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Review Article

Evidence-Based Use of Follicle-Stimulating Hormone to Prevent Ovarian Hyperstimulation Syndrome

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ABSTRACT

Objectives: Administration of follicle-stimulating hormone (FSH) is a key component of ovarian stimulation during assisted reproductive treatments (ART). Ovarian hyperstimulation syndrome (OHSS) is a complication of ovarian stimulation resulting in an exaggerated systemic response with a risk of serious morbidity. Various management strategies involving the optimisation of FSH administration are used to prevent the risk of OHSS.

Material and Methods: This review aimed to evaluate the current evidence for the use of FSH in ovarian stimulation and prevention of OHSS. A comprehensive literature search was performed using multiple electronic databases, including MEDLINE, SCOPUS and the Cochrane Library, to identify relevant systematic reviews and primary studies.

Results: Personalised dosing of FSH is associated with a lower incidence of moderate or severe OHSS, while the effect on live birth rate (LBR) remains uncertain. There is no significant difference in the risk of OHSS between using urinary and recombinant preparations of FSH. Long-acting and daily recombinant FSH preparations have a similar risk profile in predicted normal responders. Follitropin delta, a newer preparation, has shown a lower incidence of early OHSS and a higher LBR. The routine measurement of serum hormone levels in addition to ultrasound monitoring does not reduce the risk of OHSS. Coasting and FSH dose reduction may lower the incidence of OHSS in the event of response.

Conclusion: Evidence-based use of FSH should be applied in practice to optimise patient safety without compromising treatment outcomes. More studies assessing the outcomes of FSH use in various patient subgroups are required to further assess and reduce the risk of OHSS.

Keywords: Follicle-stimulating hormone, Gonadotropins, In vitro fertilisation, Ovarian hyperstimulation syndrome, Ovarian stimulation

INTRODUCTION

Ovarian stimulation during assisted reproductive treatments (ART) is achieved with the exogenous administration of follicle-stimulating hormone (FSH), a key hormone in promoting follicular growth and maturation of oocytes.[1] The most widely recognised and important complication of ART is ovarian hyperstimulation syndrome (OHSS). OHSS is an exaggerated

systemic response that most often arises following ovarian exposure to human chorionic gonadotropin after ovarian stimulation with FSH.[2–4]

Baseline predictive factors for increased risk of OHSS include high ovarian reserve markers such as antral follicle count and anti-Mullerian hormone (AMH), young age, low body mass index, polycystic ovarian syndrome, previous history of high response to ovarian stimulation and FSH receptor polymorphisms.[5] Ovarian reserve markers are used to categorise patients undergoing ART into groups based on their predicted response to ovarian stimulation: predicted low, normal and high responders.[3,6]

Prevention of OHSS is crucial due to the significant physical and psychological morbidity experienced by affected patients. Modification of OHSS risk can be achieved through optimisation of FSH administration in ovarian stimulation protocols and the use of adjuvant therapies.[7,8]

MATERIAL AND METHODS

This review aimed to identify and present the current evidence for the use of FSH in ovarian stimulation and the prevention of OHSS. A comprehensive literature search was conducted across the online databases MEDLINE, SCOPUS, EMBASE, CENTRAL, DARE and the Cochrane Library. The search focused on systematic reviews and primary studies that reported outcomes of interventions involving FSH administration in the context of OHSS risk. Relevant articles were identified using keywords including 'ovarian stimulation', 'gonadotropins', 'FSH', 'in vitro fertilisation (IVF)', 'intracytoplasmic sperm injection (ICSI)', 'OHSS', 'dosing', 'personalisation', 'monitoring' and 'coasting'. The search was restricted to full-text articles in the English language. The included articles were screened by all authors for relevance. Ovarian stimulation protocols, ovulation triggers and luteinising hormone (LH) administration were not included in the scope of this review.

STARTING DOSE OF FSH

During ovarian stimulation in IVF/ICSI cycles, both standardised and personalised daily doses of FSH are used. Personalisation of the FSH dose can be based on ovarian reserve tests and patient characteristics such as age, weight and prior ovarian response. Since ovarian response to FSH varies significantly among patients, adjusting the FSH dose based on individual factors can help modulate the risk of developing OHSS.[9]

A personalised approach to FSH dosing, tailored to ovarian reserve and other patient characteristics, has been associated with a lower risk of moderate or severe OHSS. This was demonstrated in a recent Cochrane Review that compared the outcomes of personalised versus standard FSH dosing in IVF/ICSI cycles. The review found that patients who received a personalised FSH dose had a significantly lower risk of developing moderate or severe OHSS (7 trials, 4,400 patients, OR 0.60, 95% CI 0.42–0.84). However, the effect on the incidence of severe OHSS alone was unclear (5 trials, 2,724 patients, OR 0.74, 95% CI 0.42–1.28). The impact of personalised dosing on live birth rate (LBR) was inconclusive (7 trials, 4,400 patients, OR 1.12, 95% CI 0.98–1.29).[10]

