Improved ovarian hyperstimulation syndrome (OHSS) risk management by individualised dosing of follitropin delta based on serum anti-Müllerian hormone (AMH) and body weight

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Study question

To evaluate the clinical benefits of individualised follitropin delta dosage with regard to OHSS risk management.

Summary answer

Individualised follitropin delta compared with conventional follitropin alfa reduces the need for preventive interventions for OHSS and decreases the risk of OHSS following preventive interventions.

What is known already

The risk of early OHSS increases with increasing ovarian response to gonadotropin stimulation. An individualised dosing regimen of follitropin delta (FE 999049; recombinant FSH produced from the human cell line PER.C6®) based on AMH (a preferred predictor of ovarian response to gonadotropins) and body weight (a determinant of systemic exposure to follitropin delta), targeting an adequate number of oocytes retrieved, significantly reduced the incidences of preventive interventions for early OHSS as well as preventive interventions and/or early OHSS compared to conventional follitropin alfa treatment.[1]

Study design, size, duration

Randomised, assessor-blind, controlled trial including 1326 patients undergoing their first IVF/ICSI cycle. Patients were randomised 1:1 to individualised follitropin delta (Ferring Pharmaceuticals) dosing (665 patients) or conventional follitropin alfa (Gonal-F, Merck Serono) dosing (661 patients). AMH was measured by Elecsys® AMH (Roche Diagnostics). The follitropin delta dose was fixed throughout stimulation, while the follitropin alfa dose (starting at 150 IU/day) could be adjusted upwards or downwards from day 6 of stimulation based on the individual response.

Trial registration number: NCT01956110.

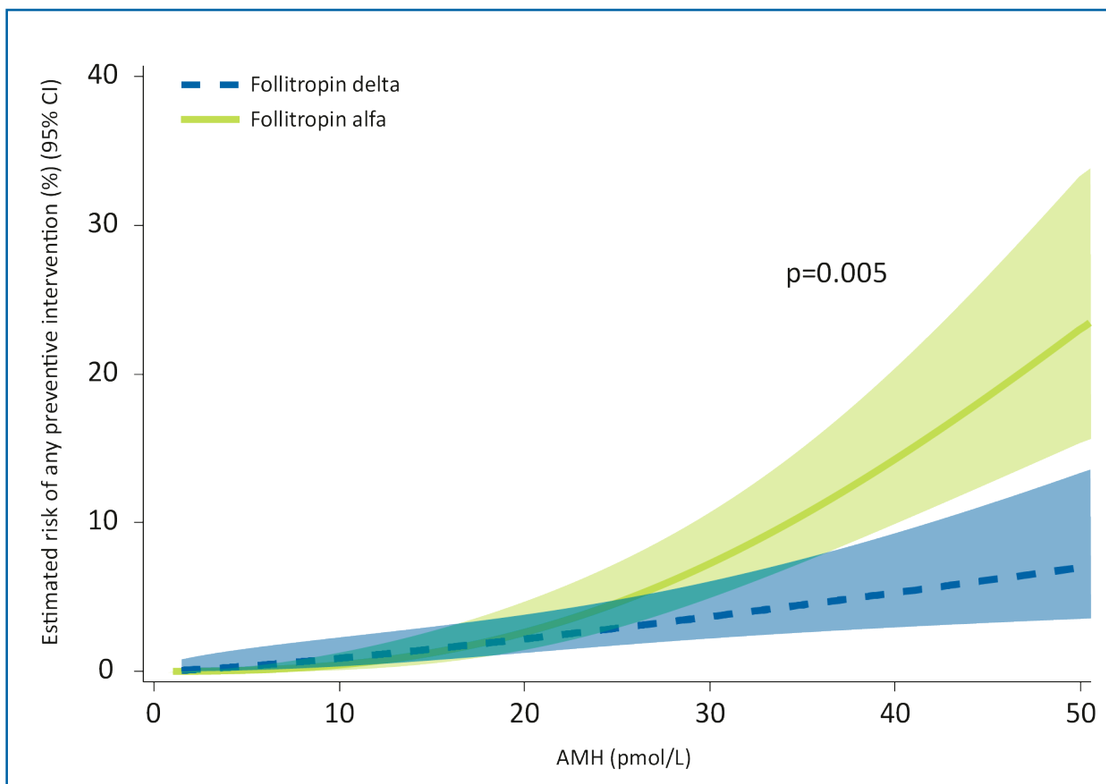
Participants/materials, setting, methods

Preventive interventions for early OHSS included cycle cancellation due to excessive ovarian response (defined as ≥25 follicles of ≥12 mm in diameter), triggering of final follicular maturation with GnRH agonist (triggering criterion 25-35 follicles of ≥12 mm) and/or administration of dopamine agonist (considered a preventive intervention if ≥20 follicles of ≥12 mm). Early and late OHSS were defined as OHSS with onset ≤9 days and >9 days, respectively, after triggering of final follicular maturation. OHSS was assessed using Golan's classification.[2] A logistic regression model was used to estimate the risk for preventive interventions as a function of log (AMH). A likelihood ratio test was used to test if the estimated profiles differed between treatment groups.

