Best Practice & Research Clinical Obstetrics and Gynaecology 86 (2023) 102301

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

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Treatment algorithms for high responders: What we can learn from randomized controlled trials, real-world data and models

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https://doi.org/10.1016/j.bpobgyn.2022.102301

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Keywords:
High responders
IVF
ICSI
Gonadotropin releasing hormone antagonist
Ovarian stimulation

A B S T R A C T

A high ovarian response to conventional ovarian stimulation (OS) is characterized by an increased number of follicles and/or oocytes compared with a normal response (10–15 oocytes retrieved). According to current definitions, a high response can be diagnosed before oocyte pick-up when >18–20 follicles ≥11–12 mm are observed on the day of ovulation triggering; high response can be diagnosed after oocyte pick-up when >18–20 oocytes have been retrieved. Women with a high response are also at high risk of early ovarian hyper-stimulation syndrome (OHSS)/or late OHSS after fresh embryo transfers. Women at risk of high response can be diagnosed before stimulation based on several indices, including ovarian reserve markers (anti-Müllerian hormone [AMH] and antral follicle count [AFC], with cutoff values indicative of a high response in patients with PCOS of >3.4 ng/mL for AMH and >24 for AFC). Owing to the high proportion of high responders who are at the risk of developing OHSS (up to 30%), this educational article provides a framework for the identification and management of patients who fall into this category. The risk of high response can be greatly reduced through appropriate management, such as individualized choice of the gonadotropin starting dose, dose adjustment based on hormonal and ultrasound monitoring during OS, the choice of down-regulation protocol and ovulation trigger, and the choice between fresh or elective frozen embryo transfer. Appropriate management strategies still need to be defined for women who are predicted to have a high response and those who have an unexpected high response after starting treatment.

Introduction

The success of assisted reproductive technology (ART) requires the balancing of efficacy (the number of oocytes retrieved to maximize cumulative live birth rate) with safety (avoiding the occurrence of the ovarian hyper-stimulation syndrome [OHSS] or thromboembolic events) [1]. OHSS is an exaggerated systemic response to ovarian stimulation (OS) characterized by a wide spectrum of clinical and laboratory manifestations. It may be classified as mild, moderate or severe according to the degree of abdominal distention, ovarian enlargement and respiratory, haemodynamic and metabolic complications [2]. However, as ovarian responsiveness to OS is highly variable, a standardized approach to OS will frequently fail to balance efficacy with safety for each patient.

Based on ovarian response, women can be classified as poor (<4 oocytes retrieved), suboptimal (4–9 oocytes retrieved), normal (10–15 oocytes retrieved) or high responders (>15 oocytes retrieved) [3,4]. A high response is defined as an exaggerated response to standard OS (150–225 IU follicle-stimulating hormone [FSH]), as characterized by the presence of more follicles and/or oocytes than intended [5].

High ovarian response is associated with a relative decline in live birth rates in fresh embryo transfer cycles when >20 oocytes are retrieved compared with normal responders of a similar age [6]. Furthermore, women with a high response are also at high risk for developing OHSS, which can be classified as early OHSS (occurring between 3 and 11 days after human chorionic gonadotropin [hCG] administration) or as late OHSS after embryo transfer, resulting in pregnancy (occurring later than 10 days after oocyte retrieval because of hCG produced by the embryonic trophoblast and detectable in maternal peripheral blood following implantation) [7]. The retrieval of >15 oocytes may also significantly increase OHSS risk without improving the live birth rate in autologous IVF cycles where a fresh embryo transfer is performed [8,9]. The occurrence of OHSS is estimated to range from 3% in normal responders to more than 30% in high responders [10].

Because severe OHSS is almost always associated with exposure to exogenous or endogenous hCG following excessive ovarian response to gonadotropin stimulation [11], there are several potential treatment scenarios that can be considered based on the potential risk for OHSS. In women who are at high risk of OHSS, a gonaotropin releasing hormone (GnRH) agonist trigger followed by elective frozen embryo transfer has been recommended [5]. For women at intermediate risk of OHSS, an individualized treatment approach could be considered that is based on either of the above options, after alignment with the wishes of the patient.

Accordingly, a clear distinction needs to be made between patients for whom treatment is started with the intention to perform a fresh embryo transfer and patients for whom an elective frozen embryo transfer approach has been decided before the start of OS for ART. Taking into account these options, an individualized approach to OS is of paramount importance and can be guided by established predictive factors for high response (see the following section), other baseline characteristics or by the response to a previous cycle of OS [12]. The deployment of therapeutic strategies based on the selective use of GnRH analogues and the fine-tuning of the gonadotrophin dose on the basis of potential ovarian response in every single woman can allow for safer and more effective ART practice and enables clinicians to give women more accurate information on their prognosis, thus facilitating counselling in cases of high ovarian response [9].

The aim of this educational article is to provide a framework for the identification and management of patients predicted to have a high response to OS before, during and after OS and to provide advice on the management of women with unanticipated high response. The content of this article is derived from the discussions during an expert panel meeting held remotely by the authors of this article in May 2021.

Identification of women at risk of high ovarian response before the start of OS

Women at risk of a high response can be diagnosed before stimulation based on several indices, including ovarian reserve markers (anti-Müllerian hormone [AMH] and antral follicle count [AFC], with cutoff values indicative of a high response in patients with PCOS of >3.4 ng/mL for AMH and >24 for AFC [13,14]), age, a history of previous high response to OS, ovarian morphology (e.g., polycystic ovary morphology), a high number of antral follicles in young patients, FSH receptor polymorphisms and body mass index (BMI) [9,13,15–23] (Table 1).

Diagnosis of high ovarian response during OS

Before oocyte pick-up: based on the number/size of ovarian follicles on the day of ovulation triggering

A high response may be predicted based on the number of pre-ovulatory follicles observed with ultrasound, whereby women at risk of high ovarian response can be identified during stimulation based on the number and the size of follicles on the day of ovulation triggering, according to established guidelines [2,5,13]. Interestingly, different thresholds for high ovarian response have been proposed, and different cutoffs for the number of follicles associated with a significantly increased risk of severe OHSS have also been recommended by different organizations [2,5,13]. The European Society of Human Reproduction and Embryology (ESHRE) guidelines state that in a GnRH agonist cycle with an ovarian response of $\geq$18 follicles $\geq$11 mm, there is an increased risk of OHSS, and preventive measures are recommended [5]. The American Society for Reproductive Medicine (ASRM) guidelines state that

Table 1
Clinical and demographic baseline predictive factors for risk of high response.

Factor	Predictive value
Ovarian reserve markers	AFC and AMH are reliable predictors of ovarian response [95], with cutoff values indicative of a high response in patients with PCOS of >3.4 ng/mL for AMH and >24 for AFC [13,14].
Age	The prevalence rate of high response in IVF cycles is estimated as 7% and varies with age, reaching around 15% in women ≤30 years, and declining with increasing age [9].
History of previous high response to ovarian stimulation for ART	This could comprise a history of OHSS, cycle cancellation due to hyper-response, or coasting in a previous stimulation cycle [17].
Ovarian morphology on ultrasound	Polycystic ovaries have a greater sensitivity to gonadotropin stimulation compared with normal ovaries, resulting in the development of more pre-antral follicles that are responsive to ovarian stimulation [23].
BMI	Women with low BMI (<18.5 kg/m^2) may be at high risk for OHSS [13].
FSH receptor polymorphisms	There is mixed evidence supporting an association between the FSH receptor Asn680Ser variant (FSHR rs6166, c.2039A > G, p.Asn680Ser) and OHSS (Achrekar, Modi et al., 2009; Tang, Yan et al., 2015; Nenonen, Lindgren et al., 2019), although the current literature remains controversial, with studies only supporting a link between some variants in gonadotropin/gonadotropin receptor genes and responsiveness to ovarian stimulation [16,21].
Additional factors for VTE	Women with moderate OHSS should be assessed for predisposing risk factors for thrombosis and prescribed either anti-embolism stockings or low-weight molecular heparin thromboprophylaxis, if indicated [96].

AFC, antral follicle count. AMH, anti-Müllerian hormone. BMI, body mass index. FSH, follicle-stimulating hormone. IVF, in vitro fertilization. OHSS, ovarian hyper-stimulation syndrome. VTE, venous thromboembolism.

an exaggerated response to OS is characterized by the presence of >24 follicles (size not specified) [13]. Finally, the International Committee for Monitoring Assisted Reproductive Technologies (ICMART) consensus characterizes an exaggerated response to OS by the presence of >20 follicles >12 mm [2].

After oocyte pick-up: based on the number of oocytes retrieved

A high response after oocyte pick-up can be confirmed based on the number of oocytes retrieved, which is defined in two sets of guidelines that have different recommended thresholds. The ESHRE guidelines state that >18 oocytes confirm a high ovarian response [5], whereas the ASRM guidelines cite a figure of >20 oocytes [13].

Recommendation

In summary, taking into account the recommendations from ESHRE, ASRM and ICMART, >18–20 follicles ≥11–12 mm on the day of ovulation triggering may be considered for the diagnosis of high response before oocyte pick-up; >18–20 oocytes been retrieved may be considered for the diagnosis of high response after oocyte pick-up.

Treatment strategies for the prevention of OHSS in patients with predicted high response.

Different treatment strategies for the prevention of OHSS in patients with predicted high ovarian response can be considered at the following critical time points: before the start of OS, during OS and after OS (Fig. 1).

