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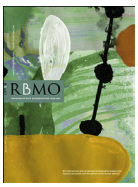

ARTICLE

Individualization of the starting dose of follitropin delta reduces the overall OHSS risk and/or the need for additional preventive interventions: cumulative data over three stimulation cycles

BIOGRAPHY

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KEY MESSAGE

Individualized follitropin delta reduces the risk of ovarian hyperstimulation syndrome (OHSS) and of preventive interventions beyond the initial stimulation cycle. Less need for GnRH agonist triggering allows more women to undergo fresh embryo transfer, reduces the time to pregnancy and the retained risk of OHSS.

ABSTRACT

Research question: Is individualization of dosing with follitropin delta in sequential ovarian stimulation cycles an effective preventive strategy for ovarian hyperstimulation syndrome risk? If so, for which patients does an individualized strategy provide the greatest OHSS risk reduction and/or the need for additional preventive interventions?

Design: A secondary analysis of three ovarian stimulation cycles in IVF/intracytoplasmic sperm injection patients included in one randomized, assessor-blinded trial comparing two recombinant FSH preparations (ESTHER-1, NCT01956110), and a second trial in women undergoing up to two additional cycles (ESTHER-2, NCT01956123). Of 1326 women (aged 18–40 years) randomized and treated with follitropin delta or alfa in cycle 1, 513 continued to cycle 2 and 188 to cycle 3. Follitropin delta and alfa doses were maintained/adjusted according to ovarian response in the previous cycle.

Results: Individualized dosing with follitropin delta significantly reduced moderate/severe OHSS and/or preventive interventions ($P = 0.018$) versus conventional dosing with follitropin alfa in patients undergoing up to three ovarian stimulation cycles. The greatest benefit was observed in patients in the highest anti-Müllerian hormone (AMH) quartile ($P = 0.012$). On evaluating separately, individualized dosing with follitropin delta significantly lowered the incidences of moderate/severe OHSS ($P = 0.036$) and preventive interventions ($P = 0.044$) versus follitropin alfa.

Conclusion: An individualized follitropin delta dosing regimen decreased the risk of moderate/severe OHSS as well as the incidence of preventive interventions versus a conventional follitropin alfa regimen. An analysis per AMH quartile indicated that these statistically significant differences are driven mainly by patients with the highest pretreatment AMH levels.

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KEYWORDS

Anti-Müllerian hormone
Follitropin delta
GnRH agonist triggering
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Preventive interventions

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INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic and potentially life-threatening complication of ovarian stimulation that occurs during the early luteal phase and/or early pregnancy (*Humaidan et al., 2010; Nelson, 2017; Practice Committee of the American Society for Reproductive Medicine, 2016; Smith et al., 2015*). Managing each woman's risk of OHSS while maximizing her potential for a successful outcome constitutes one of the major clinical challenges in IVF treatment. Excessive ovarian response during ovarian stimulation signals a potential risk for OHSS and requires modification of the IVF cycle treatment plan. If not prevented, OHSS could develop and may require active medical intervention, including hospitalization, fluid management, paracentesis and prophylactic anticoagulation.

The actual incidence of OHSS after ovarian stimulation is unknown because of a lack of systematic registration and methodological challenges: abdominal discomfort symptoms are frequently observed, but not commonly reported as mild-grade OHSS cases. Moderate-grade OHSS cases require ultrasound investigation (*Golan et al., 1989; Royal College of Obstetricians and Gynaecologists, 2016*), and additional severe OHSS cases are most likely captured by emergency/hospital units rather than the treating clinic (*Royal College of Obstetricians and Gynaecologists, 2016*). Therefore, hospital data would support the notion that the magnitude of the OHSS problem, especially those of greater clinical health significance, is indeed underestimated. In support of this, there is a shift towards identifying, reporting and evaluating more closely moderate and severe grades of OHSS, and preventing them (*Nelson, 2017*).

