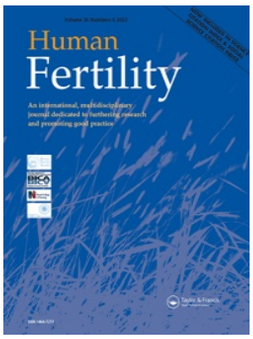

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POLICY AND PRACTICE

Prevention of ovarian hyperstimulation syndrome (OHSS): British Fertility Society policy and practice guideline

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ABSTRACT

This British Fertility Society (BFS) Policy and Practice guideline aims to support clinicians in preventing ovarian hyperstimulation syndrome (OHSS) in patients undergoing gonadotropin ovarian stimulation. A systematic literature search of the medical databases was performed. The Guideline Development Group (GDG) identified the risk factors of OHSS before and during ovarian stimulation. The relation of different pre-treatment measures and different ovarian stimulation protocols with OHSS was evaluated. The optimal monitoring during treatment was assessed. The current evidence on preventive strategies during and after ovarian stimulation and the available adjuvant preventive agents were examined. Based on this, the GDG developed evidence-based, graded recommendations for clinical practice. The evidence was evaluated within context, considering the effectiveness, cost and practical problems of assisted reproductive technology for patients and healthcare providers. Early identification and application of preventive measures identified in this guideline may reduce the incidence of OHSS or reduce its severity. Suggestions for future research on OHSS prevention are provided.

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Ovarian hyperstimulation syndrome; prevention; assisted reproductive technology; gonadotropins; ovarian stimulation

Introduction

Ovarian hyperstimulation syndrome (OHSS) is the most important short-term complication of supraphysiologic ovarian stimulation. Salient features of OHSS include ovarian enlargement and increased vascular permeability leading to third space fluid accumulation, intravascular dehydration and an increased risk of thrombo-embolism. OHSS can cause serious morbidity and, rarely, mortality. There is no universally accepted classification of OHSS severity, with the Royal College of Obstetricians and Gynaecologists (RCOG) classification being widely used in the UK (Royal College of Obstetricians and Gynaecologists, 2016).

The true incidence of OHSS is not known due to a lack of standardized classification and the absence of mandatory reporting, apart from a requirement of the Human Fertilization and Embryology Authority (HFEA) for UK clinics to report cases of severe or critical OHSS. Observational studies prior to the widespread application of Gonadotropin-Releasing Hormone (GnRH) antagonist found the risk of moderate or severe OHSS to range between 3 to 8% of stimulated IVF cycles (Delvigne & Rozenberg, 2002). A more recent UK study found moderate or severe OHSS (by the RCOG classification) in 1.6% of GnRH antagonist cycles (Sood et al., 2022). In 2021–2022, 66 cases of severe or critical OHSS were reported by UK clinics, amounting to 0.1% of IVF cycles (Human Fertilisation and Embryology Authority, 2022).

The course of OHSS is more prolonged and severe in the presence of pregnancy or exposure to human Chorionic Gonadotropin (hCG). In UK practice, most cases of severe OHSS are managed as inpatients, sometimes with recourse to intravenous colloids and paracentesis, while mild or moderate cases may be safely managed on an outpatient basis with monitoring and support (Royal College of Obstetricians and Gynaecologists, 2016).

This evidence-based guideline aims to support clinicians in preventing OHSS in women undergoing gonadotropin ovarian stimulation. It represents the views of the Guideline Development Group (GDG) which were reached after careful consideration of the

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scientific evidence available at the time of preparation. It is produced as an aid to good clinical practice and clinical decision-making. The advice expressed herein is not binding on professionals, and the British Fertility Society (BFS) cannot guarantee correctness, completeness or accuracy of the guideline in every respect. The BFS is not liable for damages related to the use of the information contained herein.

Materials and methods

The proposal for this guideline and membership of the GDG were approved by the Executive Committee of the BFS. The GDG applied the Population, Interventions, Comparisons and Outcomes (PICO) model to develop a search strategy for the interventions used in prevention of OHSS and their application in clinical practice.

A systematic literature search of the electronic databases MEDLINE/PubMed, SCOPUS, EMBASE, CENTRAL, DARE and the Cochrane Library was performed to identify systematic reviews and primary studies investigating predictive factors of OHSS and interventions aimed at reducing the risk of OHSS. Additional studies were identified through previous experience of the authors and reference lists of the studies obtained by the search. Where a high-quality systematic review was found, the search continued to identify randomized controlled trials (RCTs) published since the date of the review. The systematic search was conducted in March 2024, and limited to the English language and where full text was available. More recent publications identified by peer-review were also included.

The database search was undertaken using a combination of keywords including OHSS, *In Vitro* fertilization (IVF), intracytoplasmic sperm injection (ICSI), ovarian stimulation, oocyte donation, oocyte cryopreservation, in vitro maturation (IVM), ovarian drilling, progestin-primed ovarian stimulation (PPOS), ovulation trigger, gonadotropins, personalization, coasting, luteal phase support, clomiphene, letrozole, metformin, aspirin, melatonin, inositol, hydroxyethyl starch, calcium, cabergoline, diosmin, ketoconazole, vitamin D, albumin and vascular endothelial growth factor (VEGF) blockade. The list of the included interventions was finalized through consensus between all authors. Studies pertaining to the management of OHSS and interventions for complications associated with OHSS were excluded.

The evidence was assessed by all authors and the recommendations were graded using the RCOG criteria (Royal College of Obstetricians and Gynaecologists, 2020). The study design was appraised, and the quality of the methodology was assessed based on blinding, allocation concealment, appropriate control groups and other risks of bias. The GDG summarized the data in a narrative form to include the characteristics, quality, efficiency and conclusions of the studies included. The format including 'Mechanism of Action', 'Evidence and Classification', 'Recommendation and Grade' and 'Context' was adopted for clarity and uniformity of reporting on the different interventions. Where the quality of the evidence was poor, the grading of the recommendation was downgraded, and this is discussed further in the context.

Population	Women undergoing ovarian stimulation with gonadotropins for IVF, ICSI, oocyte donation or oocyte cryopreservation
Interventions	Various
Comparisons	No intervention or compared with another intervention or placebo
Outcomes	All OHSS, severe OHSS, hospitalization for OHSS

Evidence level	Classification criteria
1++	High-quality meta-analyses, systematic reviews of RCTs or single RCTs
1+	Well-conducted meta-analyses, systematic reviews of RCTs or single RCTs
1−	Meta-analyses, systematic reviews of RCTs or single RCTs with high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies
2+	Well-conducted case-control or cohort studies
2−	Case-control or cohort studies with high risk of confounding, bias or chance
3	Non-analytical studies (case reports, case series)
4	Expert opinion

Grade of recommendation	Supporting evidence
A	Directly applicable studies rated 1++ or 1+
B	Directly applicable studies rated 2++ or extrapolated evidence from studies rated 1++ or 1+
C	Directly applicable studies rated 2+ or extrapolated evidence from studies rated 2++
D	Evidence level 3 or 4 or extrapolated evidence from studies rated 2+
GPP	Best practice based on expert opinion

Prediction of OHSS

Several demographic and clinical factors are associated with an increased risk of developing OHSS. Identifying patients at a high risk of OHSS may allow clinicians to ensure appropriate counselling and targeted preventive measures.

Patient demographic and clinical characteristics

A cohort study using the Society for Assisted Reproductive Technology database found that compared to white women, black women were more likely to suffer from OHSS (Luke et al., 2010). There was no statistically significant difference between white, Asian and Hispanic women in the risk of severe OHSS.

A recent study on patients classed as high responders and treated with GnRH agonist trigger and freeze-all found that ethnicity was not a predictive factor in development of mild OHSS in this situation (Fernández-Sánchez et al., 2023).