The Cochrane Review also included direct comparisons of different FSH doses based on predicted ovarian response. Patients were categorised into low, normal, or high responders according to ovarian reserve tests. There was insufficient evidence for the effect of different starting doses of FSH on OHSS incidence in low or normal responders. In predicted high responders, the review found it unclear whether using a lower starting dose of FSH would reduce the incidence of moderate or severe OHSS (1 trial, 521 patients, OR 2.31, 95% CI 0.80–6.67).[10]

Mild ovarian stimulation protocols, which use lower starting doses of FSH, may be associated with a lower risk of OHSS compared with conventional protocols. However, the clinical efficacy of mild stimulation is disputed, as it results in lower numbers of eggs retrieved and embryos created.[11]

Therefore, a standard starting dose of 150 units of FSH for ovarian stimulation should be considered, as recommended by the European Society of Human Reproductive and Embryology (ESHRE).[12]

TYPES OF FSH PREPARATIONS

Gonadotropins are primarily classified into two types: urinary and recombinant. Human menopausal gonadotropin (hMG), purified FSH, and highly purified FSH are derived from the urine of postmenopausal women. These preparations contain both FSH and LH, with hMG comprising a 1:1 combination of the two.[13] In contrast, recombinant FSH (r-FSH) is produced using recombinant DNA technology, resulting in a product that is biochemically pure, free from urinary contaminants, and more consistent across production batches compared to the urinary products.[14]

This evidence suggests that, when it comes to the risk of OHSS, both urinary and r-FSH preparations carry a similar risk profile. A Cochrane Review of gonadotropin preparations for ovarian stimulation identified 32 randomised controlled trials (RCTs) reporting incidence of OHSS. The review found no significant difference in the incidence of OHSS between groups receiving urinary or r-FSH preparations (32 trials, 7,740 couples, OR 1.18, 95% CI 0.86–1.6).[13]

LONG-ACTING FSH

Long-acting FSH, such as corifollitropin alfa, is a recombinant preparation. Administered as a single injection, it provides FSH activity for up to seven days, reducing the number of injections required for ovarian stimulation. As such, long-acting FSH is a convenient alternative for some patients.[15,16]

Long-acting and daily r-FSH preparations appear to carry a similar risk of OHSS in the general IVF population. This was reported in a meta-analysis, which compared their safety and efficacy in GnRH antagonist IVF protocols. The analysis, which included 3,749 patients from 5 RCTs, found no significant difference in the overall incidence of OHSS (5 trials, 3,749 couples, RR 1.15, 95% CI 0.83–1.57). The authors also reported no significant difference in the incidence of moderate or severe OHSS between the two groups (4 trials, 3,349 couples, RR 1.17, 95% CI 0.54–2.56).[17]

No published studies compare long-acting and daily r-FSH in predicted high responders.

FOLLITROPIN DELTA

Follitropin delta is a relatively newer preparation of rFSH. Follitropin delta has been shown to exhibit a slower clearance rate and longer half-life compared to follitropin alfa, demonstrating longer activity and associated with higher ovarian responses during stimulation.[1,18] Follitropin delta is administered using a personalised dosing algorithm that takes into account patient characteristics such as body weight and serum AMH levels.[1]

Several recent studies have assessed the safety and efficacy of follitropin delta, particularly concerning OHSS and IVF outcomes. One of the largest studies, which included 1,009 patients, compared the personalised dosing of follitropin delta to a standard fixed dose of follitropin alfa. The results showed a significant 51% reduction in the incidence of early OHSS and/or the need for additional preventative interventions in the follitropin delta group (95% CI 19%–70%, $p = 0.004$). However, there was no significant difference in the incidence of late OHSS between the two groups. While the number of oocytes retrieved was significantly lower in the follitropin delta group (10.0 ± 6.1 vs. 12.4 ± 7.3, $p < 0.001$), the LBR was significantly higher (31.3% vs. 25.7%, $p = 0.023$).[19]

Further supporting these findings, a meta-analysis of high-quality studies also demonstrated a significantly higher LBR in patients with AMH levels above 15 pmol/l when treated with follitropin delta (adjusted OR 1.64, 95% CI 1.14–2.36, $p = 0.01$). The use of follitropin delta was associated with a reduced incidence of early OHSS and/or the need for further preventative measures (adjusted OR 0.27, 95% CI 0.15–0.49, $p < 0.001$), as well as a reduced risk of moderate or severe early OHSS (adjusted OR 0.30, 95% CI 0.16–0.58, $p < 0.001$).[20]