Pre-stimulation strategies

General discussion and decision-making with the patient

The first step should be to conduct a risk assessment for the potential for high response based on established predictive factors [5]. If a risk for high response has been identified, it is then important to ascertain the expectations of the patient (i.e., are they planning to have just one baby or looking to build a larger family?) and to discuss the likelihood of pregnancy and subsequent live birth within a specific

(a)

Prestimulation strategies

- Assess the potential for high response based on history and ovarian reserve markers
- Ascertain the expectations of the patient (one baby or more than one)
- Discuss and determine with the patient (joint decision-making) the intent to go for a freeze-all policy or a fresh embryo transfer based on ovarian reserve measures + patient's history + patient's expectations
- Choice of starting dose according to ovarian reserve and nomograms
- Use of GnRH antagonist protocol

(b)

Stimulation strategies

- Mainly for fresh embryo transfer: adjust (reduce) gonadotropin dose based on ovarian response from Day 5/6
- Trigger strategy: GnRH agonist in protocols with GnRH antagonist downregulation or low-dose hCG in agonist protocols
- Alternative preventive measures (coasting, dopamine agonists or metformin)

Post-stimulation strategies

- Freeze-all
- Fresh embryo transfer with intensified/modified LPS (GnRH agonist triggering) – strongly recommended if ≥20 follicles >12 mm or if >20 oocytes are retrieved
- Fresh embryo transfer with conventional LPS (hCG triggering) can be performed only in the presence of ≤ 20 follicles >12 mm or if fewer than 20 oocytes are retrieved

Fig. 1. Treatment strategies for patients with predicted high response. (A) Pre-stimulation strategies. (B) Stimulation and post-stimulation strategies.

time period and their preference for an elective frozen embryo transfer cycle or a fresh embryo transfer cycle. Furthermore, patients should also be encouraged to consider the cost and emotional aspects associated with each option.

Recommendation

During decision-making discussions with patients at risk for a high ovarian response, an appropriate balance needs to be struck between treatment safety and efficacy, and a holistic approach incorporating patient preferences for expected clinical outcomes and risks should be taken into consideration as part of an individualized care plan [24].

Stimulation strategies

Individualization of the starting dose of gonadotropins

For women with a predicted high response to OS, individualization of the gonadotropin starting dose is advised [9,25–28] to reduce the incidence of OHSS after embryo transfer and to limit cycle cancellation before oocyte retrieval or embryo transfer without reducing the probability of live birth per started OS cycle [26,29].

The selection of the starting gonadotropin dose for OS can be dependent on specific diagnoses of subfertility and is usually based on ovarian reserve biomarkers and other patient baseline characteristics [5,30–35]. To guide the individualization of the gonadotropin starting dose, nomograms have been developed based on factors such as patient age and baseline serum FSH, AMH or AFC [9,31]. Some nomograms have also included additional factors, such as BMI [36], ovarian volume, ovarian stromal blood flow and smoking status [27], or BMI, smoking history and day-2 serum FSH [37].

The outcomes of dose individualization in women with predicted high response were reported in the OPTIMIST trial, in which a starting dose of 150 IU/day recombinant human follicle stimulating hormone (r-hFSH) was compared with a starting dose of 100 IU/day [26]. A higher proportion of women in the 150 IU/day group had a high ovarian response (total number of growing follicles >15 on days 1–3 of the stimulation cycle) than the 100 IU/day group in the first cycle (38.3% [102/266] vs. 11.6% [28/253]; $p < 0.001$) and cumulatively (including all cycles) after 18 months of follow-up (30.4% [144/474] vs. 10.5% [48/459]; $p < 0.001$). The cycle cancellation rate due to excessive response in the first cycle was higher in the 150 IU/day group than in the 100 IU/day group (7.9% [21/266] vs. 2.0% [5/253]; $p = 0.002$), and the rate of OHSS (any grade) was higher in the 150 IU/day group than the 100 IU/day group after the first cycle (14.7% [39/266] vs. 4.7% [12/253]; $p < 0.001$) and cumulatively after 18 months of follow-up (11.8% [56/474] vs. 5.2% [24/456]; $p < 0.001$). There was no difference in live birth rate after fresh embryo transfer (25.2% [67/266] in the 150 IU/day dose group vs. 25.7% [65/235] in the 100 IU/day dose group) or cumulative live birth rate (39.1% [104/266] in the 150 IU/day dose group vs. 36.0% [91/235] in the 100 IU/day dose group). Overall, the OPTIMIST study demonstrated that, compared with a higher r-hFSH starting dose (150 IU/day) in predicted high ovarian responders, a lower r-hFSH starting dose (100 IU/day) results in a similar efficiency (similar live birth rate or cumulative live birth rate), but significantly reduces the risks (lower rates for high ovarian response, related cycle cancellation and related OHSS). However, several limitations of the OPTIMIST trial have been highlighted [26], and the investigators' conclusion that a standard dose of 150 IU should be used for all women entering an IVF program, regardless of their AFC, has been challenged [38]. Firstly, the long GnRH agonist protocol was used for 187 patients (73.9%) in the 100 IU group and 196 patients (73.7%) in the 150 IU group in the place of a GnRH antagonist, which is the current gold standard in predicted high responders [26]. Secondly, r-hFSH dose adjustments were not allowed during OS but only allowed between cycles, which may have increased the proportion of high response in the 150 IU starting dose group and the proportion with suboptimal response in the 100 IU group [38]. Dose adjustment during OS in ART is a common practice and occurs in up to 40–50% of cycles according to evidence from RCTs [39] and real-world data (RWD) from the US [40]. More specifically, the pooled point estimate for dose decreases was 9.5% (95% CI 8.7–10.3) in the RCTs [39] and in 25.4% of 33,962 ART cycles in a real-world setting [40]. Finally, the BMI of the women included was relatively low (23.9 [SD 3.8] kg/m2 in the 150 IU/day dose group vs. 23.8 [SD 3.6] kg/m2 in the 100 IU/day dose group);

therefore, data from the OPTIMIST trial may not apply to overweight/obese patients at risk for high ovarian response [26].

The benefits of a reduced starting dose on OHSS incidence were reported in an analysis of four randomized controlled trials (RCTs) in the Cochrane review by Lensen et al. [41]. Two of these studies recruited a general population of women undergoing IVF/ICSI and reported OHSS following fresh embryo transfers after hCG triggering [27] or frozen embryo transfers after GnRH agonist triggering [42]; one study recruited normo-ovulatory women and reported OHSS after fresh transfers [43], and one study recruited hyper-responders and reported OHSS after either fresh or frozen embryo transfers [26]. Although the live birth rates were similar between those with an individualized starting dose and those with a standard starting dose of 150 IU (OR 1.04, 95% confidence interval [CI] 0.88–1.23), there was a 42% reduction in the incidence of moderate and severe OHSS (OR 0.58, 95% CI 0.34–1.00) in those treated with an individualized dose [41]. More well-designed RCTs are now needed to better assess the effect of starting dose reduction on the live birth rate and the effect on the cumulative live birth rate. It should also be noted that reducing the starting dose carries the risk of an unexpected low response to OS; therefore, measures should be taken to avoid cycle cancellation if this occurs.

Furthermore, although the gonadotropin starting dose individualization, rather than a one-size-fits-all approach, is in line with clinical practice [39], it is not always reflected in the design of clinical studies. In the MEGASET-HR trial, in which a fixed starting dose of 150 IU r-hFSH-alfa was compared with 150 IU highly purified menopausal gonadotropin (HP-hMG) for OS in high responders, a twofold higher cancellation rate owing to excessive response (2% [6/309] vs. 1% [3/310]) and an increased rate of OHSS (21.4% vs. 9.7%) were reported for patients treated with r-hFSH-alfa, although the incidence of severe OHSS was comparable [44]. This may be explained by the design of the MEGASET-HR trial, in which participants with a high risk of OHSS were selected based on inclusion criteria (AFC levels >10 and AMH serum levels $\geq$5 ng/mL) that resulted in very high mean baseline values for both AFC (30.7) and AMH (7.7 ng/mL), far exceeding the cutoff values for AFC (>24) or AMH (>3.5 ng/mL) for high response/OHSS risk according to the ASRM guidelines [13]. It has been argued that, according to good practice guidelines in this hyper-responder population with high OHSS risk, the starting dose of r-hFSH-alfa should have been individualized to doses lower than 150 IU using existing algorithms for r-hFSH dose calculation to optimize clinical and safety outcomes [45]. This recommendation is based on extensive evidence showing that using similar IU doses for OS with r-hFSH-alfa results in a higher number of developing follicles and oocytes than OS with HP-hMG [45]. The recommended r-hFSH starting dose range of 150–225 IU/day for women undergoing OS refers to a commonly used regimen for superovulation in the general population [46–48]; however, in clinical practice, the choice of starting dose is based on the individual characteristics of each patient (e.g., whether they are predicted to be low, normal or high responders), and the starting dose can be adjusted to lower than 75 IU per day if an excessive response in terms of a number of follicles is anticipated, based on the patient's clinical profile (such as age, BMI and ovarian reserve). Furthermore, the very strict criteria for GnRH agonist administration for triggering final oocyte maturation (resulting in a number of study participants being exposed to an unnecessary high risk of OHSS), and the fact that several patients underwent fresh embryo transfer without waiting for the results of pre-implantation genetic testing for aneuploidy, are some of the methodological and statistical limitations of the MEGASET-HR trial that preclude the drawing of any firm conclusions for the management of predicted high responders [45].

