Review Article

Prediction of ovarian hyperstimulation syndrome

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Abstract OHSS is best defined as an iatrogenic condition caused by inflammatory mediators released by the hyperstimulated ovaries. OHSS is associated with significant physical and psychosocial morbidity and has been associated with maternal death. However, in most cases OHSS is self-limiting and requires supportive management and monitoring while awaiting resolution. Because OHSS is the most serious consequence of controlled ovarian stimulation, every attempt should be made to identify patients who are at highest risk. If the "at risk" women can be identified prior to or during treatment, targeted preventive measures can be applied.

Keywords: Elective cryopreservation, GnRH antagonist cycle, ovarian hyperstimulation syndrome

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INTRODUCTION

In vitro fertilization (IVF) has evolved over the last 40 years. The stimulated ovarian cycles greatly increase the likelihood of an IVF cycle resulting in a live birth, but at the same time, increases the risk of ovarian hyperstimulation syndrome (OHSS).

OHSS is best defined as an iatrogenic condition caused by inflammatory mediators released by the hyperstimulated ovaries. It causes fluid shift to third space in turn leading intravascular dehydration and further sequel of these processes. The traditional description of the syndrome generally includes a spectrum of findings, such as ovarian enlargement, ascites, hemoconcentration, hypercoagulability, and electrolyte imbalances. Theoretically, any woman undergoing ovarian stimulation with gonadotropins can develop OHSS. Because OHSS is the most serious consequence of controlled ovarian stimulation, every attempt should be made to identify patients who are at highest risk. If the "at risk" women can be identified prior to or during treatment, targeted preventive measures can be applied.

RISK FACTORS

There are primary risk factors based primarily on ovarian reserve tests which can be identified pretreatment. The secondary risk factors depend on the ovarian response during ovarian stimulation. New strategies that are being evaluated for the purpose of prediction have also been elaborated at the end [Table 1].

Primary risk factors (demographics and ovarian reserve)

(1) **Young age**: In the largest study to evaluate risk factors for OHSS, data from the Society for

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Table 1: Summary of pre- and in-treatment risk factors

Pretreatment risk factors	In-treatment risk factors
1.Young age (<30 years)	1.E2 levels
2.Low BMI	2.Number of follicles growing
3.PCOS	3.Number of oocytes retrieved
4.AMH levels	4.Number of embryos transferred
5.USS-AFC and PCO morphology	5.Pregnancy achieved
6.h/o OHSS	

BMI, body mass index; E2, estradiol; AFC, antral follicle count; PCOS, polycystic ovarian syndrome; PCO, polycystic ovary; OHSS, ovarian hyperstimulation syndrome.

Assisted Reproductive Technology (SART) database[1] were utilized and showed that among 214,219 ART cycles, younger age, black race, ovulation, tubal factor, and unexplained infertility were all associated with an increased risk of OHSS. Studies have shown that more than 60% of women, who developed OHSS, were under the age of 35.

(2) **Low body mass index (BMI):** There is conflicting reports of relationship with BMI and risk of OHSS. Whereas low BMI is thought to increase the risk of OHSS,[2] it also commonly observed in women with polycystic ovary syndrome (PCOS), who are often over-weight/obese.[3]

(3) **Anti-Müllerian hormone levels:** The serum levels of anti Mullerian hormone (AMH) are independent of intercycle variation but the sample must be assessed within 24 hours of collection. It has widely been used to decide on the treatment protocol and starting dose of stimulation for women undergoing in vitro fertilization (IVF). The usefulness of AMH levels in predicting OHSS has been evaluated in many studies. In a comparative study by Ocal *et al.* in 2011, predictive value of AMH and antral follicle count (AFC) was studied in agonist cycles by comparing 41 cases of OHSS versus 41 cases of non-OHSS.[4] The cutoff value for AMH 3.3 ng/mL (23.57 pmol/L) provided the highest sensitivity (90%) and specificity (71%) for predicting OHSS. In a retrospective cohort study carried out in antagonist cycles using long acting corifollitropin alfa was used for stimulation, the optimal thresholds for identifying excessive responders were 3.52 ng/mL (25.14 pmol/L) for AMH (sensitivity 89.5, specificity 83.8).[5] There is no consensus on the AMH cutoff level that should be used for prediction of OHSS. It has been variously described ranging from 1.5 ng/mL (10.7 pmol/L)[6] to 6.95 ng/mL (49.64 pmol/L).[7]

(4) **USG features:** AFC and polycystic ovarian (PCO) morphology − Women with PCO morphology, whether or not they express the PCO syndrome, are at increased risk of OHSS.AFC has been found to be reliable predictors of ovarian response to stimulation and high numbers especially in patients with PCO morphology and/or PCOS have been correlated with OHSS. There is no clear cutoff defined in literature, but AMH >35 pmol/L and AFC >25 are commonly used in clinical practice. A prospective cohort study was carried out to estimate the probability of live birth, adverse treatment outcome, and extremes of ovarian response at different AFC cutoff levels in a large prospective cohort of women undergoing IVF treatment.[8] The authors concluded that the risk of moderate or severe OHSS is 2.2% with AFC of ≤24, the risk increases to 8.6% at AFC of ≥24. The risk of OHSS increases further to 11% if there are signs and symptoms of PCOS.