Obviously, the best way to manage OHSS risk is to prevent it from occurring. Several OHSS preventive strategies are available to clinicians before, during or at the end of ovarian stimulation. Widely used preventive interventions after observing excessive stimulation include mid- or late-stimulation adjustment of the gonadotrophin dose, short-term coasting and administration of an oral dopamine agonist (*Alvarez et al., 2007; Busso et al., 2010*). Triggering of final maturation with gonadotrophin-releasing hormone (GnRH) agonists at the end of ovarian stimulation in a GnRH antagonist protocol with freezing of all embryos (no fresh transfer) for subsequent frozen cycle transfer currently represents one of the possible preventive interventions (*Mathur and Tan, 2014; Practice Committee of the American Society for Reproductive Medicine, 2016*). Ideally, OHSS risk should be managed before starting ovarian stimulation by identifying patients at risk of OHSS and administering lower starting doses of gonadotrophins. In this strategy, adequate selection of the predictive factors for patient stratification is critical for achieving the optimal safe and efficacious treatment outcome. Today, this can be implemented with the use of validated biomarkers that can both accurately determine the woman's ovarian reserve and predict her potential for response to stimulation to determined doses of gonadotrophins. In particular, the pretreatment evaluation of serum anti-Müllerian hormone (AMH) based on robust automated AMH assays (*Nelson et al., 2015; van Helden and Weiskirchen, 2015*) along with prospectively validated gonadotrophin dosing algorithms should today allow clinicians to more confidently stratify patients to safe ovarian stimulation without compromising efficacy.

Follitropin delta, a new recombinant FSH expressed in a host cell line of human fetal retinal origin (PER.C6), is administered according to an individualized dosing algorithm incorporating pretreatment serum AMH levels, which predict ovarian response, and body weight, which influences the distribution volume of follitropin delta. This gonadotrophin-specific algorithm was developed after a pharmacokinetic and pharmacodynamic modelling and simulation exercise derived from an AMH stratified dose–response study (*Arce et al., 2016*) that was prospectively validated in a large Phase 3 confirmatory study (*Nyboe Andersen and Nelson et al., 2017*). The objective of the individualized dosing algorithm was to modify the ovarian response and thereby reduce the risk of OHSS while maintaining efficacy. Indeed, individualized dosing of follitropin delta according to pretreatment patient characteristics resulted in similar efficacy, in terms of ongoing pregnancy rates, and was associated with an improved OHSS risk management versus conventional dosing with follitropin alfa after a single ovarian stimulation (*Nyboe Andersen and Nelson et al., 2017*). With availability of additional sequential ovarian stimulation data, the aim of the present investigation was to evaluate the impact of individualized dosing with follitropin delta as a preventive strategy for OHSS risk in subsequent ovarian stimulation cycles and to characterize in more detail the patients for whom the proposed individualized strategy reduces the risk to the greatest extent.

MATERIALS AND METHODS

This investigation covers up to three ovarian stimulation cycles (cycles 1, 2 and 3) in women undergoing stimulation with follitropin delta or follitropin alfa. The participating women were originally included in a randomized, controlled, assessor-blind, international, multicentre trial (Evidence-based Stimulation Trial with Human rFSH in Europe and Rest of World [ESTHER-1] trial; cycle 1). A detailed description of the methods, CONSORT flow diagram and primary results from this cycle were described previously (*Bosch et al., 2018; Nyboe Andersen and Nelson et al., 2017*). Women who did not achieve ongoing pregnancy in cycle 1 had the opportunity to be invited to join a trial covering up to two repeated treatment cycles (ESTHER-2 trial; cycles 2 and 3). The treatment allocation to follitropin delta or follitropin alfa was the same throughout the cycles, and the blinding of the assessor was maintained throughout the investigation. In total, 37 sites from 11 countries participated in ESTHER-1 and 32 of the 37 sites participated in ESTHER-2 (see Appendix).

Both trial protocols were approved by the local regulatory authorities and the independent ethics committees covering all participating centres. The trials were performed in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice Guidelines and local regulatory requirements. The studies meet the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement (*Schulz et al., 2010*).