Ovulation triggering protocol

GnRH agonist ovulation triggering in a GnRH antagonist cycle is recommended for women at high risk of OHSS where no fresh embryo transfer is performed, and all oocytes/embryos are frozen [5]. In a Cochrane review of GnRH agonist versus hCG for oocyte trigger followed by fresh embryo transfer, Youssef et al. reported that a GnRH agonist trigger in a GnRH antagonist protocol was associated with a significantly lower risk of moderate/severe OHSS compared with a hCG trigger among women at high risk of OHSS (OR 0.09, 95% CI 0.02–0.52; four studies; 112 women; $I^2 = 0\%$) [49]. In a more recent systematic review and meta-analysis of a general population of women undergoing IVF/IVSI, Haahr et al. reported no difference in the incidence of moderate OHSS after GnRH agonist ovulation triggering followed by oocyte retrieval, embryo transfer and modified luteal phase support (LPS) using luteinizing hormone (LH) activity (either a single 1500 IU bolus of hCG or six doses of 300 IU recombinant human

LH [r-hLH] every other day from the day of oocyte retrieval until day 10) compared with hCG ovulation triggering followed by oocyte retrieval, embryo transfer and standard LPS (OR 0.48, 95% CI 0.15–1.60; five studies; 859 women). However, the proportion of women with moderate late-onset OHSS was numerically lower following GnRH agonist ovulation triggering (0.9% [4/446] vs. 1.7% [7/413]), and the quality of the evidence for this comparison was deemed as very low by the authors [50].

Minimizing exposure to hCG using the lowest effective dose in high responders may reduce the risk of OHSS. In a retrospective audit of IVF clinical data by Schmidt et al. reducing the dose of hCG used for final oocyte maturation triggering in high responders (E2 levels $\geq$2500 pg/mL but <4000 pg/mL) from 5000 IU to 3300 IU resulted in similar proportions of mature eggs (81.6% vs. 81.9%), fertilization rate (70.5% vs. 68.7%), biochemical pregnancy (58.7% vs. 58.7%) and clinical pregnancy (50.0% vs. 43.5%), although there was no difference in the incidence of mild (5000 IU 8.5% [4/47] vs. 3300 IU 6.3% [3/47]), moderate (5000 IU 2.1% [1/47] vs. 3000 IU 10.6% [5/47]) or severe (5000 IU 0% [0/47] vs. 3000 IU 4.2% [2/47]) OHSS (total OHSS incidence 10.6% [4/47] in the 5000 IU group vs. 21.3% [10/47] in the 3300 IU group; $p = 0.357$) [51]. However, the benefit of low-dose hCG for the prevention of OHSS is not clear as data are sparse and the studies that have been conducted comprised small sample sizes, involved a small number of cycles or were not powered to detect a difference in OHSS rate [52].

Alternative preventive measures

Coasting could be considered, whereby gonadotrophin administration is withheld and hCG ovulation triggering is delayed [53], although a GnRH agonist trigger with or without a freeze-all strategy is preferred over a coasting strategy in patients at risk of OHSS [5], which is only possible in GnRH antagonist protocols. Furthermore, there is no evidence to suggest a benefit of coasting compared with no coasting or other interventions in patients at high risk of OHSS [54]. Therefore, coasting should only be considered when the alternative is cycle cancellation.

Dopamine agonists (with or without co-interventions) probably reduce the incidence of moderate/severe OHSS compared with placebo or no intervention in women at high risk of developing OHSS, although there are no data on adverse events and pregnancy outcomes (live birth, clinical pregnancy and miscarriage) following treatment with a dopamine agonist [55]. Dopamine agonists include oral cabergoline (e.g., 0.5 mg daily for 8 days beginning on the day of hCG injection), bromocriptine (e.g., 2.5 mg daily for 14 days beginning the day of hCG administration) and quinagolide (e.g., 150 μg daily for 15 days beginning on the day of hCG administration) [55].

The suppression of insulin levels using metformin and other insulin-sensitizing agents may be useful for women with polycystic ovarian syndrome (PCOS) undergoing OS, potentially by ameliorating the effects of OS; furthermore, metformin may also act directly on ovarian thecal cells, decreasing androgen production [56]. Adjunct metformin therapy (1000–2550 mg daily, started at the beginning of GnRH agonist treatment) could be used before and/or during OS with FSH in women with PCOS undergoing IVF or intracytoplasmic sperm injection (ICSI) with a GnRH agonist protocol [56,57]. Metformin may reduce the incidence of OHSS (RR 0.46, 95% CI 0.29–0.72; $p < 0.00012$; 11 RCTs; 1091 women; $I^2 = 38\%$; low-quality evidence). However, this effect was driven by a reduction in OHSS in cycles in which women were treated with a long agonist GnRH protocol (RR 0.40, 95% CI 0.26–0.60; nine studies; 898 women; $I^2 = 15\%$), whereas no effect was seen in women treated with a short antagonist protocol (RR 0.97, 95% CI 0.32–2.98; two studies; 193 women; $I^2 = 26\%$) [56].

Recommendation

Individualization of the starting dose of gonadotropin is recommended. The selection of the starting gonadotropin dose for OS can be dependent on specific diagnoses of subfertility, is usually based on ovarian reserve biomarkers, other patient baseline characteristics and past ovarian response to OS and can be guided through the use of dedicated algorithms.

Dose adjustment during OS for ART is common practice in RCTs [39] and real-world practice [40], and is likely intended to avoid both suboptimal and exaggerated ovarian response; however, more studies are needed to evaluate its value in high responders. In agreement with the ESHRE guidelines, we recommend the use of a GnRH antagonist protocol with a GnRH agonist trigger for women with PCOS or those with a predicted high response, with respect to improved safety but with equal efficacy to a long GnRH agonist protocol [5]. Additional measures for the prevention of OHSS, such as coasting,

dopamine agonists or metformin, could be considered, although the respective benefits of these options are unclear.

Post-stimulation strategies: options for embryo transfer strategy

Several options are available for the timing of embryo transfer after OS, depending on the individual conditions and the joint decision made between the physician and the patient.

Freeze all, resulting in an elective frozen embryo strategy

The segmentation of IVF treatment and freeze-all strategy following GnRH agonist trigger has been a breakthrough towards an "OHSS-free clinic" [58]. According to ESHRE guidelines, an elective embryo freezing strategy is recommended in hyper-responders to eliminate the risk of late-onset OHSS in both GnRH agonist and GnRH antagonist protocols [5]. However, it should be noted that sporadic cases of OHSS have also been reported when using this strategy [59]. Furthermore, patients should be strongly advised to avoid sexual intercourse during OS and after oocyte pick-up to avoid spontaneous pregnancy and the occurrence of late OHSS.

Three recent meta-analyses have reported a low risk of OHSS with an elective embryo freezing strategy. In a meta-analysis of data from RCTs, Roque et al. reported the risk of moderate/severe OHSS in a population of normal and high responders/PCOS as being significantly lower after an elective embryo freezing strategy compared with a fresh embryo transfer (OR 0.42, 95% CI 0.19–0.96; $I^2 = 76\%$; seven studies; 5111 patients) following hCG or GnRH agonist ovulation triggering (six studies used a hCG trigger in both arms, and one study used a GnRH agonist trigger in both arms followed by modified LPS with low-dose [1500 IU hCG at oocyte retrieval] in the fresh embryo transfer group), and higher live birth rates in PCOS/hyper-responders following elective frozen embryo transfer versus fresh embryo transfer (RR 1.16, 95% CI 1.05–1.28; $I^2 = 0\%$; four studies; 2035 patients) [60]. In a meta-analysis of normal (four RCTs; 3255 women) and high responders (four RCTs; 2010 women) conducted by Bosdou et al. moderate/severe OHSS was lower with elective frozen embryo transfer compared with fresh transfers in high responders (RR 0.19, 5% CI 0.10–0.37; one study; 1508 women) and in normal responders (RR 0.39, 95% CI 0.19–0.80; two studies; 2939 women). However, a higher live birth rate was reported for high responders following frozen embryo transfer versus fresh transfer (RR 1.18, 95% CI 1.06–1.31 [three studies; 3398 women]), whereas there was no difference in the live birth rate in normoresponders following fresh or frozen embryo transfers (RR 1.13, 95% CI 0.90–1.41; three studies; 1608 women) [61]. Finally, in a meta-analysis including data from RCTs and observational studies, Ioannidou et al. assessed the incidence of severe OHSS after GnRH agonist ovulation triggering in women at high risk of OHSS and reported that the occurrence of severe OHSS was eliminated in these women following GnRH agonist triggering and freeze all (pooled incidence of OHSS 0%, 95% CI 0–0%; $I^2 = 0\%$; 14 data sets; 983 women) [62], whereas the incidence of severe OHSS in high-risk women in whom hCG was added to standard LPS was 1% (95% CI 0.0–2.0, $I^2 = 27.02\%$, random-effects model, ten data sets, 707 women) and 1% (95% CI 0.0–3.0, one study, 182 women) in high-risk women triggered by a combination of GnRHa and hCG (dual triggering) who received standard LPS. Pregnancy and live birth rates were not reported in this meta-analsis.

Improved reproductive outcomes have also been reported after elective frozen embryo transfer cycles in PCOS/high responder women after either hCG or GnRH agonist ovulation triggering. In the meta-analysis by Roque et al. live birth rates were higher in patients who had elective frozen embryo transfers than in those who had fresh embryo transfers in the overall population (risk ratio 1.12, 95% CI 1.01–1.24; $I^2 = 46\%$; nine studies; 5379 women) and in a subpopulation of PCOS/high-responders (risk ratio 1.16, 95% CI 1.05–1.26; $I^2 = 0\%$; four studies; 2035 women) [60]. However, only one study included in this analysis [63] compared elective frozen embryo transfer with fresh transfer following GnRH agonist ovulation triggering. Additionally, in women with PCOS receiving OS in a GnRH antagonist down-regulation cycle, followed by ovulation triggering with hCG, an elective frozen embryo cycle policy resulted in a higher live birth rate after the first embryo transfer (relative risk [RR] 1.16, 95% CI 1.05–1.28) and a lower rate of moderate/severe OHSS (RR 0.42; 95% CI 0.19–0.96) compared with fresh embryo transfers [64].