A retrospective study of patients with polycystic ovary syndrome (PCOS) undergoing assisted reproduction found BMI to be slightly lower among those who developed OHSS compared to those who did not (23.72 ± 3.54 vs 24.08 ± 3.57) (Sun et al., 2020). A systematic review found no difference in the incidence of OHSS in patients with BMI ≤ 25 or >25 (Koning et al., 2012).

An inverse association between age and OHSS risk has been demonstrated in several studies, but without a clinically useful cut-off identified for either an increased or reduced risk of OHSS. Younger age was identified as a risk factor, together with high ovarian reserve and a lower requirement for gonadotropins in a multivariate logistic regression analysis of 33 cases of moderate or severe OHSS in 300 consecutive IVF cycles predominantly using GnRH agonist in a Chinese population (Ma et al., 2020). A UK observational study of 2362 consecutive GnRH agonist cycles found that patients with late-onset OHSS were significantly younger than those without OHSS (median (range) 32 (28–38) years vs 34 (19–49) years), but there was no statistically significant difference between patients with early-onset OHSS and those without OHSS (Mathur et al., 2000). In GnRH antagonist cycles with hCG trigger, women who developed OHSS were found to be younger than women who did not develop OHSS (mean ± SD 32.8 ± 3.5 years vs 34.8 ± 4.5 years) (Sousa et al., 2015).

Several studies have identified polycystic ovarian morphology on ultrasound as well as PCOS as risk factors for OHSS (Jayaprakasan et al., 2012; Luke et al., 2010; MacDougall et al., 1992; Mathur et al., 2000; Swanton et al., 2010). A meta-analysis of 11 studies identified a significantly higher risk of OHSS in women with PCOS compared to women without this diagnosis (OR 4.96, 95% CI 3.73–6.60, $I^2 = 0$) (Sha et al., 2019).

Pre-stimulation patient characteristics

Serum anti-mullerian hormone (AMH) concentrations and Antral Follicle Count (AFC) are markers of ovarian reserve that have been shown to predict the risk of OHSS.

Several cohort studies on women undergoing ovarian stimulation in GnRH agonist cycles have found elevated AMH to be a marker for the risk of OHSS, with varying thresholds and levels of sensitivity and specificity (Aghssa et al., 2015; Lee et al., 2008; Nakhuda et al., 2006; Ocal et al., 2011; Salmassi et al., 2015).

A cohort study on GnRH antagonist cycles using corifollitropin examined the risk of excessive ovarian response (defined as >20 oocytes collected) rather than the risk of established OHSS. Receiver-Operating Curve (ROC) analysis showed the optimal AMH threshold for identifying patients with >20 oocytes retrieved was 3.52 ng/mL (25.5 pmol/l; 1 ng/ml = 7.18 pmol/l), with a sensitivity of 89.5% and specificity of 83.8% (Polyzos et al., 2013).

The predictive value of ovarian reserve markers to identify the risk of moderate or severe OHSS in GnRH antagonist cycles with daily FSH dosing was studied by Sood et al. (2022) in a cohort of 1492 consecutive cycles. AMH was measured within 6 months of the start of stimulation using a Roche Elecsys assay. AMH concentration of 22.5 pmol/l yielded the best combination of sensitivity (87.5%) and specificity (60.6%) in predicting moderate or severe OHSS. A higher concentration of 35 pmol/l was associated with lower sensitivity (54.2%) but improved specificity (99.1%), with positive and negative predictive values of 4.4% and 80.7% respectively.

In GnRH agonist cycles, AFC was found to be a predictor of the risk of OHSS by Ocal et al. (2011), Jayaprakasan et al. (2012) and Ashrafi et al. (2015). Jayaprakasan et al. (2012) documented a risk of moderate or severe OHSS of 2.2% with AFC of <24, and 8.6% with AFC of >24. Polyzos et al. (2013) found that AFC of >16 predicted the risk of excessive ovarian response in GnRH antagonist cycles using corifollitropin. In GnRH antagonist cycles with daily FSH dosing, Sood et al. (2022) found that an AFC cut-off of 20 was associated with a sensitivity of 54.2%, specificity

72.2%, positive predictive value 3.1% and negative predictive value of 99% for moderate or severe OHSS.

The risk of OHSS is higher in women with a predicted high response to ovarian stimulation as shown by young age, PCO morphology, PCOS, raised AMH and raised AFC. Evidence level 2++

Ovarian response to stimulation

The ovarian response to stimulation has been investigated as a predictor of OHSS using oestradiol concentrations and follicle number at the end of the stimulation period, and the number of oocytes retrieved.

Elevated oestradiol (E2) levels during ovarian stimulation have been found by some investigators to be associated with increased OHSS risk in patients receiving long protocol GnRH agonist treatment (Delvigne & Rozenberg, 2002; Hendriks et al., 2004; Lee et al., 2008), although this has not been found in relation to late OHSS in such cycles (Lyons et al., 1994; Mathur et al., 2000).

E2 levels were found to be a poor predictor of the risk of OHSS in GnRH antagonist cycles by Papanikolaou et al. (2006), especially for late-onset and severe OHSS. Similarly, Sood et al. (2022) found that E2 levels did not distinguish between OHSS and non-OHSS cycles in women receiving GnRH antagonist.

The number of follicles developing in response to stimulation has been found to correlate with the risk of OHSS, for both GnRH agonist and antagonist cycles (Danninger et al., 1996; Griesinger et al., 2016; Ma et al., 2020; Papanikolaou et al., 2006; Tarlatzi et al., 2017). The threshold diameter for inclusion of follicles in this count has varied from 10 mm (Tarlatzi et al., 2017) to 11 mm (Griesinger et al., 2016; Papanikolaou et al., 2006) and 12 mm (Ma et al., 2020). In an analysis of 2433 women who received hCG trigger in a GnRH antagonist cycle, Griesinger et al. (2016) found that a threshold of 19 follicles $\geq$ 11 mm on the day of hCG identified a risk of moderate-to-severe OHSS (sensitivity and specificity 62.3% and 75.6%, respectively) and of severe OHSS (sensitivity and specificity 74.3% and 75.3%, respectively). The multivariate logistic regression analysis by Ma et al. (2020) found that the number of follicles over 12 mm was the best predictor of moderate or severe OHSS in Chinese women undergoing GnRH antagonist regime with hCG trigger. The presence of 17 follicles predicted OHSS with a sensitivity and specificity of 84.85% and 77.15%, respectively (Ma et al., 2020).

E2 concentration in response to ovarian stimulation is a poor predictor of OHSS risk, especially for late-onset OHSS. Evidence level 2−

Increased number of follicles of greater than 10 mm diameter on the day of trigger predicts an increased risk of OHSS. Evidence level 2+

Studies in both GnRH antagonist and agonist cycles have shown an increased risk of OHSS with increased number of oocytes retrieved (Chen et al., 2015; Drakopoulos et al., 2016; Magnusson et al., 2018; Mathur et al., 2000; Sood et al., 2022). Sood et al. (2022) identified an oocyte number of 20 as providing sensitivity of 25% and specificity of 93% (negative predictive value 98.7%) for moderate or severe OHSS in GnRH antagonist cycles. In a retrospective analysis, Magnusson et al. (2018) cross-linked data collected from the Swedish National Quality Registry of Assisted Reproduction for the years 2007–2014 with the Swedish National in-patient Register. The cumulative live birth per oocyte collection rose with oocyte number until a maximum of 19 oocytes. The incidence of severe OHSS increased significantly with increasing number of retrieved oocytes. The increase had a steeper slope from 18 oocytes where the incidence of severe OHSS was 1%, reaching 2.5% at 25 oocytes retrieved. A retrospective study by Chen et al. (2015) found that the perceived risk of OHSS increased significantly above an oocyte number cut-off of 12, but they did not report the actual incidence of OHSS in their patients.