MONITORING DURING OVARIAN STIMULATION

Ultrasound monitoring is a key component of IVF cycles during ovarian stimulation, primarily used to time the administration of the ovulation trigger in preparation for oocyte retrieval. It also provides a valuable opportunity to identify patients at risk of developing OHSS and to implement preventive measures where necessary.[21]

The additional routine measurement of serum hormone levels has not been shown to reduce the incidence of OHSS. A Cochrane Review published in 2021 examined the incidence of OHSS in IVF cycles using ultrasound monitoring alone compared with cycles that incorporated the additional measurement of serum oestradiol levels. Five of the six studies included in the review reported outcomes in an unselected patient cohort, while one study excluded patients with a history of severe OHSS in a previous treatment cycle. The review found no significant difference in the risk of OHSS when serum oestradiol levels were measured in addition to ultrasound monitoring (6 trials, 781 couples, OR 1.03, 95% CI 0.48–2.20). Additionally, the authors of the review categorised the evidence as of low quality.[22] A further study has similarly shown no added advantage in using serum progesterone or LH concentrations during ovarian stimulation to reduce the risk of OHSS.[23]

COASTING AND DOSE REDUCTION

Coasting is a strategy used to reduce the risk of OHSS in patients who exhibit a hyper-response during ovarian stimulation. The approach involves withholding further doses of FSH while maintaining a downregulated state. By reducing FSH levels, coasting aims to prevent the additional development of smaller, gonadotropin-dependent follicles. Larger follicles, however, are typically gonadotropin-independent and will continue to mature even with discontinuation of exogenous FSH administration.[1]

A meta-analysis on coasting in patients undergoing GnRH agonist IVF protocols found a significant reduction in the incidence of OHSS when coasting was used compared to no intervention (2 trials, 207 couples, OR 0.11, 95% CI 0.05–0.24). However, the thresholds for coasting varied widely between the included studies, and there was insufficient evidence to draw firm conclusions about the impact of coasting on treatment outcomes due to this heterogeneity.[24] There are no RCTs assessing the effects of coasting in GnRH antagonist protocols. One RCT comparing coasting between GnRH

Table 1: Summary of the Evidence.

- Personalised dosing of FSH is associated with a lower incidence of moderate or severe OHSS, while the effect on LBR remains uncertain.
- There is no significant difference in the risk of OHSS between using urinary and recombinant preparations of FSH.
- Long-acting and daily r-FSH preparations have a similar risk profile in predicted normal responders.
- Follitropin delta, a newer preparation, has shown a lower incidence of early OHSS and a higher LBR.
- The routine measurement of serum hormone levels in addition to ultrasound monitoring does not reduce the risk of OHSS.
- Coasting and FSH dose reduction may lower the incidence of OHSS in the event of response.

FSH: Follicle-stimulating hormone, OHSS: Ovarian hyperstimulation syndrome, LBR: Live birth rate.

agonist and GnRH antagonist protocols found no incidence of OHSS in either group (190 women).[25]

Some clinicians use a modified approach to coasting, using reduced FSH doses instead of completely withholding FSH administration. However, pharmacokinetic studies on rFSH have shown that serum FSH levels remain elevated for several days after discontinuation, potentially stimulating further follicular development despite the dose reduction.[1]

One study reported a reduced incidence of OHSS when FSH doses were reduced in GnRH agonist cycles for patients showing a hyper-response.[26]

Overall, the evidence for the use of coasting for the reduction of OHSS incidence is limited due to the small number of RCTs available and the lack of studies comparing different IVF protocols. Coasting may be an option for patients undergoing GnRH agonist IVF protocols with hyper-response when GnRH agonist trigger is not an option. The effect of coasting on IVF treatment outcomes, such as pregnancy rates, remains unclear.

CONCLUSION

Following a comprehensive review of the literature, we identified the following conclusions based on previous studies, which are consistent with recommendations in the recently published guidelines from the British Fertility Society, ESHRE and the American Society for Reproductive Medicine. Evidence-based use of FSH should be applied in practice to optimise patient safety without compromising treatment outcomes. Clinicians should consider factors such as patient characteristics, availability of specific FSH preparations and the associated pecuniary commitment when making decisions regarding treatment protocols. Further studies reporting OHSS outcomes are necessary to compare the safety of various FSH applications across patient subgroups for improved risk stratification and counselling patients on predicted outcomes.

Author contribution

YA: Acquisition of review articles, analysis and interpretation, design and preparation of manuscript, accountable for all aspects of work. NT: Acquisition of review articles, analysis and interpretation, design and preparation of manuscript, revising it for critical intellectual content, final approval of the version to be published, accountable for all aspects of work. RM: Concept and design of article, revising it for critical intellectual content, final approval of the version to be published, accountable for all aspects of work.

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