When a freeze-all policy is considered, it is important to be aware that the number of available oocytes/embryos is positively correlated with the cumulative live birth rate per started OS cycle [65], which is increasingly being regarded as the most informative outcome from IVF treatment across several perspectives, including from the point of view of the patient [66]. In a recent discrete choice experiment of 164 women at ten Dutch IVF clinics who completed an online questionnaire at the start of an IVF treatment, cumulative live birth rate was identified as the most important attribute of the treatment. Treatment preferences were also influenced by the number of embryos suitable for transfer, while the number of transfers needed until pregnancy and the effect on the quality of life did not influence treatment preferences in the aggregated data, although the quality of life was more relevant in women aged ≥36 years [67].

In a real-world evidence study of 9073 patients, including those with low prognosis and normal responders (defined according to the POSEIDON criteria), regression analysis showed that the number of embryos obtained (in addition to the number of embryos transferred per patient, the number of oocytes retrieved, female age, the duration of infertility and BMI) directly and positively affected the cumulative live birth rate ($p < 0.001$) [68]. In a multi-centre study of ~15,000 patients, in which all patients included in the analysis had either delivered a baby or had used all their embryos after their first stimulated cycle, the cumulative live birth rate steadily increased, with the number of oocytes reaching 70% when ≥25 oocytes were retrieved. No plateau in a cumulative live birth was seen, although only a moderate increase of 5.1%, on average, was seen beyond 27 oocytes [69]. Two retrospective cohort studies of cumulative live birth following a single stimulation cycle in mixed populations have reported on the association between the number of oocytes retrieved and this outcome. Of 2226 women (2987 cycles) undergoing a single retrieval cycle, Vaughan et al. reported higher pregnancy rates when ≥15 oocytes were retrieved (289 of 699 [41.3%]) compared with when <15 oocytes were retrieved (518 of 1,419 [36.5%]). After controlling for age, estradiol, BMI, pre-genetic screening, fertilization rate and progesterone levels on the day of trigger, the chance of two or more live births increased by 8% (OR 1.08, 95% CI 1.06–1.11; $p = 0.0001$) with each additional oocyte retrieved up to and including 30 oocytes retrieved [70]. In a study of 1099 women, Drakopoulos et al. reported a significant increase in cumulative live birth rate with the number of oocytes retrieved (χ^2 test for trend $p < 0.001$), with significantly higher cumulative live birth rates for high responders (>15 oocytes) versus poor responders (0–3 oocytes; $p < 0.001$), suboptimal responders 4–9 oocytes; $p < 0.001$) and normal responders (10–15 oocytes; $p = 0.014$); multivariate logistic regression analysis showed that the ovarian response category remained an independent predictive factor ($p < 0.001$) for cumulative live birth rate [71]. In a study of the Italian National Registry, incorporating a total of 10,260 fresh cycles performed between January 2015 and April 2016 (resulting in 9273 oocyte retrievals and 3266 subsequent warming cycles from the same oocyte retrievals performed up to December 2016), the relative contribution of cryopreservation to the cumulative live birth rate increased in relation to the ovarian response (9.6%, 16.5%, 31.0%, 45.3% and 80.6% for poor (≤3 oocytes), suboptimal (4–6 oocytes), normal (7–10 oocytes), good (11–15 oocytes) and high (>15 oocytes) responders, respectively [72]. Finally, in a systematic review of the literature (16 studies), Law et al. concluded that while the optimal number of oocytes at which live birth after the fresh transfer was maximized was between 12 and 18 oocytes, the cumulative live birth rate continued to increase with the number of oocytes retrieved [65].

Fresh embryo transfer with modified/intensified LPS

A GnRH agonist trigger is the preferred option when a fresh embryo transfer cycle is considered, followed by a modified LPS strategy. This modified LPS strategy has been reported to include a low-dose hCG bolus administered on the day of oocyte retrieval (representing off-label use of hCG preparations) in combination with a standard LPS or an intensified LPS strategy (supplementation with exogenous progesterone and E2) [10]. The adoption of these strategies has substantially decreased the occurrence of OHSS while maintaining good reproductive outcomes in patients with high ovarian response in IVF cycles with fresh embryo transfer [73], although further investigation is needed on an individualized approach for the management of the LPS to optimize live birth rates but without increasing the risk of OHSS for each patient.

Modified LPS, adding LH activity to standard LPS

In modified LPS, luteinizing hormone activity is added on the retrieval day to standard exogenous hormonal supplementation (e.g., micronized vaginal progesterone 90 mg/day and 4 mg oral E2) [74]. In a systematic review and meta-analysis of RCTs (five studies; 859 patients) by Haahr et al. no differences in live birth rate (OR 0.84, 95% CI 0.62−1.14) or OHSS (OR 0.48, 95% CI 0.15−1.60) were reported for patients with GnRH agonist ovulation triggering followed by LPS with LH activity (hCG or LH), compared with hCG ovulation triggering followed by standard LPS in fresh embryo transfer cycles [50]. This effect was achieved by the inclusion of studies in which miscarriage rates were reduced through the use of modified LPS using low-dose hCG compared with GnRH agonist ovulation triggering with standard LPS [50].

A RCT by Humaidan et al. described the administration of a single bolus of 1500 IU hCG after oocyte retrieval in two groups of patients (high risk of OHSS [N = 118] and low risk of OHSS [N = 266]) receiving a GnRH agonist as an ovulation trigger versus patients receiving 5000 IU hCG as an ovulation trigger. Both groups received conventional LPS (micronized progesterone vaginally, 90 mg twice daily and E2 4 mg a day taken orally). In the women at risk of OHSS who received the GnRH agonist ovulation trigger and the single bolus of 1500 IU hCG (n = 60) no cases of OHSS were reported, whereas two cases of OHSS (3.4%) were reported in the women who received the hCG ovulation trigger (n = 58). No statistically significant difference was reported in the delivery rate per patient (24% vs. 31%; p = 0.16) [75], although the effect of the small sample size on this result cannot be excluded. Additionally, in a retrospective case study of 275 women at high risk for OHSS who were given one bolus of 1500 IU hCG within an hour after GnRH agonist ovulation triggering followed by LPS with vaginal progesterone and twice daily E2, a clinical pregnancy rate per cycle of 48.1% was achieved, with two cases of severe OHSS (0.72%) [76].

It should be noted, however, that any dose of hCG, whether administered at the time of ovulation triggering with or without a GnRH agonist or later in the context of LPS, should be used with caution as it may increase the risk of OHSS [62]. Santos-Riberio et al. have recently reported the first RCT to investigate the head-to-head comparison of pregnancy rates and safety outcomes with GnRH agonist ovulation triggering followed by freeze-all and elective frozen embryo transfer (n = 104) or fresh transfer with low-dose (1500 IU) hCG 1 h after oocyte retrieval for intensified LPS (n = 105). While no differences in clinical pregnancy were seen between the groups (relative risk 1.13, 95% CI 0.87−1.47; P = 0.41), moderate-to-severe OHSS occurred exclusively in the women who received low-dose hCG (risk difference −8.6%, 95% CI −13.9% to −3.2%; p < 0.01) [77].

Intensified LPS, increasing progesterone and/or oestrogen doses during LPS

In intensified LPS, high-dose intramuscular progesterone (up to 75 mg/day and optional micronized vaginal progesterone) and oestrogen supplementation (a maximum of four 0.1 mg patches every other day and/or oral micronized E2) are used, with doses adjusted according to serum steroid levels [78]. In a RCT of 66 women with PCOS or high response, participants were randomized to receive either GnRH agonist ovulation trigger, fresh embryo transfer with LPS and early pregnancy supplementation with intramuscular progesterone and E2 (study group) or hCG ovulation trigger, fresh embryo transfer and LPS with intramuscular progesterone only (control group) [17]. No cases of OHSS were reported in the study group compared with 31% (10/32) in the control group. Furthermore, there were no significant differences in the implantation (22/61 [36.0%] vs. 20/64 [31.0%]), clinical pregnancy (17/30 [56.7%] vs. 15/29 [51.7%]) and ongoing pregnancy (16/30 [53.3%] vs. 14/29 [48.3%]) rates between the groups; however, the results should be interpreted with caution owing to the small sample sizes. Based on the findings of a SWOT (strengths, weaknesses, opportunities, threats) analysis of progress made to optimize ongoing pregnancy rates after a GnRH agonist ovulation trigger [79], Engmann et al. made recommendations for intensive LPS based on peak serum E2 levels or the number of follicles aspirated. If peak serum E2 is $\geq$ 4000 pg/ml, they recommended a GnRH agonist ovulation trigger followed by intensive LPS with intramuscular progesterone (50 mg/day starting the evening after oocyte retrieval, increasing if necessary to a maximum of 75 mg/day to maintain a serum level above 20 ng/mL) and transdermal E2 (three 0.1 mg transdermal E2 patches every other day starting the day after oocyte retrieval, increasing if necessary to a maximum of four 0.1 mg patches every other day and/or addition

of oral micronized E2 2 mg twice a day to maintain the serum E2 level above 200 pg/mL) [80]. If peak serum E2 is < 4000 pg/mL, the recommendation from the SWOT analysis was a GnRH agonist ovulation trigger combined with simultaneous injection of hCG 1000 IU. In the case of <25 follicles, the recommendation from the SWOT analysis was for a GnRH agonist ovulation triggering followed by hCG 1500 IU 35 h later, without additional LPS. In the case of >25 follicles, the recommendation from the SWOT analysis was to freeze all oocytes/embryos.