Retrieval of 20 or more oocytes predicts an increased risk of OHSS. Evidence level 2++

All patients undergoing gonadotropin ovarian stimulation should be advised about the risk of OHSS. Grade GPP

Patients with a predicted high response to gonadotropins based on clinical features or ovarian reserve tests should be counselled about their elevated risk of OHSS and specific preventive measures should be considered (see below). Due to variation between assays, it is not possible to be categorical about a threshold of AMH that constitutes a high risk, however, levels above 22.5 pmol/l have been shown to have an optimum balance of sensitivity and specificity. A higher AMH threshold is associated with greater specificity but lower sensitivity (see text). AFC above 20 has been associated with an increased risk of OHSS. Grade B

E2 concentrations following stimulation should not be used on their own to determine whether

preventive measures for OHSS are indicated. Women with a high ovarian reserve should be considered at increased risk of OHSS even in the presence of E2 levels below arbitrary thresholds. Grade D

The number of recruited follicles on the final ultrasound scan prior to trigger should be considered in planning the nature of the trigger. If more than 17–19 follicles greater than or equal to 11-12 mm in diameter are observed on day of trigger, preventive measures should be considered. Grade C

If 20 or more oocytes are retrieved, consideration should be given to preventive measures, such as elective freeze-all. Grade B

The GDG considered that several risk factors for OHSS have been identified, but these are not exhaustive, either individually or in combination, due to the significant overlap between the values of various parameters in patients with and without OHSS. As a result, all patients undergoing gonadotropin stimulation should be considered potentially at risk of OHSS. Establishing evidence-based cut-offs is at present difficult. However, the GDG felt that the evidence allows it to propose cut-offs for follicle and oocyte number which clinicians may find useful. Clinical judgement and patient counselling remain key to decision-making in individual cases. Clinicians should bear in mind that severe OHSS has been described in situations that would be considered 'low-risk' by common criteria of ovarian response (Delvigne & Rozenberg, 2002).

Prevention of OHSS prior to ovarian stimulation

Pre-treatment with combined oral contraceptive pill (COCP)

COCP pre-treatment has been used in clinical practice to aid scheduling of treatment cycles and help synchronize the recruitment of a cohesive cohort of follicles. It is plausible that these actions may affect the risk of OHSS.

A Cochrane meta-analysis identified two RCTs of COCP pre-treatment in women undergoing GnRH antagonist cycles, which included OHSS incidence as an outcome. No difference was identified in the incidence of OHSS between COCP and control groups (OR 0.98, 95% CI 0.28 to 3.40; 2 RCTs; 642 women; $I^2 = 0\%$, low-quality evidence) (Farquhar et al., 2017).

The risk of OHSS in GnRH antagonist cycles is not altered by COCP pre-treatment. Evidence Level 1++

COCP pre-treatment should not be considered for reducing the risk of OHSS. Grade A

Ovarian drilling

Ovarian drilling has endocrine effects including a reduction in androgen, luteinizing hormone (LH) and AMH levels and restoration of the pituitary-ovarian feedback mechanism in women with PCOS. It is plausible that these effects may alter the incidence of OHSS in subsequent controlled ovarian stimulation.

A Cochrane review in 2020 identified a single trial and found no impact of laparoscopic ovarian drilling prior to IVF on the risk of OHSS in women with PCOS (1 RCT; OR 0.27, 95% CI 0.04 to 1.69, n = 50) (Bordewijk et al., 2020). A further RCT in which 34 women with PCOS and a history of at least two failed IVF cycles were randomized to laparoscopic ovarian drilling or no surgery prior to undergoing IVF using GnRH antagonist regime with hCG trigger reported a lower incidence of OHSS (severity and ascertainment not described) in the group that underwent ovarian drilling (1/17 vs 6/17, p = 0.04) (Moini et al., 2023).

The RCT showing a potential benefit of ovarian drilling in reducing the risk of OHSS included a small number of participants with two previous failed cycles and did not include the use of GnRH agonist trigger and freeze-all. The severity of OHSS and the mode of ascertainment of OHSS are not described. Moreover, ovarian drilling is an invasive procedure and carries associated risks.

There is insufficient evidence to conclude whether laparoscopic drilling prior to controlled ovarian stimulation reduces the risk of OHSS. Evidence Level 1−

Ovarian drilling should not be considered for reducing the risk of OHSS. (Grade C)

GnRH agonist vs. GnRH antagonist

Both GnRH agonist and GnRH antagonist protocols suppress the endogenous LH surge, allowing efficient controlled ovarian stimulation. However, the mechanism of action differs - agonists cause down-regulation of pituitary GnRH receptors and desensitization of gonadotrophs, while antagonists act via competitive binding to GnRH receptors. GnRH antagonist use also provides the option to trigger oocyte maturation with a GnRH agonist rather than hCG.

General IVF population

A meta-analysis of 73 RCTs, 36 of which reported on OHSS, revealed a lower incidence of any grade of OHSS in GnRH antagonist cycles (OR 0.61, 95% CI 0.51 to 0.72, n = 7,944; $I^2 = 31\%$, moderate-quality evidence). Most studies utilizing GnRH antagonist protocols employed an hCG trigger for final oocyte maturation. However, some studies used a GnRH agonist trigger in antagonist cycles to further reduce OHSS risk, particularly in high responders (e.g. PCOS patients). The evidence suggests that assuming an 11% risk of OHSS following GnRH agonist protocol, the risk following GnRH antagonist protocol would be between 6% and 9%. Additionally, GnRH antagonist cycles exhibited a lower incidence of cycle cancellation for a perceived risk of OHSS compared to GnRH agonist cycles (OR 0.47, 95% CI 0.32 to 0.69; 19 RCTs, n = 4256, $I^2 = 0\%$). Twelve RCTs reported on live birth rate, and no difference was found between the groups (Al-Inany et al., 2016).

A subsequent systematic review and meta-analysis confirmed that antagonist use resulted in significantly lower OHSS incidence rates than agonist in the general population (22 trials, 5598 couples; RR 0.63, CI 0.50–0.81. $I^2 = 0$). All studies in this meta-analysis used hCG triggers in cycles with GnRH antagonist protocols. The study did not report on live birth rates; however, it reported lower ongoing pregnancy rates after the use of antagonists (RR 0.89, 95% CI 0.82–0.96. $I^2 = 0\%$). There was no difference in ongoing pregnancy rate between antagonist and agonist when a fixed antagonist protocol was used without oral hormonal programming (9 trials, 3327 couples; RR 0.94, 95% CI 0.83–1.05, $I^2 = 0\%$) (Lambalk et al., 2017).

Another meta-analysis found that the antagonist treatment significantly reduced the OHSS rate compared to the long-acting follicular agonist (RR 1.63; 95% CI 1.15, 2.32; p = 0.0058; $I^2 = 0\%$) (Yang et al., 2021).

GnRH antagonist protocols are associated with a lower risk of OHSS compared with GnRH agonist protocols in the general population. Evidence levels 1+

Predicted normal responders

A meta-analysis of 21 RCTs found that the incidence of OHSS was significantly lower with the use of GnRH antagonist compared to agonist protocol (OR 0.69, 95% CI 0.57 to 0.83, n = 5,763; $I^2 = 15\%$). Additionally, despite the GnRH antagonist protocols resulting in fewer oocytes being retrieved, there were no significant differences observed in ongoing pregnancy rates and live birth rate. GnRH antagonist group retrieved significantly fewer oocytes compared to the agonist group (mean difference −1.41, 95% CI −1.84 to −0.99). Despite this, there were no significant differences observed in ongoing pregnancy rates (OR 0.88, 95% CI 0.77 to 1.00) or live birth rates (OR 0.95, 95% CI 0.74 to 1.09) between the two groups (Wang et al., 2017).