Study participants

Women naïve to assisted reproductive technology, aged 18–40 years, with regular ovulatory cycles and diagnosed with tubal infertility, unexplained

TABLE 1 ESTHER-1 AND ESTHER-2 PATIENT FLOW, INCLUDING FROZEN CYCLES

Series of events[a]	Follitropin delta in individualized dosing regimen *n*	Follitropin alfa in conventional dosing regimen *n*	Total *n*
Total starting cycle 1	665	661	1326
Cycle 1 only	298	281	579
Cycle 1 and frozen cycle(s) only	115	119	234
Cycle 1, frozen cycles, starting cycle 2	46	50	96
Cycle 1, starting cycle 2 directly	206	211	417
Total starting cycle 2	252	261	513
Cycle 2 only	114	124	238
Cycle 2 and frozen cycle(s) only	43	44	87
Cycle 2, frozen cycles, starting cycle 3	13	10	23
Cycle 2, starting cycle 3 directly	82	83	165
Total starting cycle 3	95	93	188
Cycle 3 only	66	72	138
Cycle 3 and frozen cycle(s)	29	21	50

[a] One patient could undergo more than one frozen cycle.

infertility, endometriosis stage I/II or with partners diagnosed with male factor infertility participated in cycle 1. Full characterization of the population has been provided elsewhere (*Nyboe Andersen and Nelson et al., 2017*). Women who failed to achieve an ongoing pregnancy in cycle 1 were eligible for cycle 2, and those who failed to achieve an ongoing pregnancy in cycle 2 were eligible for cycle 3. In all three cycles, the remaining blastocysts were cryopreserved according to local guidelines. Cryopreserved blastocysts were replaced in natural or stimulated cycles (TABLE 1). Patients with any clinically relevant change to any of the eligibility criteria or any clinically relevant medical history since the previous cycle(s) were not eligible for participation in cycles 2 or 3. Patients with severe OHSS in a previous cycle were excluded.

Study procedures

Study procedures in cycles 1, 2 and 3 were similar. Gonadotrophin therapy was initiated on days 2–3 of the menstrual cycle. In cycle 1, women randomized to follitropin delta (FE 999049, Rekovelle, Ferring Pharmaceuticals) were given a daily subcutaneous dose, determined by their serum AMH level (Elecsys AMH immunoassay, Roche Diagnostics GmbH, Mannheim, Germany) at screening (before randomization) and body weight at randomization, and that dose was fixed throughout stimulation [AMH <15 pmol/l: 12 µg; AMH ≥15 pmol/l: 0.10–0.19 µg/kg; the maximum daily dose was 12 µg; a detailed description has been published previously (*Nyboe Andersen and Nelson et al., 2017*)]. Women randomized to follitropin alfa (Gonal-F, EMD Serono) were administered a daily subcutaneous dose of 150 IU for the first 5 days, in line with labelling and international recommendations (*Gianaroli et al., 2012; Gonal-F, 2017*); thereafter, the dose could be adjusted by ±75 IU from stimulation day 6 based on the individual response, with 450 IU as the maximum daily dose allowed (*Gonal-F, 2017*).

In cycles 2 and 3, the daily dose of follitropin delta and the daily starting dose of follitropin alfa were dependent on the ovarian response in the previous cycle. In case of appropriate ovarian response (8–14 oocytes retrieved), the same daily dose/starting dose was repeated in the next cycle. If the number of oocytes retrieved in the previous cycle was out of the targeted range, the dose was adjusted. Women with <4 oocytes or 4–7 oocytes in the previous cycle were given a follitropin delta dose 50% and 25% higher, respectively, and a follitropin alfa dose 75 and 37.5 IU higher, respectively. Similarly, women with 15–19 oocytes and ≥20 oocytes had the dose reduced by 20% and 33% for follitropin delta, respectively, and by 37.5 and 75 IU for follitropin alfa, respectively. Women whose cycles were cancelled before oocyte retrieval due to either poor or excessive ovarian response had their doses adjusted similar to the women with <4 oocytes and ≥20 oocytes, respectively. The maximum starting daily dose of follitropin delta was 18 µg in cycle 2 and 24 µg in cycle 3, with no adjustments within the cycle. For follitropin alfa, the maximum starting doses were 225 and 300 IU, respectively, with a maximum daily dose of 450 IU after dose adjustments.