Fresh embryo transfer after conventional ovulation triggering with hCG, associated with conventional LPS

Lower starting doses of gonadotropin can be considered if the decision is to go for a fresh embryo transfer with hCG ovulation triggering and conventional LPS. Although this may increase the risk of cycle cancellation due to poor response, the risk can be reduced by selectively and carefully increasing the follitropin alfa dose (i.e., with a low dose of 12.5 IU increments [81]) during OS. In a RCT of predicted high responders (AFC >15), Oudshoorn et al. reported no difference in cumulative live birth rate (RR 0.95, 95% CI 0.85–1.07; p = 0.423) between those randomized to an FSH starting dose of 100 IU/day (n = 255) and those randomized to a starting dose of 150 IU/day (n = 266). The occurrence of any grade of OHSS was lower in the 100 IU/day group than in the 150 IU/day group (RR 0.44, 95% CI 0.28–0.71; p = 0.001), although the occurrence of severe OHSS did not differ between groups (RR 1.25, 95% CI 0.38–4.07). In this study, final oocyte maturation was achieved by the administration of hCG when ≥3 follicles of 17 mm were present, and LPS comprised 600 mg micronized progesterone in three separate doses starting one day after oocyte retrieval and continuing until 18 days after oocyte pick-up [26].

Recommendations

In agreement with the ESHRE guidelines, we recommend an elective embryo freezing strategy in patients with expected high ovarian response to substantially reduce the risk of late-onset OHSS and improve clinical outcomes in both GnRH agonist and GnRH antagonist protocols [5]. However, if a fresh embryo transfer is the preferred option, a GnRH trigger should be used, followed by luteal phase rescue using either intensified/modified or conventional LPS, bearing in mind the potential for OHSS following exposure to any dose of hCG used for ovulation triggering and/or LPS.

Treatment strategies for patients with unexpected high response

Different strategies should be considered for women with an unexpected high response to OS than for women with a predicted high response (Fig. 2). These include different stimulation strategies and different GnRH agonist/antagonist protocols.

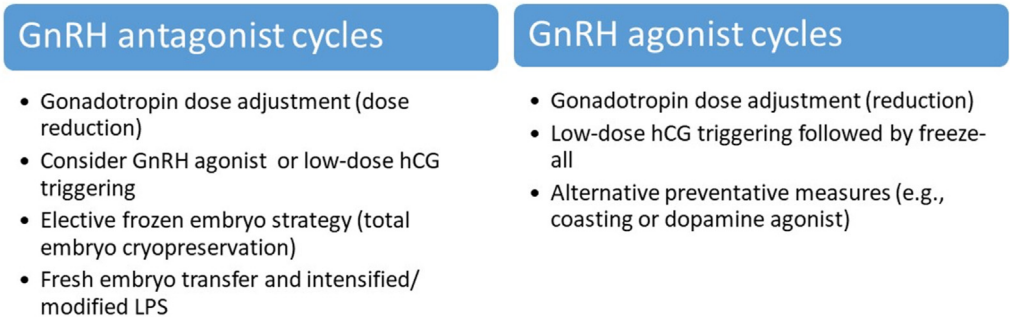

Fig. 2. Treatment strategies for patients with unexpected high response.

Stimulation strategies

Dose adjustment during stimulation

Patients with an unexpected high ovarian response to OS (measured by close monitoring with ultrasound assessment of follicular development and monitoring of E2 levels) with a starting dose in the conventional range (e.g., 150–225 IU/day for r-hFSH) may require a dose reduction (i.e., intra-cycle dose adjustment) [39]. Such reductions during the stimulation cycle may reduce the likelihood of moderate/severe OHSS [41]. The dosage of many follitropin preparations can be adjusted during stimulation according to their label based on the patient's ovarian response to OS [46–48,82], although this is not indicated for all follitropin preparations (e.g., corifollitropin alfa [83] and follitropin delta [84]).

Reduction in gonadotropin dose during a stimulation cycle is common in both clinical trials and clinical practice. In a systematic review and meta-analysis, Fatemi et al. evaluated the occurrence of dose adjustment depending on the response at Day 5/6 of stimulation in RCTs of OS for ART in which a fresh embryo transfer was planned. Out of 18 eligible studies, 11 reported dose decreases, eight reported dose increases and decreases and in five the direction of adjustment was not specified [39]. A reduction in the starting dose was also reported in an analysis of RWD obtained in the US. Of 13,823 cycles in which there was dose adjustment, 25.4% had $\geq$1 dose decrease, 8.1% had $\geq$1 dose decrease and $\geq$1 dose increase [40]. In the study by Fatemi et al. adjustments were more common in patients receiving GnRH agonists than those receiving GnRH antagonists [39]; in the study by Mahony et al. adjustments were more common in younger versus older patients, in those with a high versus low ovarian reserve or those with ovulation disorders/polycystic ovary syndrome versus other primary diagnoses of infertility [40].

The ability to adjust doses in small increments can help reduce the risk of OHSS [37,43,85]. Dose adjustments with 12.5 IU increments are possible with some formulations of follitropin alfa, which may result in a lower dose per oocyte retrieved and a lower OHSS incidence [81,86–91], although further data are needed on whether small adjustments affect clinical outcomes.

GnRH antagonist protocols

In women treated with a GnRH antagonist protocol, ovulation triggering with a GnRH agonist should be considered, although low-dose hCG ovulation triggering could be used in patients with very low endogenous LH. A reduction in the gonadotropin dose could also be considered in GnRH antagonist protocols, based on the close assessment of the patient response at Day 5/6 [39] or earlier [46–48,82]. Finally, an elective embryo freezing strategy is recommended [5] or, if the patient chooses a fresh embryo transfer, a GnRH agonist ovulation trigger in combination with modified/intensified LPS should be considered.

GnRH agonist protocols

Adjustment of the starting dose, ovulation triggering with low-dose hCG and/or an elective frozen embryo strategy should be considered for women treated with a GnRH agonist protocol who have an unexpected high response. Further preventive measures could also be implemented to reduce the risk of OHSS.

Alternative preventive measures

Based on the evidence discussed in the section above on expected high responders, coasting and dopamine agonists can also be considered in women with unexpected high responses.

Recommendations

In women with an unexpected high response to OS, as indicated by hormonal and ultrasound monitoring, we recommend that the dose of gonadotropin should be reduced during the stimulation cycle, which is consistent with the research study design and real-world clinical practice. Furthermore, the option to adjust the dose in small increments may be particularly beneficial. Ovulation triggering with a GnRH agonist is recommended for women with pituitary down regulation using a GnRH antagonist; if the use of a GnRH agonist for down-regulation precludes the use of a GnRH agonist

trigger, we recommend elective frozen embryo transfer after hCG triggering in GnRH agonist down-regulation protocols. Additional measures for the prevention of OHSS, such as coasting or dopamine agonists, could be considered, although the respective benefits of these options are unclear.

Discussion

In this educational article, we provide an evidence-based framework for the management of predicted and unexpected high responders to conventional OS that covers aspects relevant before, during and after stimulation. In line with the published ESHRE guidelines [5], our recommended strategy is to reduce the risk of OHSS by using an elective frozen embryo transfer following GnRH agonist ovulation triggering. This strategy may be in agreement with the expectations of most patients, as reported in a recent survey using a discrete choice experiment technique of infertile couples, conducted between August 2018 and January 2019 [24]. This survey found that an elective embryo freezing strategy was acceptable to patients if the success rate can be improved or neonatal complications reduced. Indeed, the main factors that drove patient preference were live birth rates, risk of neonatal complications, miscarriage rates and costs, rather than differences in the treatment process (including the delay of embryo transfer linked to an elective frozen embryo strategy and the risk of OHSS associated with fresh embryo transfer) [24]. However, we recognize that elective frozen embryo transfer may not be a viable option for some patients or may not be in accord with the wishes of the patient; therefore, we have also provided recommendations for patient management in other scenarios.

During the development of these recommendations, we identified several gaps in the published literature on the management of high responders that could be addressed in future studies. For example, in the case of elective frozen embryo transfer after GnRH agonist ovulation triggering, from a safety perspective (e.g., residual OHSS risk or possible complications related to oocyte aspiration if > 30 follicles are available), what would be the maximum number of oocytes that can be retrieved, the maximum limit for the optimal gonadotropin starting dose, or the maximum number of follicles >10 mm (with or without assessment of E2 levels) above which consideration should be given to cancelling the cycle, even if the use of a GnRH agonist trigger is considered? Regarding these points, we fully acknowledge that the strong incentive to maximize oocyte yield and routinely apply a GnRH agonist trigger, as well as the possible practice of banking eggs for fertility preservation and egg donation, present difficulties in forming a recommendation. Another gap in the literature is the extent to which dose adjustment only during OS (i.e., in cycles without individualization of the starting dose) has an impact on reproductive outcomes and risk for OHSS or cycle cancellation. Current trials have typically used different starting doses [26,29], making it difficult to ascertain the true, independent value of dose adjustment solely during stimulation.

During the course of the discussion, several opportunities for future investigation were also identified. Firstly, we identified the potential of looking at different subgroups or phenotypes of high responders. For example, there may be specific subgroups of high responders in whom even low doses of hCG during LPS should be avoided [92,93]. For example, Seyhan et al. recommended that hCG luteal phase rescue should be avoided in women with $\geq$18 follicles of 10–14 mm on the day of the GnRH agonist trigger, even if the number of larger follicles is limited [93]. Furthermore, with regard to fresh embryo transfers, we recognized the potential for the existing algorithms for starting dose calculation [9,27,31,36] to be incorporated and validated into an easy-to-use calculator for gonadotrophin starting dose for predicted high responders, taking into account the number of oocytes needed to achieve one euploid blastocyst (e.g., similar to the ART calculator [94]). Moreover, we hypothesized whether there is potential for these updated algorithms to be applied differentially for OS cycles with a fresh embryo transfer or cycles with freezing of all available embryos (elective embryo freezing strategy).