GnRH antagonist protocols are associated with a lower risk of OHSS compared with GnRH agonist protocols in predicted normal responders. Evidence level 1+

Predicted high responders

In PCOS patients, a recent meta-analysis revealed that using GnRH antagonist protocol significantly reduced the risk of OHSS compared to long GnRH agonist protocols (9 RCTs; OR 0.65, 95% CI 0.52 to 0.82, n = 1,114; $I^2 = 0\%$). All included studies used hCG trigger. Additionally, there were no significant differences in miscarriage rate, live birth rate (one RCT), or ongoing pregnancy rate between the GnRH antagonist protocols and the long GnRH agonist protocol (RR = 0.92, 95% CI: 0.78 to 1.08; p = 0.31; $I^2 = 0\%$; high-quality evidence) (Kadoura et al., 2022).

GnRH antagonist protocols are associated with a lower risk of OHSS compared with GnRH agonist protocols in predicted high responders even when hCG trigger is used. Evidence level 1++

GnRH antagonist protocols should be considered for the prevention of OHSS in the general IVF population and predicted normal responders. Grade A

GnRH antagonist protocols are recommended for prevention of OHSS for predicted high responders. Grade A

In assessing GnRH antagonist and agonist protocols, the GDG emphasized the importance of considering safety, treatment burden and cost-effectiveness. GnRH antagonist protocols are favoured for their lower risk of OHSS and shorter timelines relative to GnRH agonist protocols.

Progestin-Primed ovarian stimulation (PPOS)

Progestins administered during the early follicular phase suppress the LH surge, preventing premature luteinization. This may affect the size of the follicular cohort. Due to effects on the endometrium, PPOS inherently involves cryopreservation of all oocytes/embryos and thus effectively eliminates the risk of late-onset OHSS.

A meta-analysis found no difference in the incidence of OHSS when comparing PPOS with GnRH antagonist in women with normal ovarian reserve with a relative risk (RR) of 0.55 (95% CI: 0.11–2.80, $p = 0.76$, $I^2 = 0.00\%$) (Guan et al., 2021). An analysis of 8 RCTs and cohort studies involving 2,156 women with PCOS found no significant difference in the incidence of OHSS between PPOS and GnRH analogue regimes in women with in the RCT subgroup (RR = 3.00, 95% CI: 0.13–71.40, $p = 0.50$) (Deng et al., 2024).

PPOS is associated with a similar risk of OHSS as GnRH antagonist protocols. Evidence Levels: 2++

PPOS could be considered as an alternative to the GnRH-antagonist protocol for the purpose of OHSS prevention where fresh embryo transfer is not anticipated. Grade B

PPOS offers some advantages such as oral administration and potential cost-effectiveness. However, PPOS does not allow the possibility of fresh embryo transfer, and some studies suggest that it may necessitate higher doses of gonadotropins, possibly affecting its overall cost-benefit balance (Deng et al., 2024).

Starting dose of FSH – universal vs personalized

Standard daily FSH doses and individualized dosing based on patients' characteristics have both been used in controlled ovarian stimulation (Yates et al., 2011). Different doses of FSH may result in different degrees of ovarian response and may affect the risk of developing OHSS.

A recent systematic review and meta-analysis assessed the safety and efficacy of individualized gonadotropin dosing, based on ovarian reserve tests (ORT), compared to utilization of a universal dose or a dose not based on ORT. FSH doses based on ORT algorithms were associated with a reduced risk of moderate or severe OHSS compared to standard doses (Peto OR 0.60, 95% CI 0.42 to 0.84; $I^2 = 0\%$; 7 studies, 4400 women; low-certainty evidence). There was insufficient evidence to determine whether the groups differed in the risk of severe OHSS (Peto OR 0.74, 95% CI 0.42 to 1.28; $I^2 = 0\%$; 5 studies, 2724 women; low-certainty evidence). However, of the five studies included in the analysis, two included women receiving long protocol GnRH agonist treatment (Ngwenya et al., 2024).

When direct dose comparison studies were considered, there was no evidence of an impact of starting dose on the risk of OHSS in predicted low or normal responders (very low certainty). In predicted high responders, the OR for severe OHSS was 0.72 (0.16 to 3.19) and moderate or severe OHSS 2.31 (0.80 to 6.67) with the use of a starting dose lower than 150 IU FSH (very low-quality evidence). The results were skewed by Oudshoorn et al. (2017), where an agonist protocol was used and the freeze-all approach was not utilized.

Mild ovarian stimulation for IVF is defined as a protocol in which the ovaries are stimulated with a lower dose of gonadotropins, aiming for the development of a few follicles. The definition of mild stimulation in studies and practice is variable. The ESHRE COS Guideline defines the daily dose of FSH of 150-225 IU as conventional, while mild stimulation is achieved by a lower dose of FSH, or a delayed start (The Eshre Guideline Group On Ovarian Stimulation et al., 2020).

Datta et al. (2021) found a lower incidence of OHSS with mild ovarian stimulation protocols. However, their meta-analysis included some studies where the daily dose of FSH was 150 IU, which would fall under the ESHRE COS guideline definition of conventional stimulation. There was a reduction in the number of oocytes retrieved when mild stimulation was used for poor and normal responders, but the live birth rate was not affected.

ORT-based dose of FSH is associated with a lower incidence of moderate or severe OHSS. Evidence level 1+

FSH dose lower than 150 IU daily may be associated with lower risk of OHSS in GnRH agonist protocols. Evidence level 1−

ORT-based dose of FSH should be considered to reduce the risk of OHSS. Grade A

A reduced gonadotropin dose could be considered in predicted high responders receiving GnRH agonist protocols to decrease the risk of OHSS. Grade B

A conventional gonadotropin dose should be considered for safety and efficacy when a GnRH antagonist protocol is used. Grade B

The GDG considered that the literature on ORT-based starting doses of FSH shows a lower incidence of moderate or severe OHSS, but not severe OHSS alone, compared to standard dosing. The group also acknowledged that in practice ORT have a wider application in counselling patients about their reproductive options and chances of success. FSH daily dose of less than 150 IU may be associated with a lower rate of OHSS in predicted high responders undergoing GnRH agonist cycles, but the GDG cautions that GnRH antagonist is preferable in this group as it carries a lower risk of OHSS. The GDG did not find convincing

evidence of a benefit from a reduced FSH dose in antagonist cycles. There is consistent evidence indicating a linear association between the number of oocytes retrieved and the cumulative live birth rate per treatment started (Neves et al., 2023; Polyzos et al., 2018), and this should be considered when planning treatment. A conventional daily dose of FSH is associated with an optimal balance of safety and efficacy in GnRH antagonist protocols.

Types of gonadotropins

Different types of gonadotropins include human Menopausal Gonadotropin (hMG), Recombinant FSH (rFSH), Purified FSH (p-FSH), highly purified FSH (hp-FSH) and Recombinant LH (rLH). hMG, p-FSH and hp-FSH are human derived, produced from the urine of postmenopausal women. hMG regimes contain LH in a 1:1 ratio, when p-FSH and hp-FSH contain minimal LH (van Wely et al., 2011). rFSH is produced using recombinant DNA technology. The rFSHs are biochemically pure preparations, free from urinary protein contaminants and provide minimal batch-to-batch discrepancy (Bergh, 1999). It is plausible that the different pharmacokinetic properties of various gonadotropin preparations could affect the risk of OHSS.