(5) **Polycystic ovarian syndrome:** Women with PCOS by definition have high AFC, putting them at high risk of OHSS. Ovarian response to ovarian stimulation vary widely among patients with PCOS and when some patients are more likely to show resistance to controlled ovarian hyperstimulation (COH), other experienced an exaggerated response.

History of OHSS

Secondary risk factors

The secondary risk factors depend on ovarian response to ovarian stimulation. The ovarian response to exogenous stimulation may indicate an increased risk of OHSS, but is not as sensitive or specific as ovarian reserve in predicting the risk of OHSS. Features of concern include a large number of follicles, high serum estradiol (E2) concentration, and a high number of oocytes collected. There is no agreement on what levels should be used as threshold values to determine "high-risk" cycles. The following are commonly used in clinical practice: E2 >15,000 pmol/L or >19 medium/large follicles at the end of stimulation and >20 oocytes collected.

(1) **E2 levels:** Traditionally, a rapid increase in E2 levels and serum E2 concentrations >2500 pg/mL was thought to be important predictive factors, although recent studies have concluded that it is incapable of independently forecasting OHSS. The poor value of serum E2 in predicting the risk of OHSS has been described in long protocol gonadotropin-releasing hormone (GnRH) agonist cycles.[4,9] The European society of human reproduction and embryology (ESHRE) guideline for ovarian stimulation also does not recommend the use of E2 for monitoring ovarian response.[10]

(2) **Number of follicles growing:** Several prospective studies have demonstrated that a high number of growing follicles is an independent predictor of OHSS. In a prospective cohort study of 624

patients undergoing their first IVF cycle in Sweden, multivariate analysis identified a model to predict the occurrence of OHSS with 82% sensitivity and 90% specificity if the following thresholds were met: >25 follicles at retrieval; >19 large/medium-sized follicles before human chorionic gonadotropin (hCG); and >24 oocytes retrieved.[11] Papanikolaou *et al.* in their prospective cohort of 2524 GnRH antagonist cycles have identified the combination of ≥18 follicles on ultrasound (diameter ≥11 mm) and E2 ≥5000 ng/L on the day of hCG trigger to be more useful (sensitivity 83%, specificity 84%) than E2 concentrations alone in the prediction of severe OHSS.[12]

(3) **Number of oocytes retrieved:** In clinical practice, if more than 20 oocytes are collected, women are offered elective cryopreservation to circumvent the risk of OHSS. A retrospective analysis of 2253 consecutive cycles of IVF was done to find thresholds oocyte numbers that would optimally predict OHSS.[13] Of these, 289 cycles resulted in the retrieval of 20 or more oocytes, and only these were evaluated for inclusion in the study. Receiver operator characteristic (ROC) curves were calculated to determine threshold values that might predict OHSS in women with ≥20 oocytes. For the prediction of early onset OHSS, ROC curves showed that an optimal balance between sensitivity and specificity was achieved using thresholds of 24 oocytes (79%, 60%). The authors recommended that cryopreservation of all embryos may be offered to these women. A large population-based registry study suggests a shift at approximately 18 to 20 oocytes where the cumulative delivery rate per aspiration levels off and, at the same time, the incidence of severe OHSS increases more rapidly.[14] Hence, there is evidence to the use of cutoff at 20 oocytes. Utilizing the SART registry, analysis of 256,381 cycles demonstrated that retrieval of >15 oocytes significantly increases the risk of OHSS without improving live-birth rate in fresh autologous cycles.[1]

(4) **Number of embryos transferred:** In the year 2007, in United Kingdom, one in four births from IVF were multiple births, which was 20 times higher than natural conception.[15] Multiple pregnancy increases the risk of various complications for the mother. The chance of developing OHSS is also higher in the event of multiple births. Human Fertility and Embryology Authority launched a campaign "One at a time" with a target of reducing multiple births to 10%, which advocates the policy of single embryo transfer.[15]

(5) **Pregnancy achieved:** Pregnancy occurring in a treatment cycle increases the risk of, specifically, late OHSS due to the effect of hCG. In a study by Mathur *et al.*, in cycles that resulted in conception, OHSS was appreciably more likely to be severe than in those not ending in conception ($P < 0.001$).[9] In the same study, the OHSS became more severe as the number of gestation sacs increased. Eliminating the chance of pregnancy by elective cryopreservation of all embryos is associated with the elimination of late OHSS, though the early form can still occur.[9]

MODERN IVF

The IVF has evolved over years and the stimulation regimens have become safer over years. Still today despite liberal use of antagonist cycles, agonist trigger, and elective cryopreservation, "OHSS-free clinic" is more of an aspiration than a reality.