Summary

The success of ART treatment requires balancing efficacy (the number of oocytes retrieved to maximize cumulative live birth rate) with safety (avoiding the occurrence of OHSS or thromboembolic

events). Women can be classified as poor, suboptimal, normal or high responders to OS, depending on the number of developing follicles and the number of oocytes retrieved following OS. Women with a high response are also at high risk for cycle cancellation and early OHSS, which is associated with substantial physical and psychosocial morbidity. Women at risk of high response can be identified before stimulation based on several indices; the outcome from a previous cycle, ovarian reserve markers (AFC and AMH) and age are reliable predictors of ovarian response. However, some women may have an unexpected high response to OS that is only diagnosed after OS has started. In this article, we have provided evidence-based recommendations for the identification of women at risk of high response before stimulation and the use of modern treatment strategies before, during and after stimulation, for both expected and unexpected high responders, with the aim to help minimize OHSS risk and improve efficacy.

Practice points

- Women can be classified as poor, suboptimal, normal or high responders to OS, depending on the number of developing follicles and the number of oocytes retrieved following OS.
- Women at risk of high response can be identified before stimulation based on several indices; the outcome from a previous cycle, ovarian reserve markers (AFC and AMH) and age are reliable predictors of ovarian response. However, some women may have an unexpected high response to OS that is only diagnosed after OS has started.
- To encompass the recommendations from the guidelines from three international organizations, a value of $>18-20$ follicles $\geq 11-12$ mm on the day of the ovulation triggering may be considered for the diagnosis of high response before oocyte pick-up.
- Nomograms can be used to individualize the gonadotropin starting dose according to the patient's age and other baseline parameters.
- The gonadotropin dose can be adjusted based on the ovarian response from Day 5/6 of stimulation.
- A freeze-all strategy is recommended to fully eliminate the risk of late-onset OHSS in both GnRH agonist and GnRH antagonist protocols.

Research agenda

- The incidence of moderate/severe OHSS should be routinely monitored and reported, to assess performance in ART clinical practice.
- Different thresholds for high-response phenotypes of PCOS have been proposed, and different cutoffs for the number of follicles associated with a significantly increased risk of severe OHSS have also been defined. Therefore, further research is needed to provide an individualized approach.
- Further discussion is needed regarding how to avoid unexpected low ovarian response in patients with high BMI and PCOS; these discussions should focus on individualized higher starting FSH doses, dose adjustment during stimulation, the potential use of LH for GnRH agonist ovulation triggering and the choice between fresh embryo transfer or elective frozen embryo transfer cycles.
- Is there an upper limit for the number of follicles >10 mm (with or without the assessment of E2 levels) available after OS for ART in GnRH antagonist cycles where, in the interests of safety, cycle cancellation should be considered rather than GnRH agonist ovulation triggering, oocyte aspiration and elective frozen embryo transfer cycles?

Funding

This study was funded by Merck (CrossRef Funder ID: 10.13039/100009945). Merck Healthcare KGaA (Darmstadt, Germany) designed and approved the study, took part in data collection and data analysis, and contributed to the data interpretation and final draft of the manuscript.

Authors' contributions

All authors contributed to the conception and design of the analysis, as well as the interpretation of data and critical review of this manuscript. All authors approved the manuscript for submission to the journal.

Data availability

Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck's Data Sharing Policy. All requests should be submitted in writing to Merck's data sharing portal https://www.merckgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html. When Merck has a co-research, co-development, or co-marketing or co-promotion agreement, or when the product has been out-licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, Merck will endeavour to gain agreement to share data in response to requests.

Declaration of competing interest

PD declares research grants and honoraria from Merck KGaA, Darmstadt, Germany, MSD, Ferring Pharmaceuticals; and paid consultancy work from Merck KGaA, Darmstadt, Germany.

YaK received lecture fees/honoraria/grants from MSD; Merck KGaA, Darmstadt, Germany; Besins Healthcare; Gedeon Richter; Abbott; Bayer; ISBA; LD Collins; Ferring and Sun Pharma.

SCE declares the receipt of unrestricted research grants from Merck and lecture fees from Merck, Event Planet, and Med.E.A.

NP declares research grants and honoraria from Merck KGaA, Darmstadt, Germany; MSD; Organon; Ferring Pharmaceuticals; Besins International; Roche Diagnostics; IBSA; Theramex; Gedeon Richter.

SKS has received speaker fees for non-promotional educational symposia by Merck KGaA, Darmstadt, Germany; MSD; Ferring; Pharmasure.

DS has participated in Speaker's bureaus for both Merck KGaA, Darmstadt, Germany and Organon.

BR has no conflicts of interest to declare.

HY has no conflicts of interest to declare.

MC has declared past sponsorship from Merck KGaA, Darmstadt, Germany, for scientific conference presentations.

YuK received speaker fees/honoraria/grants from MSD, Merck KGaA, Darmstadt, Germany; Besins Healthcare; Gedeon Richter; Abbott; Bayer; and Sun Pharma.

BS received research grants and honoraria from Merck KGaA, Darmstadt, Germany and Gedeon Richter.

ML and TDH are employees of Merck Healthcare KGaA, Darmstadt, Germany.

ALM declares research grants and honoraria from Merck KGaA, Darmstadt, Germany; MSD; Ferring Pharmaceuticals; Gedeon Richter; ISBA; Theramex; Organon; Roche; Beckman Coulter.

Acknowledgments

Medical writing assistance was provided by Steven Goodrick, inScience Communications, Springer Healthcare Ltd., London, UK, and funded by Merck Healthcare KGaA, Darmstadt, Germany.

References

*[1] Magnusson A, Källen K, Thurin-Kjellberg A, Bergh C. The number of oocytes retrieved during IVF: a balance between efficacy and safety. Hum Reprod 2018;33:58–64.
[2] Zegers-Hochschild F, Adamson D, Dyer S, Racowsky C, de Mouzon J, Sokol R, et al. The international glossary on infertility and fertility care, 2017. Fertil Steril 2017;108:394–406.
[3] Esteves SC, Roque M, Bedoschi GM, Conforti A, Humaidan P, Alviggi C. Defining low prognosis patients undergoing assisted reproductive technology: POSEIDON criteria-the why. Front Endocrinol 2018;9:461.
[4] Polyzos NP, Sunkara SK. Sub-optimal responders following controlled ovarian stimulation: an overlooked group? Hum Reprod 2015;30(9):2005–8.
*[5] Bosch E, Broer S, Griesinger G, Grynberg M, Humaidan P, Kolibianakis E, et al. ESHRE guideline: ovarian stimulation for IVF/ICSI. Human Reproduction Open 2020;2. hoaa009.
*[6] Sunkara S, Rittenberg V, Raine-Fenning N, Bhattacharya S, Zamora J, Coomarasamy A. Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles. Hum Reprod 2011;26:1768–74.
[7] Nastri C, Ferriani R, Rocha I, Martins W. Ovarian hyperstimulation syndrome: pathophysiology and prevention. J Assist Reprod Genet 2010;27:121–8.
*[8] Steward R, Lan L, Shah A, Yeh J, Price T, Goldfarb J, et al. Oocyte number as a predictor for ovarian hyperstimulation syndrome and live birth: an analysis of 256,381 in vitro fertilization cycles. Fertil Steril 2014;101:967–73.
[9] La Marca A, Sunkara S. Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice. Hum Reprod Update 2014;20:124–40.
[10] Humaidan P, Polyzos N. Human chorionic gonadotropin vs. gonadotropin-releasing hormone agonist trigger in assisted reproductive technology–"the king is dead, long live the king. Fertil Steril 2014;102:339–41.
[11] Gat I, Shlush E, Quach K, Librach C. The continuum of high ovarian response: a rational approach to the management of high responder patient subgroups. Syst Biol Reprod Med 2015;61:336–44.
[12] Mol BW, Bossuyt PM, Sunkara SK, Garcia Velasco JA, Venetis C, Sakkas D, et al. Personalized ovarian stimulation for assisted reproductive technology: study design considerations to move from hype to added value for patients. Fertil Steril 2018;109(6):968–79.
*[13] ASRM. Practice Committee of the American society for reproductive medicine. Fertil Steril 2016;106:1634–47.
[14] Sun B, Ma Y, Li L, Hu L, Wang F, Zhang Y, et al. Factors associated with ovarian hyperstimulation syndrome (OHSS) severity in women with polycystic ovary syndrome undergoing IVF/ICSI. Front Endocrinol 2020;11:615957.
[15] Achrekar S, Modi D, Desai S, Mangoli V, Mangoli R, Mahale S. Poor ovarian response to gonadotrophin stimulation is associated with FSH receptor polymorphism. Reprod Biomed Online 2009;18:509–15.
[16] Alviggi C, Conforti A, Santi D, Esteves S, Andersen C, Humaidan P, et al. Clinical relevance of genetic variants of gonadotrophins and their receptors in controlled ovarian stimulation: a systematic review and meta-analysis. Hum Reprod Update 2018;24:599–614.
[17] Engmann L, DiLuigi A, Schmidt D, Nulsen J, Maier D, Benadiva C. The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized controlled study. Fertil Steril 2008;89:531–3.
[18] Freour T, Masson D, Dessolle L, Allaoua D, Dejoie T, Mirallie S, et al. Ovarian reserve and in vitro fertilization cycles outcome according to women smoking status and stimulation regimen. Arch Gynecol Obstet 2012;285:1177–82.
[19] La Marca A, Spada E, Sighinolfi G, Argento C, Tirelli A, Giulini S, et al. Age-specific nomogram for the decline in antral follicle count throughout the reproductive period. Fertil Steril 2011;95:684–8.
[20] Nenonen H, Lindgren I, Prahl A, Trzybulska D, Kharraziha I, Hulten M, et al. The N680S variant in the follicle-stimulating hormone receptor gene identifies hyperresponders to controlled ovarian stimulation. Pharmacogenetics Genom 2019;29:114–20.
*[21] Polyzos N, Neves A, Drakopoulos P, Spits C, Alvaro Mercadal B, Garcia S, et al. The effect of polymorphisms in FSHR and FSHB genes on ovarian response: a prospective multicenter multinational study in Europe and Asia. Hum Reprod 2021;36:1711–21.
[22] Tang H, Yan Y, Wang T, Zhang T, Shi W, Fan R, et al. Effect of follicle-stimulating hormone receptor Asn680Ser polymorphism on the outcomes of controlled ovarian hyperstimulation: an updated meta-analysis of 16 cohort studies. J Assist Reprod Genet 2015;32:1801–10.
[23] Webber LJ, Stubbs S, Stark J, Trew G, Margara R, Hardy K, et al. Formation and early development of follicles in the polycystic ovary. Lancet 2003;362:1017–21.
[24] Abdulrahim B, Scotland G, Bhattacharya S, Maheshwari A. Assessing couples' preferences for fresh or frozen embryo transfer: a discrete choice experiment. Hum Reprod 2021;36:2891–903.
[25] Lunenfeld B, Bilger W, Longobardi S, Kirsten J, D'Hooghe T, Sk S. Decision points for individualized hormonal stimulation with recombinant gonadotropins for treatment of women with infertility. Gynecol Endocrinol 2019;35:1027–36.
[26] Oudshoorn S, van Tilborg T, Eijkemans M, Oosterhuis G, Friederich J, van Hooff M, et al. Individualized versus standard FSH dosing in women starting IVF/ICSI: an RCT. Part 2: the predicted hyper responder. Hum Reprod 2017;32:2506–14.
*[27] Popovic-Todorovic B, Loft A, Bredkjaeer H, Bangsbøll S, Nielsen I, Andersen A. A prospective randomized clinical trial comparing an individual dose of recombinant FSH based on predictive factors versus a 'standard' dose of 150 IU/day in 'standard' patients undergoing IVF/ICSI treatment. Hum Reprod 2003;18:2275–82.
[28] Humaidan P, Nelson S, Devroey P, Coddington C, Schwartz L, Gordon K, et al. Ovarian hyperstimulation syndrome: review and new classification criteria for reporting in clinical trials. Hum Reprod 2016;31:1997–2004.
[29] Broekmans F. Individualization of FSH doses in assisted reproduction: facts and fiction. Front Endocrinol 2019;10:181.
[30] Griesinger G, Verweij P, Gates D, Devroey P, Gordon K, Stegmann B. Prediction of ovarian hyperstimulation syndrome in patients treated with corifollitropin alfa or rFSH in a GnRH antagonist protocol. PLoS One 2016;11:e0149615.