A meta-analysis on the efficacy and safety of different gonadotropin preparations identified 42 studies (9606 participants), of which 32 reported the incidence of OHSS. There was no difference in the OHSS rate when using recombinant or human-derived gonadotropins (7740 patients, OR 1.18, 95% CI 0.86 to 1.61) (van Wely et al., 2011). Subsequent studies have not demonstrated different results (Devroey et al., 2012; Parsanezhad et al., 2017; Selman et al., 2013; Sohrabvand et al., 2012; Witz et al., 2020).

The risk of OHSS is similar between recombinant and urinary gonadotropins. Level of evidence 1++

Both urinary and recombinant gonadotropins may be considered for ovarian stimulation from the point of view of OHSS risk. Grade A

The GDG agreed that evidence shows a similar risk of OHSS with the use of different gonadotropins. Therefore, the choice of gonadotropin can be made based on availability, cost, ease of administration and patient characteristics.

Long-acting FSH

Corifollitropin alfa is a recombinant, long-acting FSH. A single injection can provide follicle-stimulating activity for 7 days, reducing the number of the injections required. Serum FSH immunoreactivity is higher up to stimulation day 5 for corifollitropin than for daily rFSH injections (Fauser et al., 2010).

A meta-analysis included eight RCTs, comparing corifollitropin alfa and daily recombinant FSH. Two RCTs included poor responders. No difference was observed in the incidence of OHSS (5 RCTs; RR 1.15, 95% CI, 0.83 to 1.57, n = 3,749; $I^2 = 0\%$), as well as moderate-to-severe OHSS (4 RCTs; RR 1.17, 95% CI, 0.54 to 2.56, n = 3,349; $I^2 = 0\%$;). All the included studies used an antagonist protocol (Cozzolino et al., 2019). There are no studies on high responders.

The risk of OHSS is similar between daily and long-acting recombinant FSH in normal responders in GnRH antagonist protocols. Evidence level 1+

Both daily and long-acting recombinant FSH may be considered for normal responders. Grade A

Long-acting FSH with sustained follicle-stimulating activity for the induction of multi-follicular growth is a convenient and safe option for normal responders.

Follitropin Delta

Follitropin delta is an rFSH with a pharmacokinetic profile characterized by slower clearance, inducing a higher ovarian response compared to previous rFSH preparations, when administered at equal doses of biological activity (Nyboe Andersen et al., 2017; Olsson et al., 2014). An individualized dosing algorithm incorporating body weight and AMH levels is used (Olsson et al., 2014).

Several studies have assessed the safety and efficacy of follitropin delta (Ishihara et al., 2021; Nyboe Andersen et al., 2017; Qiao et al., 2021; Yang et al., 2022). The largest, low risk of bias, study by Qiao et al. (2021) compared the outcomes of ovarian stimulation with individualized dose of follitropin delta vs 150 IU of follitropin alfa, adjusted after day 5 depending on the response and found no significant difference in the risk of early-onset or late-onset OHSS between the two groups. However, there was a lower incidence of preventive measures for early OHSS in the follitropin delta group (1.2% vs 3.5%, p = 0.012). Follitropin delta was associated with an increased live birth rate (p = 0.023) at 31.3% compared to 24.7% with follitropin alfa, but not a different ongoing (156 (31.3) vs 131 (25.7), 95% CI (0.2%; 11.0%) p = 0.057)and clinical pregnancy rate (180 (36.1) vs 159 (31.2), 95% CI (0.9%; 10.7%) p = 0.099), as well as a significantly lower number of oocytes retrieved (10.0 ± 6.1 vs 12.4 ± 7.3,

$p < 0.001$) (Qiao et al., 2021). The recent individual participant data meta-analysis by Nelson et al. (2024) revealed high-quality evidence that the use of follitropin delta resulted in an increased LBR (adj OR 1.64, 95% CI 1.14, 2.36) in patients with an AMH level >15pmol/L. Safety outcomes were also improved with high-quality evidence of a reduced risk of both early OHSS and/or the need for preventive interventions (adj OR 0.27, 95% CI 0.15, 0.49) and early moderate or severe OHSS (adj OR 0.30, 95% CI 0.16, 0.58).

Follitropin delta used in doses according to an algorithm including weight and AMH may be associated with a reduction in risk of OHSS Evidence level 1+

Follitropin delta used in doses according to an algorithm based on weight and AMH may be considered for prevention of OHSS. Grade A

The GDG took into account evidence showing a reduced need for preventive measures and a lower risk of OHSS in patients with AMH> 15 pmol/l who were treated with follitropin delta in doses based on an algorithm incorporating weight and AMH.

Prevention of OHSS during ovarian stimulation

Monitoring

Monitoring of COS cycles is used to determine the timing of trigger injection for final oocyte maturation and oocyte retrieval. It may allow early detection of hyper-response and consideration of preventive measures prior to trigger.

A Cochrane Review included 6 trials (781 women) undergoing monitoring of COS with transvaginal ultrasound scan (TVUS) alone or combination of TVUS and E2 concentrations (Kwan et al., 2021). All studies included an unselected population, except one which excluded patients with previous history of severe OHSS (Lass & UK Timing of hCG Group, 2003). The risk of OHSS was not affected by the addition of E2 concentrations (OR 1.03; 95% CI 0.48 to 2.20; 6 studies; N = 781; $I^2 = 0\%$; low-quality evidence). Golan et al. (1994) investigated any potential benefit of additional monitoring with progesterone and LH levels and found no difference.

The addition of E2 or other biomarkers to ultrasound scan monitoring does not reduce the risk of OHSS in unselected patients. Evidence Level 1+

The addition of serum E2, progesterone or LH concentration to ultrasound monitoring should not be considered in unselected patients from the point of view of OHSS risk. Grade A

The evidence does not show reduced risk of OHSS when biochemical markers such as E2 are added to TVUS for monitoring ovarian response in unselected women undergoing IVF. Further, serum E2 concentrations are not good predictors of the risk of late OHSS *(see Section 'Prediction of OHSS')*. The GDG also considered the increased cost and time required for serial blood tests and agreed to the above recommendation.

Coasting

Coasting refers to discontinuation of gonadotropins while maintaining pituitary down-regulation during COS in women who manifest an 'excessive' response to gonadotropins. It aims to reduce circulating gonadotropin levels, leading to apoptosis of granulosa cells in small- and medium-sized follicles, while larger follicles that are gonadotropin-independent continue to develop. A similar mechanism of action is postulated for reducing the dose of FSH. However, studies on FSH pharmacokinetics show that following discontinuation of recombinant FSH, serum FSH levels remain above the threshold for follicular development for several days (Olsson et al., 2014).

A meta-analysis showed that coasting was associated with a reduced OHSS risk compared to no coasting in GnRH agonist cycles with an excessive response to stimulation (2 RCTs; OR 0.11, 95% CI 0.05 to 0.24, n = 207; $I^2 = 0\%$). There was significant variation in the cut-off level of serum E2, follicle size, or both, at the onset of coasting and at hCG administration. There was insufficient evidence to assess the number of oocytes retrieved, the live birth, clinical pregnancy and miscarriage rates, due to the statistical heterogeneity of the studies (D'Angelo et al., 2017). There are currently no published RCTs investigating coasting in GnRH antagonist cycles. One RCT compared coasting in a GnRH agonist regime with GnRH antagonist regime. No cases of OHSS were seen in either group (n = 190) (Aboulghar et al., 2007). An RCT of reduced hMG dose followed by coasting found a reduced incidence of OHSS in women with an excessive ovarian response in a GnRH agonist cycle (Aboulghar et al., 2000).