Main results

In total, 17 and 20 cases of early OHSS were observed in the follitropin delta and follitropin alfa groups, respectively. Statistically significantly fewer patients in the follitropin delta group required preventive interventions for early OHSS compared to the follitropin alfa group (15 vs 30, p=0.005) (Figure 1). The majority of the preventive interventions were performed in women with AMH ≥25.35 pmol/L (Table 1). The type of preventive interventions employed were GnRH agonist triggering in 10 women in the follitropin delta group and 23 women in the follitropin alfa group (Figure 2) and administration of dopamine agonist in 5 vs 10 women, respectively. Three women in the follitropin alfa group received both types of intervention. Among women with preventive interventions, 10 had early OHSS; 1 in the follitropin delta group and 9 in the follitropin alfa group. In women with GnRH agonist triggering, early OHSS did not occur in the follitropin delta group, but occurred in 7 women in the follitropin alfa group (Figure 2). Of these OHSS cases, 3 were mild and 4 were moderate. All 7 women had a starting dose of 150 IU, which was either maintained or reduced during stimulation. The improved OHSS risk management observed with individualised follitropin delta in relation to early OHSS was also observed for late OHSS, where the number of OHSS cases were reduced to half in the follitropin delta group compared to follitropin alfa (6 vs 12 cases).

Figure 1. Estimated risk of any preventive intervention for early OHSS by AMH

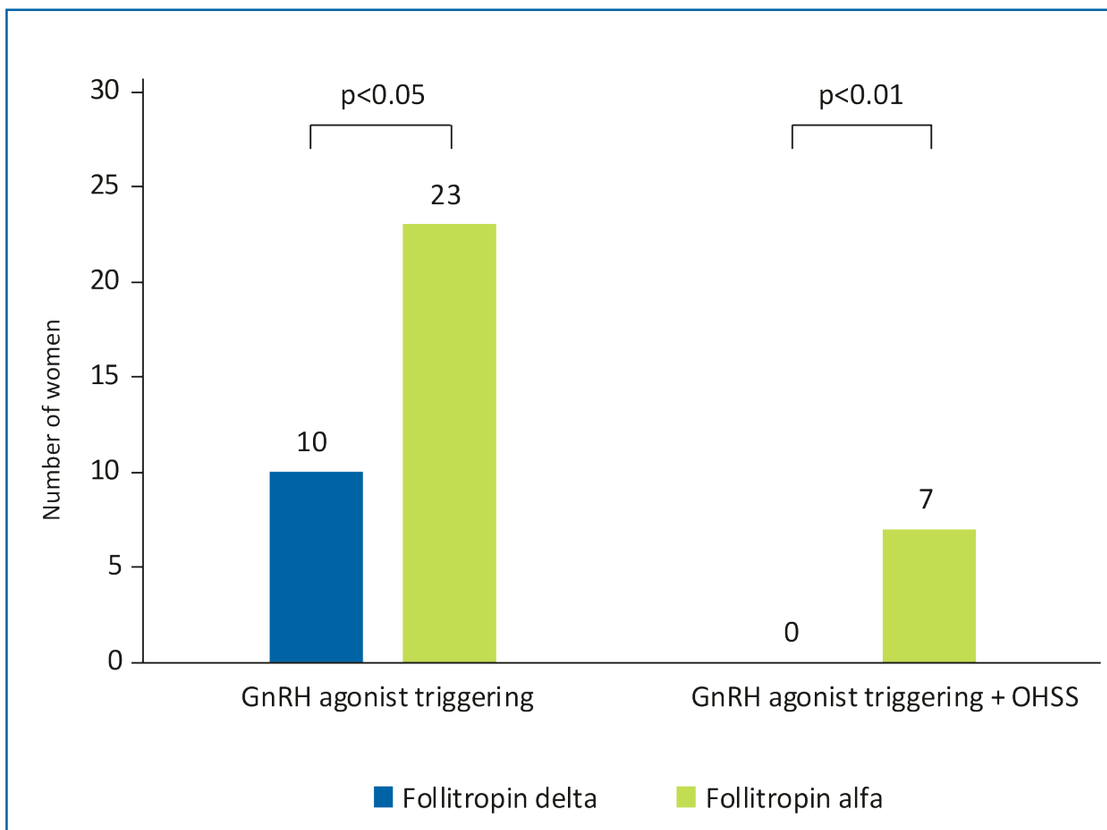


P-value based on likelihood ratio test comparing nested logistic regression models including log(AMH) as covariate.

Table 1. Observed incidence of preventive interventions for early OHSS by AMH

AMH at screening divided by quartiles	Follitropin delta		Follitropin alfa	
	n	%	n	%
<8.99 pmol/L	0	0.0%	0	0.0%
8.99 - <16.14 pmol/L	2	1.2%	2	1.2%
16.14 - <25.35 pmol/L	5	2.8%	3	1.9%
≥25.35 pmol/L	8	5.0%	25	14.5%

Figure 2. Cases of GnRH agonist triggering, and cases of GnRH agonist triggering and OHSS



P-values based on Fisher's exact test.

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