In cycles 1, 2 and 3, the GnRH antagonist (cetrorelix acetate, Cetrotide, EMD Serono) 0.25 mg/day was initiated on stimulation day 6 and continued throughout stimulation. Triggering of final follicular maturation was performed when ≥3 follicles were ≥17 mm in diameter. For women with <25 follicles with a diameter ≥12 mm, 250 µg recombinant human chorionic gonadotrophin (HCG; choriogonadotrophin alfa, Ovitrelle, EMD Serono) was administered. For women with 25–35 follicles ≥12 mm, 0.2 mg GnRH agonist (triptorelin acetate, Gonapeptyl, Ferring Pharmaceuticals) could be administered or the cycle cancelled. In cases of excessive follicular development (>35 follicles with a diameter ≥12 mm) or poor follicular development (investigator judging that ≥3 follicles ≥17 mm could not be reached by day 20), the cycle was cancelled. In cycles 1, 2 and 3, oocytes were retrieved 36 ± 2 h after triggering of final follicular maturation and inseminated by IVF or intracytoplasmic sperm injection. For women who received HCG, blastocyst transfer was performed on day 5, whereas all blastocysts were cryopreserved for women who received GnRH agonist.

The blastocyst transfer policy took into consideration that the risk of multiple pregnancies should be reduced, but also acknowledged that the trial population in subsequent cycles were women who had been unsuccessful in achieving an ongoing pregnancy in the previous cycle(s), and therefore the transfer policy gradually became more flexible. In cycle 1, women aged ≤37 years and women aged ≥38 years with a good-quality blastocyst available (blastocyst grade 3BB or higher) had a single blastocyst transfer, while women aged ≥38 years with no good-quality blastocysts had a double blastocyst transfer (if two blastocysts were available). In cycle 2, women with a good-quality blastocyst available had a single blastocyst transfer, while women with no good-quality blastocysts had a double blastocyst transfer (if two blastocysts were available). In cycle 3, women could have a single or a double blastocyst transfer, independent of age and blastocyst quality. In all three cycles, remaining blastocysts could be cryopreserved in accordance with local guidelines and/or regulations for use after trial completion. Vaginal progesterone tablets (Lutinus/Endometrin, Ferring Pharmaceuticals) 100 mg three times daily were provided for luteal phase support from the day after oocyte retrieval until the day of the beta HCG test visit (a beta HCG test was performed 13–15 days after transfer). Clinical and ongoing pregnancy was confirmed by transvaginal ultrasound at 5–6 and 10–11 weeks after transfer, respectively. OHSS symptoms were classified by the investigators using Golan's system into five grades (*Golan et al., 1989*); based on these grades, all OHSS cases were categorized as mild, moderate and severe. Mild OHSS comprised grade 1 and 2 symptoms including abdominal distension and discomfort, nausea, vomiting and/or diarrhoea, with ovaries enlarged to 5–12 cm. Moderate OHSS has grade 3 symptoms with mild features of OHSS and ultrasound evidence of ascites, whereas severe OHSS has grade 4 and 5 symptoms defined by features of moderate OHSS along with clinical evidence of ascites and/or hydrothorax. Other symptoms of severe OHSS include change in blood volume, increased blood viscosity, haemoconcentration and coagulation abnormalities, and diminished renal perfusion and function leading to hospitalization. In addition, patients requiring paracentesis were to be reported as grade 4 and patients with hospitalization due to OHSS symptoms as grade 5. Early OHSS was defined as OHSS with onset ≤9 days after triggering of final follicular maturation and late OHSS was defined as OHSS with onset >9 days after triggering of final follicular development. Per protocol, preventive interventions for early OHSS covered (i) cycle cancellation if >35 follicles were ≥12 mm, (ii) triggering of final follicular maturation with GnRH agonist (and subsequent cryopreservation of all blastocysts) or cycle cancellation if 25–35 follicles were ≥12 mm and (iii) administration of dopamine agonist if ≥20 follicles ≥12 mm were observed on ultrasound at the end of stimulation.