Coasting is associated with a reduced incidence of OHSS in patients receiving GnRH agonist who show an excessive response to stimulation. Evidence level 1+

Coasting could be considered in patients at high risk of OHSS based on ovarian response in GnRH agonist protocols. Grade A

Coasting should not be considered for prevention of OHSS in GnRH antagonist protocols. Grade GPP

Evidence is lacking to compare coasting to GnRH agonist trigger in GnRH antagonist cycles. Currently the GnRH antagonist protocol is recommended for high and normal responders. However, when a GnRH agonist protocol is used and unexpected over-response occurs, coasting could be considered to reduce the risk of OHSS.

Choice of trigger in GnRH antagonist cycles

Follicular and oocyte maturation prior to oocyte retrieval requires activation of LH receptors and can be achieved in GnRH antagonist cycles through the use of hCG, GnRH agonist or recombinant LH. hCG has a longer half-life than endogenous LH and causes more sustained stimulation of luteal cells. GnRH agonists induce an endogenous LH and FSH surge, the duration of which is shorter than that of a physiological surge.

GnRH agonist vs. Urinary hCG

A Cochrane review of 17 RCTs with 1,847 participants compared GnRH agonists to hCG as the follicular maturation trigger. GnRH agonists significantly reduced OHSS risk (OR 0.15, 95% CI 0.05 to 0.47, n = 989; $I^2 = 42\%$, moderate-quality evidence) but lowered live birth rates (OR 0.47, 95% CI 0.31 to 0.70, n = 532; $I^2 = 56\%$, moderate-quality evidence) and increased early miscarriage rates in fresh autologous cycles. This approach often necessitates a freeze-all strategy (Youssef et al., 2014).

GnRH agonist trigger is associated with a lower risk of OHSS compared to hCG trigger. Evidence level 1+

Type of hCG

A Cochrane systematic review by Youssef et al. (2016) compared rhCG and rLH with uhCG in IVF cycles, including 18 RCTs with 2,952 participants. The results showed no significant differences in OHSS incidence between the rhCG/rLH and uhCG groups. The quality assessment indicated high quality, though the certainty of evidence of data was low.

The use of urinary or recombinant hCG carries a similar risk of OHSS. Evidence level 1+

Altering uhCG dosage

An RCT of 98 ICSI patients compared uhCG doses of 5000 IU vs. 10,000 IU. The incidence of mild OHSS was similar between groups (Shaltout et al., 2006). An RCT of 80 PCOS patients examined 2500 IU, 5000 IU and 10,000 IU hCG doses. There was no significant difference in OHSS rates (Kolibianakis et al., 2007). An RCT by Madani et al. (2013) assigned 180 women undergoing ICSI to receive either 10,000 IU uhCG, 250 μg rhCG, or 500 μg rhCG. OHSS incidence did not differ significantly among the groups.

In a study with 164 IVF/ICSI patients, Lin et al. (2011) compared uhCG doses of 4000 IU vs. 6000 IU. The results showed no statistically significant difference in OHSS rates (3.6% vs. 4.9%). However, the 4000 IU group experienced significantly lower pregnancy rates compared to the 6000 IU group (36.5% vs. 57.0%).

The use of uhCG doses between 4000 IU and 10,000 IU for trigger carries a similar risk of OHSS in the general IVF population. Evidence level 1−

Dual trigger

Meta-analysis by Hu et al. (2021) focused on the efficacy of dual trigger (GnRH agonist and hCG) vs. hCG alone for follicular maturation in women undergoing IVF, without specifically targeting patients at high risk of OHSS. Dual trigger treatment was associated with a significantly higher live birth rate per started cycle compared to the hCG trigger treatment (Risk Ratio (RR) = 1.37 [1.07, 1.76], $I^2 = 0\%$, moderate evidence). The study did not find an increase in the incidence of OHSS with the use of dual trigger compared to hCG alone (RR = 1.00 [0.14, 7.34]).

Dual trigger with GnRH agonist and hCG has a similar risk of OHSS as hCG trigger alone in the general IVF population. Evidence level 1+

GnRH agonist trigger should be considered for OHSS prevention in preference to urinary or recombinant hCG in GnRH antagonist cycles. Grading of Recommendation A

uhCG doses lower than 5000 IU should not be considered for prevention of OHSS. Grading of Recommendation: B

GnRH agonist trigger is effective relative to hCG in preventing OHSS but requires either a freeze-all strategy or provision of enhanced luteal support, if a fresh embryo transfer is performed. hCG use is associated with an increased risk of OHSS compared to GnRH agonist trigger, irrespective of the type of hCG.

Cycle cancellation

Cycle cancellation and withholding the ovulatory trigger eliminates the risk of OHSS, as this is a post-ovulatory

phenomenon relating to activation of LH receptors on granulosa cells.

There are no identified systematic reviews or experimental studies reporting the efficacy of cycle cancellation in the context of OHSS.

Cycle cancellation could be considered for the prevention of OHSS in the event of excessive ovarian response. Grade: GPP

Cycle cancellation is an effective method in OHSS prevention and could be considered where alternate strategies are not available or are unlikely to be effective. Clinicians should consider the psychological impact and financial burden of cycle cancellation on patients. This includes recognizing previous patient experience and preference.

Prevention of OHSS during luteal phase

Cryopreservation of all embryos

Cryopreservation of all embryos avoids fresh embryo transfer within the stimulated cycle and, by avoiding pregnancy, prevents the endogenous production of hCG, preventing late-onset OHSS (Bourdon et al., 2021).

A Cochrane Systematic Review of fresh versus frozen embryo transfers identified 6 RCTs, 2 using GnRH agonist and 4 using GnRH antagonist protocols. Only 3 studies focused on OHSS prevention as an indication for elective cryopreservation. The incidence of OHSS was significantly lower in the freeze-all group (9 per 100 women) compared to the fresh embryo transfer group (33 per 1000 women) (OR 0.26, 95% CI 0.17–0.39, 6 RCTs, 4478 women). There was no difference in the cumulative live birth rate (OR 1.08, 95% CI 0.95–1.22, 8 RCTs, 4712 women) (Zaat et al., 2021).

Cryopreservation of all embryos is associated with a lower incidence of OHSS compared with fresh embryo transfer. *Evidence level: 1+*

Cryopreservation of all embryos should be considered for the prevention of OHSS in individuals at high risk. Grade A

Cryopreservation of all embryos is an effective risk-reducing strategy that will, by definition, prevent late-onset OHSS, but it may prolong the time to conception. Patients should be counselled regarding 'freeze-all' prior to commencing ovarian stimulation in the presence of a high ovarian reserve or in the event of an unexpected excessive response. Patients should also be advised that studies do not show a difference in cumulative live birth rate with this approach compared to a fresh embryo transfer. The combination of GnRH antagonist protocol, GnRH agonist trigger and elective cryopreservation of all embryos provides a powerful combination of evidence-based tools to reduce the risk of OHSS.

Luteal phase support

OHSS is a post-ovulatory phenomenon, and the risk of OHSS may be influenced by medications used in the luteal phase.

Luteal phase support with progesterone vs hCG

A Cochrane Review of luteal phase support in assisted reproduction cycles found no RCTs that reported OHSS incidence when comparing progesterone with a placebo. Other studies reported an increased risk of OHSS with the use of hCG compared with progesterone alone (OR 0.46, 95% CI 0.30–0.71, 5 RCTs, 1293 women) (van der Linden et al., 2015).

The review also compared the risk of OHSS with the use of progesterone alone or in combination with oestrogen. There was no significant difference in OHSS incidence with addition of oestrogen (OR 0.56, 95% CI 0.2–1.63, 2 RCTs, 461 women) (van der Linden et al., 2015).