*[31] La Marca A, Papaleo E, Grisendi V, Argento C, Giulini S, Volpe A. Development of a nomogram based on markers of ovarian reserve for the individualisation of the follicle-stimulating hormone starting dose in in vitro fertilisation cycles. BJOG 2012;119:1171–9.
[32] La Marca A, Sighinolfi G, Radi D, Argento C, Baraldi E, Artenisio A, et al. Anti-Mullerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART). Hum Reprod Update 2010;16:113–30.
[33] Nelson S, Yates R, R F. Serum anti-Mullerian hormone and FSH: prediction of live birth and extremes of response in stimulated cycles–implications for individualization of therapy. Hum Reprod 2007;22:2414–21.
[34] Rose T, Roshammar D, Erichsen L, Grundemar L, Ottesen J. Characterisation of population pharmacokinetics and endogenous follicle-stimulating hormone (FSH) levels after multiple dosing of a recombinant human FSH in HEalthy women. Drugs 2016;16:165–72.
[35] Sadeghi M. How can personalized medicine improve assisted reproduction technology outcomes? J Reproduction Infertil 2017;18:265–6.
[36] Magnusson A, Nilsson L, Olerod G, Thurin-Kjellberg A,CB. The addition of anti-Mullerian hormone in an algorithm for individualized hormone dosage did not improve the prediction of ovarian response-a randomized, controlled trial. Hum Reprod 2017;32:811–9.
*[37] Yovich J, Alsbjerg B, Conceicao J, Hinchliffe P, Keane K. PIVET rFSH dosing algorithms for individualized controlled ovarian stimulation enables optimized pregnancy productivity rates and avoidance of ovarian hyperstimulation syndrome. Drug Des Dev Ther 2016;10:2561–73.
[38] La Marca A, Blockeel C, Bosch E, Fanchin R, Fatemi H, Fauser B, et al. Individualized FSH dosing improves safety and reduces iatrogenic poor response while maintaining live-birth rates. Hum Reprod 2018;33:982–3.
[39] Fatemi H, Bilger W, Denis D, Griesinger G, La Marca A, Longobardi S, et al. Dose adjustment of follicle-stimulating hormone (FSH) during ovarian stimulation as part of medically-assisted reproduction in clinical studies: a systematic review covering 10 years (2007–2017). Reprod Biol Endocrinol 2021;19:68.
[40] Mahony M, Hayward B, Mottla G, Richter K, Beall S, Ball D, et al. Recombinant human follicle stimulating hormone alfa dose adjustment in US clinical practice: an observational, retrospective analysis of a real-world electronic medical records database. Front Endocrinol 2021;12:1660.
[41] Lensen S, Wilkinson J, Leijdekkers J, La Marca A, Mol B, Marjoribanks J, et al. Individualised gonadotropin dose selection using markers of ovarian reserve for women undergoing in vitro fertilisation plus intracytoplasmic sperm injection (IVF/ICSI). Cochrane Database Syst Rev 2018;2:CD012693.
[42] Nyboe Andersen A, Nelson SM, Fauser BC, García-Velasco JA, Klein BM, Arce JC. Individualized versus conventional ovarian stimulation for in vitro fertilization: a multicenter, randomized, controlled, assessor-blinded, phase 3 noninferiority trial. Fertil Steril 2017;107(2):387–96. e4.
[43] Olivennes F, Trew G, Borini A, Broekmans F, Arriagada P, Warne D, et al. Randomized, controlled, open-label, non-inferiority study of the CONSORT algorithm for individualized dosing of follitropin alfa. Reprod Biomed Online 2015;30:248–57.
[44] Witz C, Daftary G, Doody K, Park J, Seifu Y, Yankov V, et al. Randomized, assessor-blinded trial comparing highly purified human menotropin and recombinant follicle-stimulating hormone in high responders undergoing intracytoplasmic sperm injection. Fertil Steril 2020;114:321–30.
[45] Batista A, Akbas E, Coulidiaty G, Schwarze J-E, Kohlhepp F, Gupta S, et al. Comment on: randomized, assessor-blinded trial comparing highly purified human menotropin and recombinant follicle-stimulating hormone in high responders undergoing intracytoplasmic sperm injection. 2021 [Available from: https://www.fertstertdialog.com/documents/comment-by-batista-et-al-regarding-article-randomized-assessor-blinded-trial-comparing-highly-purified-human-menotropin-and-recombinant-follicle-stimulating-hormone.
[46] Information BEP. Bemfola: summary of product characteristic London. UK: European Medicines Agency; 2019. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/bemfola.
[47] Information OEP. Ovaleap: summary of product charactersitics. London, UK: European Medicines Agency; 2019. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/ovaleap.
[48] Information G-fEp. Gonal-f: summary of product characteristics. Amsterdam, Netherlands: European Medicines Agency; 2020. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/gonal-f.
[49] Youssef M, Van der Veen F, Al-Inany H, Mochtar M, Griesinger G, Nagi Mohesen M, et al. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology (Review). Cochrane Database Syst Rev 2014;50:CD008046.
[50] Haahr T, Roque M, Esteves S, Humaidan P. GnRH agonist trigger and LH activity luteal phase support versus hCG trigger and conventional luteal phase support in fresh embryo transfer IVF/ICSI cycles-A systematic PRISMA review and meta-analysis. Front Endocrinol 2017;8:116.
[51] Schmidt DW, Maier DB, Nulsen JC, Benadiva CA. Reducing the dose of human chorionic gonadotropin in high responders does not affect the outcomes of in vitro fertilization. Fertil Steril 2004;82(4):841–6.
[52] Fiedler K, Ezcurra D. Predicting and preventing ovarian hyperstimulation syndrome (OHSS): the need for individualized not standardized treatment. Reprod Biol Endocrinol : RBE (Rev Bras Entomol) 2012;10:32.
[53] Sher G, Salem R, Feinman M, Dodge S, Zouves C, Knutzen V. Eliminating the risk of life-endangering complications following overstimulation with menotropin fertility agents: a report on women undergoing in vitro fertilization and embryo transfer. Obstet Gynecol 1993;81(6):1009–11.
[54] D'Angelo A, Amso N, Hassan R. Coasting (withholding gonadotrophins) for preventing ovarianhyperstimulation syndrome. Cochrane Database Syst Rev 2017;15:CD002811.
[55] Tang H, Mourad S, Wang A, Zhai SD, Hart R. Dopamine agonists for preventing ovarian hyperstimulation syndrome. Cochrane Database Syst Rev 2021;4:CD008605.
[56] Tso LO, Costello MF, L E T A, Andriolo RB, Macedo CR. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. Cochrane Database Syst Rev 2020;21:CD006105.

