle, the use of HES, and dopamine agonists.

CLINICAL IMPLICATIONS OF THE REVIEW FINDINGS

OHSS is a preventable condition, and implementation of evidence-based prevention strategies should enable us to significantly reduce its occurrence. Recent clinical investigations into the prevention of OHSS have produced encouraging results. The evidence for GnRH antagonist use as part of treatment strategies to reduce the rate of OHSS is reassuring. In terms of hCG for ovulation triggering, although some evidence exists in support of lower doses without a negative impact on clinical outcomes, there is a need for further prospective randomized controlled trials to confirm the lower rates of OHSS. Finally, GnRHa triggering appears to be a promising new therapeutic strategy to further reduce OHSS; however, this also remains to be tested in a sufficiently large clinical trial, and remaining LPS issues still need to be resolved. Improved understanding of the pathogenesis of OHSS and more accurate predictive tests should facilitate more individualized IVF treatment protocols designed to produce the optimal ovarian response for each patient and minimize the occurrence of OHSS.

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