The incidence of OHSS is increased with the use of hCG compared with the use of progesterone alone for luteal support. *Evidence level: 1+*

Addition of oestrogen to progesterone for luteal phase support does not affect the incidence of OHSS. *Evidence level: 1+*

Intensified luteal phase support with low-dose hCG

One RCT investigated administration of low-dose hCG with oral oestrogen and vaginal progesterone after a GnRH agonist trigger compared with a freeze-all in hyper-responders. There was a significant increase in moderate-to-severe OHSS in the group receiving low-dose hCG (RD −8.6%, 95% CI −13.9% to −3.2%, $p < 0.01$, 1 RCT, 209 women) (Santos-Ribeiro et al., 2020).

Intensified luteal phase support with low-dose hCG following GnRH agonist trigger increases the risk of OHSS. *Evidence level: 1+*

Luteal phase support with GnRH agonist

A systematic review on luteal phase support with GnRH agonist did not find a significant difference in OHSS incidence compared with traditional luteal

phase support (RR 0.96, 95% CI 0.32–2.89; p = 0.94, 2 RCTs, 523 women) (Ma et al., 2020). A subsequent RCT reported no cases of OHSS with daily GnRH agonist administration after GnRH agonist trigger (44 women) (Salehpour et al., 2021).

Luteal phase support with GnRH agonist does not affect the incidence of OHSS. *Evidence level: 1+*

The use of hCG for luteal phase support is not recommended from the point of view of OHSS risk. Grade A

If hCG is used for luteal phase support in women who have a fresh embryo transfer after a GnRH agonist trigger, clinicians and patients should be aware of the increased risk of developing OHSS. Grade A

The use of a GnRH agonist for luteal phase support is not recommended for reducing OHSS incidence. Grade B

The use of hCG in the luteal phase increases the risk of OHSS. The GDG considered that there may be situations when, following a GnRH agonist trigger, fresh embryo transfer is performed with intensified luteal support. In such circumstances, clinicians should bear in mind that even a low dose of hCG may increase the risk of developing OHSS, and this should be included in patient counselling.

Adjuvant treatments for prevention of OHSS

Luteal GnRH antagonist

GnRH antagonist administration following oocyte retrieval has been proposed to prevent and reduce severity of OHSS. A possible mechanism is by suppressing endogenous LH and thus inducing early luteolysis.

There are no RCTs directly reporting incidence of OHSS following luteal GnRH antagonist administration. One prospective cohort study investigated the effect of 0.25 mg of cetrorelix administered from days 3 to 5 post-oocyte retrieval in women who had all embryos cryopreserved for a perceived high risk of OHSS. The incidence of moderate-to-severe OHSS was lower compared to the control group (11/61 (18%) vs 13/35 (37%), p = 0.04). However, there was no significant difference in hospital admission rate or duration of inpatient stay (Zeng et al., 2019). One RCT investigated the administration of cetrorelix for 3 days post-oocyte retrieval with embryo cryopreservation and reported significant reduction in OHSS indicators, including sequential serum oestradiol levels, pain scores, gastrointestinal symptoms and severity of ascites (48 women) (Salama et al., 2017).

Luteal GnRH antagonist may reduce the incidence of OHSS, in women who have cryopreservation of all embryos. *Evidence level 2−*

GnRH antagonist administration could be considered for prevention of moderate to severe OHSS following elective cryopreservation of all embryos. Grade D

The GDG identified only limited evidence for luteal GnRH antagonist for prevention of OHSS and considered the potential benefit of preventing moderate-to-severe OHSS.

Clomiphene citrate/Letrozole co-treatment

Clomiphene citrate stimulates endogenous FSH and LH secretion by competing for oestrogen receptors at the hypothalamic level. Letrozole is an aromatase inhibitor, which inhibits androgen aromatization into oestrogens in granulosa cells leading to an increase in endogenous FSH and LH. The mechanism for a possible reduction in the risk of OHSS is not completely understood.

A Cochrane review assessed the effect of Clomiphene citrate (4 RCTs) and Letrozole (1 RCT) during ovarian hyperstimulation on the risk of OHSS. There was evidence of reduced OHSS incidence in women co-treated with Clomiphene citrate or Letrozole when all 5 RCTs were combined (Peto OR 0.21, 95% CI 0.11 to 0.41, 5 RCTs, n = 1067, $I^2 = 0\%$, low-quality evidence). However, all 4 RCTs on Clomiphene compared it to the use of GnRH agonist, limiting their applicability to modern practice (Kamath et al., 2017).

A meta-analysis reported lower OHSS rates following co-treatment with letrozole during ovarian stimulation (RR 0.43, 95% CI 0.24 to 0.79, $I^2 = 0\%$, 5 RCTs, 422 patients), but not when administered in the luteal phase (RR 0.62, 95% CI 0.25 to 1.57, $I^2 = 82\%$, 2 RCTs, 302 patients) (Jiang et al., 2024).

Letrozole co-treatment during ovarian stimulation may be associated with a lower risk of OHSS in GnRH antagonist cycles. Evidence level 1−

Letrozole co-treatment during ovarian stimulation could be considered to reduce the incidence of OHSS in selected high-risk patients. Grade C

The GDG did not identify trials comparing the use of Clomiphene with GnRH antagonist cycles. The meta-analysis included studies assessing the effect of letrozole in both agonist and antagonist protocols.

The oestradiol levels were reduced in the letrozole groups when co-administration occurred during ovarian stimulation or during luteal phase, but the number of studies and included patients was overall low to draw definitive conclusions.

Metformin

Metformin has been proposed as a preventive agent for OHSS, through mechanisms involving inhibition of VEGF, which is the chief mediator of increased vascular permeability in OHSS (Elia et al., 2013).

A Cochrane review included 11 randomized controlled trials, 9 of which were in GnRH agonist cycles, assessing the role of Metformin co-treatment during controlled ovarian hyperstimulation in women with PCOS. When all studies were combined, Metformin was associated with a reduced incidence of OHSS compared with placebo/no treatment (RR 0.46, 95% CI 0.29 to 0.72; 11 RCTs; 1091 women; $I^2 = 38\%$; low-quality evidence). Two trials in GnRH antagonist cycles showed no difference in the risk of OHSS with the use of Metformin (RR 1.32, 95% CI 0.59–2.94; 2 RCTs. n = 153 women) (Tso et al., 2020).

Metformin administration reduces the risk of OHSS in women with PCOS undergoing GnRH agonist cycles, but not in women receiving GnRH antagonist. Evidence level 1+

Metformin co-treatment could be considered to reduce the risk of OHSS in women with PCOS who are receiving GnRH agonist protocols. Grade A

Metformin co-treatment should not be considered to reduce the risk of OHSS in women with PCOS who are receiving GnRH antagonist protocols. Grade A

Most of the included studies in the Cochrane meta-analysis used a long agonist protocol, which is not recommended in women with PCOS and a high risk of OHSS. One RCT in GnRH antagonist cycles suggested that Metformin may reduce live birth rate compared with placebo/no treatment with low level of evidence (Jacob et al., 2016). The gastrointestinal side effects of Metformin should be considered when counselling about co-treatment.

Aspirin

Aspirin has been proposed as a therapeutic agent for reducing the risk of OHSS through modulating the pathophysiological cascade triggered by elevated VEGF levels.

Three RCTs evaluated the use of aspirin co-treatment during COS with an aim to reduce the incidence of OHSS. Revelli et al. (2008) administered aspirin and prednisolone co-treatment in a GnRH agonist protocol in 97 patients who were compared with a control group of 298 patients to suggest a lower incidence of severe OHSS in the treatment group (1.7% vs 6.5%). Várnagy et al. (2010) randomized 1503 patients to receive co-treatment with low-dose aspirin alongside a long agonist protocol and compared them with a control group of 922 patients to suggest a lower incidence of OHSS in the high-risk patients allocated to aspirin group (0.25% vs 8.4%). Namavar Jahromi et al. (2019) reported a similar risk of OHSS (34.9% vs 30.5%) in PCOS patients undergoing GnRH agonist long protocol treatment randomized to low-dose aspirin (n = 109) or placebo (n = 105).