[57] Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. International PCOS Network. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertil Steril 2018;110:364–79.
[58] Devroey P, Polyzos NP, Blockeel C. An OHSS-Free Clinic by segmentation of IVF treatment. Hum Reprod 2011;26(10):2593–7.
[59] Kol S. A case of severe early-onset OHSS after GnRH-agonist triggering. Fertil Steril 2011;98:E151.
*[60] Roque M, Haahr T, Geber S, Esteves S, Humaidan P. Fresh versus elective frozen embryo transfer in IVF/ICSI cycles: a systematic review and meta-analysis of reproductive outcomes. Hum Reprod Update 2018;25:2–14.
[61] Bosdou JK, Venetis CA, Tarlatzis BC, Grimbizis GF, Kolibianakis EM. Higher probability of live-birth in high, but not normal, responders after first frozen-embryo transfer in a freeze-only cycle strategy compared to fresh-embryo transfer: a meta-analysis. Hum Reprod 2019;34(3):491–505.
[62] Ioannidou P, Bosdou J, Lainas G, Lainas T, Grimbizis G, Kolibianakis E. How frequent is severe ovarian hyperstimulation syndrome after GnRH agonist triggering in high-risk women? A systematic review and meta-analysis. Reprod Biomed Online 2021;42:635–50.
[63] Aflatoonian A, Mansoori-Torshizi M, Farid Mojtahedi M, Aflatoonian B, Khalili MA, Amir-Arjmand MH, et al. Fresh versus frozen embryo transfer after gonadotropin-releasing hormone agonist trigger in gonadotropin-releasing hormone antagonist cycles among high responder women: a randomized, multi-center study. International journal of reproductive biomedicine 2018;16(1):9–18.
*[64] Chen Z-J, Shi Y, Sun Y, Zhang B, Liang X, Cao Y, et al. Fresh versus frozen embryos for infertility in the polycystic ovary syndrome. N Engl J Med 2016;375:523–33.
[65] Law YJ, Zhang N, Kolibianakis EM, Costello MF, Keller E, Chambers GM, et al. Is there an optimal number of oocytes retrieved at which live birth rates or cumulative live birth rates per aspiration are maximized after ART? A systematic review. Reprod Biomed Online 2021;42(1):83–104.
[66] Maheshwari A, McLernon D, Bhattacharya S. Cumulative live birth rate: time for a consensus? Hum Reprod 2015;30(12):2703–7.
[67] Cornelisse S, Vos MS, Groenewoud H, Mastenbroek S, Ramos L, Braat DDM, et al. Women's preferences concerning IVF treatment: a discrete choice experiment with particular focus on embryo transfer policy. Hum Reprod Open 2022;2022(3):hoac030.
[68] Esteves S, Yarali H, Vuong L, Carvalho J, Özbek I, Polat M, et al. Cumulative delivery rate per aspiration IVF/ICSI cycle in POSEIDON patients: a real-world evidence study of 9073 patients. Hum Reprod 2021;36:2157–69.
*[69] Polyzos N, Drakopoulos P, Parra J, Pellicer A, Santos-Ribeiro S, Tournaye H, et al. Cumulative live birth rates according to the number of oocytes retrieved after the first ovarian stimulation for in vitro fertilization/intracytoplasmic sperm injection: a multicenter multinational analysis including 15,000 women. Fertil Steril 2018;110:661–70.
[70] Vaughan DA, Leung A, Resetkova N, Ruthazer R, Penzias AS, Sakkas D, et al. How many oocytes are optimal to achieve multiple live births with one stimulation cycle? The one-and-done approach. Fertil Steril 2017;107(2):397–404. e3.
[71] Drakopoulos P, Blockeel C, Stoop D, Camus M, de Vos M, Tournaye H, et al. Conventional ovarian stimulation and single embryo transfer for IVF/ICSI. How many oocytes do we need to maximize cumulative live birth rates after utilization of all fresh and frozen embryos? Hum Reprod 2016;31(2):370–6.
[72] Scaravelli G, Levi-Setti P-E, Livi G, La Sala G, Ubaldi F, Greco E, et al. Contribution of cryopreservation to the cumulative live birth rate: a large multicentric cycle-based data analysis from the Italian National Registry. J Assist Reprod Genet 2019;36:2287–95.
[73] Humaidan P, Kol S, Papanikolaou E. GnRH agonist for triggering of final oocyte maturation: time for a change of practice? Hum Reprod Update 2011;17:510–24.
[74] Humaidan P. Luteal phase rescue in high-risk OHSS patients by GnRHa triggering in combination with low-dose HCG: a pilot study. Reprod Biomed Online 2009;18:630–4.
*[75] Humaidan P, Polyzos N,P, Alsbjerg B, Erb K, Mikkelsen A, Elbaek H, et al. GnRHa trigger and individualized luteal phase hCG support according to ovarian response to stimulation: two prospective randomized controlled multi-centre studies in IVF patients. Hum Reprod 2013;28:2511–21.
[76] Iliodromiti S, Blockeel C, Tremellen K, Fleming R, Tournaye H, Humaidan P, et al. Consistent high clinical pregnancy rates and low ovarian hyperstimulation syndrome rates in high-risk patients after GnRH agonist triggering and modified luteal support: a retrospective multicentre study. Hum Reprod 2013;28:2529–36.
[77] Santos-Ribeiro S, Mackens S, Popovic-Todorovic B, Racca A, Polyzos NP, Van Landuyt L, et al. The freeze-all strategy versus agonist triggering with low-dose hCG for luteal phase support in IVF/ICSI for high responders: a randomized controlled trial. Hum Reprod 2020;35(12):2808–18.
[78] Humaidan P, Engmann L, Benadiva C. Luteal phase supplementation after gonadotropin-releasing hormone agonist trigger in fresh embryo transfer: the American versus European approaches. Fertil Steril 2015;103:879–85.
[79] Engmann L, Benadiva C, Humaidan P. GnRH agonist trigger for the induction of oocyte maturation in GnRH antagonist IVF cycles: a SWOT analysis. Reprod Biomed Online 2016;32:274–85.
[80] Engmann L, Benadiva B, Humaidan P. GnRH agonist trigger for the induction of oocyte maturation in GnRH antagonist IVF cycles: a SWOT analysis. Reprod Biomed Online 2016;32:274–85.
[81] Choi B, Zhou C, Ye H, Sun Y, Zhong Y, Gong F, et al. A comparative, observational study evaluating dosing characteristics and ovarian response using the recombinant human follicle-stimulating hormone pen injector with small-dose dial in assisted reproductive technologies treatment in Asia: IMPROVE study. Reprod Biol Endocrinol 2022;20:15.
[82] Information PEP. Puregon: summary of product characteristics. London, UK: European Medicines Agency; 2021. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/puregon.
[83] Information EEP. Elonva: summary of product charateristics. London, UK: European Medicines Agency; 2021. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/elonva.
[84] Information REP. Amsterdam, Netherlands: European Medicines Agency; 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/rekovelle-epar-product-information_en.pdf.

[85] Yovich J, Stanger J, Hinchliffe P. Targeted gonadotrophin stimulation using the PIVET algorithm markedly reduces the risk of OHSS. Reprod Biomed Online 2012;24:281–92.
[86] Abbotts C, Salgado-Braga C, Audibert-Gros C. A redesigned follitropin alfa pen injector for infertility: results of a market research study. Patient Prefer Adherence 2011;5:315–31.
[87] Jeannerot F, Cusin A, Schertz J. Dose accuracy of the redesigned follitropin alfa pen injector for infertility treatment. Expet Opin Drug Deliv 2016;13:1661–9.
[88] Jeannerot F, Stüdeli T, Gunther-LaVergne L, Hirning D. Usability engineering study in the European Union of a redesigned follitropin alfa pen injector for infertility treatment. Expet Opin Drug Deliv 2016;13:1221–9.
[89] Schertz J, Worton H. Nurse evaluation of the redesigned fertility pen injector: a questionnaire-based observational survey. Expet Opin Drug Deliv 2018;15:435–42.
[90] Schertz J, Worton H. Patient evaluation of the redesigned follitropin alfa pen injector. Expet Opin Drug Deliv 2017;14:473–81.
[91] Longobardi S, Seidler A, Martins J, Beckers F, MacGillivray W, D'Hooghe T. An evaluation of the use and handling errors of currently available recombinant human follicle-stimulating hormone pen injectors by women with infertility and fertility nurses. Expet Opin Drug Deliv 2019;16:1003–14.
[92] Fatemi H, Popovic-Todorovic B, Humaidan P, Kol S, Banker M, Devroey P, et al. Severe ovarian hyperstimulation syndrome after gonadotropin-releasing hormone (GnRH) agonist trigger and "freeze-all" approach in GnRH antagonist protocol. Fertil Steril 2014;101:1008–11.
*[93] Seyhan A, Ata B, Polat M, Son W-Y, Yarali H, Dahan M. Severe early ovarian hyperstimulation syndrome following GnRH agonist trigger with the addition of 1500 IU hCG. Hum Reprod 2013;28:2522–8.
[94] Esteves S, Carvalho J, Bento F, Santos J. A novel predictive model to estimate the number of mature oocytes required for obtaining at least one euploid blastocyst for transfer in couples undergoing in vitro fertilization/intracytoplasmic sperm injection: the ART calculator. Front Endocrinol 2019;10:99.
*[95] Broer S, Dólleman M, van Disseldorp J, Broeze K, Opmeer B, Bossuyt P, et al. Prediction of an excessive response in in vitro fertilization from patient characteristics and ovarian reserve tests and comparison in subgroups: an individual patient data meta-analysis. Fertil Steril 2013;100:420–9.
[96] RCOG. Royal college of obstetricians and gynaecologists: The management of ovarian hyperstimulation syndrome. Royal College of Obstetricians and Gynaecologists; 2016. Available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg5/.