The risk factors discussed above should be evaluated with a perspective of modern day IVF practice. A recent study published evaluated whether ovarian reserve or ovarian response to the stimulation was a better predictor of OHSS.[16] A total of 1492 cycles were carried out over 18 months. Moderate/severe OHSS occurred in 24 cycles (1.6%). AMH of 35 pmol/L and/or AFC of 20 or more identified 18/24 (76%) OHSS cases. The optimal thresholds for predicting OHSS were 22.5 pmol/L for AMH (sensitivity 87.5%, specificity 60.6%), 19.5 for AFC (sensitivity 70.8%, specificity 67%), and 9.5 for egg numbers (sensitivity 83.5%, specificity 62.7%). Peak E2 levels had no predictive value. The number of eggs retrieved would be a more useful measure of ovarian response than E2, but this information is only available after the trigger has been administered, thereby restricting its clinical value. It was concluded that ovarian reserve parameters are better than ovarian response at predicting the risk of significant OHSS in GnRH antagonist cycles in modern clinical practice. Relying on measures of ovarian response during stimulation may provide false reassurance in women with high ovarian reserve undergoing GnRH-antagonist cycles. Patients with a high ovarian reserve are at risk of OHSS even if their ovarian response is not excessive. Decisions about preventative measures should be based on ovarian reserve rather than ovarian response. ESHRE guideline for ovarian stimulation recommends the assessment for high response is advised prior to start of stimulation and does not recommend the use of E2 for monitoring ovarian response.[10] A recent systematic review and meta-analysis showed a higher live-birth rate in elective frozen embryo transfer (eFET) cycles

than fresh cycles in hyper-responders [relative risk (RR) = 1.16, 95% confidence interval (CI) 1.05–1.28].[17] The same meta-analysis showed that the risk of moderate/severe OHSS was significantly lower with eFET than fresh cycle (RR 0.42, 95% CI 0.19–0.96). This adds support to the concept that OHSS prevention can be accomplished without sacrificing overall outcome, by judicious use of GnRH agonist trigger and elective freeze all.

PRACTICE POINTS

(1) Ovarian reserve: AMH and AFC should be performed for every patient prior to start of the stimulation. Dose should be decided based on reserve testing/response of previous cycle. Commonly used cutoff for AMH − 35 pmol/L and for AFC − >20, should be considered as risk for OHSS.
(2) Ovarian response should be monitored with ultrasound scan for number of follicles. >19 large/medium-sized follicles before trigger are at risk for OHSS.
(3) E2 measurements are not reliable and can provide "false reassurance".
(4) High risk patients (based on ovarian reserve) should be offered agonist trigger and elective cryopreservation.
(5) Egg numbers >20 should be offered elective cryopreservation.

NEWER MARKERS UNDER EVALUATION/ FUTURE ASPECTS

Melatonin levels in follicular fluid and concentration of melatonin receptor 2 (MT2) expression in granulose cells have been found to be increased in OHSS.[18]

VEGF levels show that the serum and follicular fluid VEGF concentrations are significantly higher than those of control group on the day of ovum retrieval, indicating that VEGF may play an important role in the pathogenesis of OHSS. Serum VEGF concentrations in combination with consecutive E2 measurements can assist in predicting OHSS.[19]

Soluble urokinase plasminogen activator receptor in the preovulatory follicular fluid has been found to be significantly lower in women developing OHSS, but the authors said that it did not provide a satisfactory predictive value.[20]

Proteomic biomarkers: Qualitative proteomic analysis has been explored to provide deeper insights into pathophysiology of OHSS. Fifty-seven such proteins have been identified that are differentially expressed in OHSS patients with PCOS. This analysis identified haptoglobin, fibrinogen, and lipoprotein lipase as potential biomarkers to discriminated OHSS in patients with PCOS.[21]

Serum miRNAs are differentially expressed in patients with PCOS likely to suffer from severe OHSS. The miR-16 and miR-223 expression levels were found to be significantly reduced in the patients who were likely to develop severe OHSS than in the control subjects who were likely to develop mild or no OHSS.[22] These can potentially be used as novel noninvasive biomarkers to accurately predict OHSS before COH for patients with PCOS.

CONCLUSION

As the old adage goes, prevention is better than cure. As it stands, there is no perfect strategy which completely eliminates OHSS. There are factors however which we can take into consideration to reduce its incidence. Being aware of the risk factors for OHSS will allow clinicians to pre-empt its occurrence and thereby reduce its incidence during ovarian stimulation. It also should be noted, however, that women without any risk factors can develop OHSS as there is some degrees of hyperstimulation in all stimulation protocols. The possibility of OHSS therefore should always remain at the back of the clinicians mind in any woman undergoing COH.

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Conflicts of interest
There are no conflicts of interest.

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