Aspirin use may be associated with a lower risk of OHSS in women undergoing IVF using GnRH agonist protocols, but evidence is inconsistent. Evidence level 1−

Aspirin should not be considered to prevent OHSS during controlled ovarian hyperstimulation. Grade C

The GDG identified only limited and contradictory evidence, mostly in GnRH agonist cycles.

Melatonin

Melatonin has been proposed as a potential agent for the prevention of OHSS through mechanisms involving reactive oxygen species and regulation of apoptosis (Zheng et al., 2023).

A systematic review and meta-analysis of RCTs identified 5 trials, of which one reported on the need for interventions to reduce the risk of OHSS as a surrogate marker for OHSS. Data were insufficient to draw any conclusions (Seko et al., 2014).

There is no evidence that melatonin co-administration reduces the risk of OHSS. Evidence level 1-

Melatonin should not be considered to prevent OHSS. Grade B

The GDG identified only limited clinical evidence in this area.

Inositol

Inositol, a carbocyclic sugar present in nine iso-forms, has been proposed as a preventive measure for OHSS

through reduced vascular permeability, VEGF and COX-2 expression (Turan et al., 2015).

Two RCTs evaluated the use of inositol for the prevention of OHSS. Mendoza et al. (2019) randomized 60 PCOS patients to receive Myo-inositol and a high or low dose of D-chiro-inositol for 3 months prior to the start of controlled ovarian stimulation and reported lower OHSS rates in the high dose group (3.44% vs 18.5%). Rajasekaran et al. (2022) randomized 102 PCOS patients to receive either Myo-inositol or metformin for 3 months prior to the start of controlled ovarian stimulation and reported similar OHSS rates.

There is insufficient evidence to support the role of Inositol in decreasing the risk of OHSS. Evidence level 1−

Inositol should not be considered for the prevention of OHSS. Grade C

The GDG did not identify any high-quality RCTs comparing Inositol with placebo for the prevention of OHSS.

Volume expanders

Various volume expanders such as albumin and hydroxyethyl starch (HES) have been investigated for their potential prevention of severe OHSS through mechanisms involving increased intravascular volume and reduction of coagulability due to reduced platelet aggregation (Morris et al., 1995).

A network meta-analysis of RCTs evaluating the role of various adjuvants in the prevention of moderate-to-severe OHSS included 31 studies (4964 women) and reported lower incidence of OHSS following the use of HES (RR 0.25, 95% CI 0.07, 0.73), but not with the use of albumin (Wu et al., 2022).

The use of albumin is not associated with a reduced incidence of OHSS. Evidence level 1+

Albumin should not be considered for the prevention of OHSS. Grade A

HES is no longer approved for use in the UK since 2013. Albumin use has been associated with reduced pregnancy rates (Wu et al., 2022). The quality of evidence is poor and mostly relates to long protocol GnRH agonist cycles.

Calcium infusion

Calcium may reduce the incidence of OHSS through mechanisms involving reduced VEGF expression in luteinized granulosa cells (Herr et al., 2010).

An RCT involving 200 women compared the use of calcium gluconate infusion versus placebo on the 4 days starting with the day of oocyte collection in GnRH agonist long protocol cycles. The incidence of severe, moderate and all cases of OHSS was lower in the intervention group (El-Khayat & Elsadek, 2015).

The Cochrane review of the use of dopamine agonists for preventing OHSS reported similar OHSS rates following the use of cabergoline and calcium (OR 1.83, 95% CI 0.88 to 3.81; $I^2 = 81\%$; 2 studies, 400 participants; very low-quality evidence) (Tang et al., 2021).

There is insufficient evidence to support the use of calcium infusion for the prevention of OHSS. Evidence level 1−

Calcium infusion should not be considered for the prevention of OHSS. Grade B

The GDG considered the cost and inconvenience of calcium infusions and the lack of superiority over alternative preventive measures.

Dopamine agonists

Dopamine agonists may selectively inhibit VEGF-induced vascular permeability, which is part of the pathophysiology of OHSS (Soares, 2012).

The Cochrane review on the use of dopamine agonists such as cabergoline, quinagolide and bromocriptine, in the context of OHSS concluded that dopamine agonists probably lowered the risk of moderate or severe OHSS compared to placebo or no intervention in long agonist protocols (OR 0.32, 95% CI 0.23 to 0.44; 10 studies, 1202 participants; moderate-quality evidence). There was no evidence of an effect of dopamine agonists on live birth rates (OR 0.96, 95% CI 0.60 to 1.55; 3 studies, 362 participants; low-quality evidence) (Tang et al., 2021). The RCT by Busso et al. (2010) randomized 148 agonist and 34 antagonist cycles to quinagolide or placebo from the day of hCG trigger and reported similar efficacy of quinagolide in both groups.

Dopamine agonists may reduce the risk of OHSS in long agonist protocols. Evidence level 1++

Dopamine agonists may reduce the risk of OHSS in antagonist protocols. Evidence level 1+

Dopamine agonists should be considered following trigger or on the day of oocyte retrieval in long agonist protocols to reduce the incidence of OHSS in selected high-risk patients. Grade A

Dopamine agonists could be considered following trigger or on the day of oocyte retrieval in

antagonist protocols to reduce the incidence of OHSS in selected high-risk patients. Grade B

The GDG considered the low cost, availability, ease of use and safety of dopamine agonists. The Cochrane review included studies in which a dopamine agonist was started on either day of hCG trigger or day of oocyte collection. Most of the included studies used a daily dose of 0.5 mg of cabergoline, for 7 or 8 days. The study population included both women who had a fresh embryo transfer or elective cryopreservation of all embryos. Most studies used long agonist protocol, but the multicentre study including both agonist and antagonist protocols has not reported any difference of effects between protocols (Busso et al., 2010).

In vitro maturation (IVM)

IVM involves the culture of immature oocytes retrieved without exogenous ovarian stimulation or with minimal doses of gonadotropins, avoiding the need for supraphysiological ovarian stimulation (Dahan et al., 2016; Das & Son, 2023).

A Cochrane Systematic Review of the use of IVM in women with PCOS, including two RCTs with high risk of bias, found no cases of OHSS in the IVM or control groups (n = 71) (Siristatidis et al., 2018). A systematic review in 2023, including two RCTs and one retrospective cohort study, also found no cases of OHSS in the IVM group (n = 1056), while the incidence of OHSS in the control arms varied from 0.7 to 6.3% (Vuong et al., 2023).

IVM is associated with a reduction of the risk of OHSS in women at risk of hyper-response to ovarian stimulation. Evidence level: 1−

IVM may be considered for the prevention of OHSS in individuals at high risk. Grade B

The use of IVM avoids the need for supraphysiological ovarian stimulation and has not been found to be associated with a risk of OHSS. However, ongoing pregnancy rates may be lower after IVM compared with controlled ovarian stimulation (Vuong et al., 2023). Provision of IVM is dependent on availability of the technology and expertise at fertility clinics.

Research recommendations

The GDG identified the following unanswered questions from the review of the evidence:

1. Further work is required to determine safe regimes for fresh embryo transfer following GnRH agonist trigger.
2. The efficacy and safety of oral ovulation induction agents with conventional doses of FSH in GnRH antagonist protocol requires further study.
3. The role of dopamine agonist in conjunction with elective freeze-all requires further study.
4. The optimal AMH cut-off level for recommending an 'elective freeze-all' strategy to prevent OHSS in different patient populations.
5. The role of Kisspeptin as a novel trigger of follicular maturation requires further study to assess benefit and risk in comparison to GnRH agonist trigger.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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