Ethics approval

The 37 study sites in 11 countries that participated in the ESTHER programme were approved by the leading ethics committees in each country. The corresponding approval dates and reference numbers were as follows: Belgium (17 Sept 2013: 2013/192 and 2013/193), Brazil (21 May 2014: 656.380 and 656.375), Canada (9 Jan 2014: 201307286 and 201307285), Czech Republic (24 July 2013: EK-920/13 and EK-921/13; 2 April 2014: EK-920/13 and EK-921/13), Denmark (19 August 2013: H-4-2013-075 and H-4-2013-076), France (14 Feb 2014: CPC 13/65), Italy (10 April 2014 and 10 June 2014: 69/2014 and 70/2014), Poland (11 July 2013: KB/893/13 and KB/894/13), Russia (14 March 2014: reference number not applicable), Spain (5 August 2013 and 4 Dec 2013: 3938 and 3939) and UK (29 August 2013 and 21 Jan 2014: 13/EE/0208 and 13/EE/0209).

Statistical analysis

The co-primary endpoint of the ESTHER-1 (cycle 1 data) was ongoing pregnancy rate and ongoing implantation rate, while for ESTHER-2 (cycles 2 and 3 data) the primary endpoint was treatment-induced anti-FSH antibodies after up to two repeated ovarian stimulation cycles. OHSS and/or preventive interventions were collected in cycles 1, 2 and 3 and were reported as secondary endpoints in both ESTHER-1 and ESTHER-2 trials. The data were analysed and reported on subject level. Direct comparisons between treatment groups were performed using the likelihood ratio test. Because the risk of OHSS is known to be associated with serum AMH levels, a logistic regression model was used to compare the risk of moderate/severe OHSS and/or preventive interventions between treatment groups taking AMH into account. The risk as a function of AMH at screening was modelled using a logistic regression model. The risk of OHSS and/or preventive interventions was assumed to increase with increasing AMH concentrations (*Lee et al., 2008*). Having established an appropriate model, treatment group and the interaction between treatment group and AMH were added to the linear predictor. The two models were then compared using the likelihood ratio test to evaluate whether the model including treatment group and interactions provided a significantly better fit to the observed data. In case of a significant result, the estimated risk as a function of AMH was plotted for each treatment group to illustrate the magnitude of the difference and its relation to AMH at screening.

RESULTS

A total of 1329 women were randomized in cycle 1, 1326 of whom were exposed either to follitropin delta in an individualized dosing regimen (n = 665) or to follitropin alfa in a conventional dosing regimen (n = 661). In the subsequent cycles, women continued treatment with the same gonadotrophin, and with the fixed daily dose of follitropin delta or the starting dose of follitropin alfa, as applicable, maintained or adjusted based on the ovarian response in the previous cycle. The repeated cycles comprised 513 women in cycle 2 (n = 252 for follitropin delta, n = 261 for follitropin alfa) and 188 women in cycle 3 (n = 95 for follitropin delta, n = 93 for follitropin alfa).

In line with the protocol, of the 252 women who started a second cycle in the follitropin delta group, 13.5% started on a lower dose and 45.6% started on a higher dose than in the first cycle. For the 95 women who proceeded to cycle 3, these dose adjustments were made for 10.5% and 46.3%, respectively. The incidence of dose decreases and increases at the start of stimulation for women in the follitropin alfa group was 15.3% and 51.0% in the second cycle and 7.5% and 50.5% in the third cycle, respectively.

Preventive interventions, early and late OHSS association to ovarian response

TABLE 2 displays the demographics and ovarian response for women according to the presence or absence of OHSS, early

TABLE 2 DEMOGRAPHICS, OVARIAN RESPONSE AND ENDOCRINE PROFILE AT END OF STIMULATION IN PATIENTS BY OHSS CHARACTERISTICS

Parameter	No moderate/severe OHSS or preventive interventions (*n* = 1937)	Early moderate/severe OHSS and no preventive interventions (*n* = 18)	Preventive interventions and no early moderate/severe OHSS (*n* = 50)	Preventive interventions and early moderate/severe OHSS (*n* = 5)	Late moderate/severe OHSS (*n* = 17)
Age, years	33.5 (3.9)	32.6 (4.5)	31.6 (3.7)[a]	34.0 (2.9)	32.5 (4.0)
Body weight, kg	64.5 (10.6)	64.3 (9.2)	61.4 (9.0)[c]	66.1 (16.6)	64.4 (12.6)
Anti-Müllerian hormone, pmol/l	17.6 (13.1)	36.3 (29.6)[a]	40.2 (20.7)[a]	42.9 (20.2)[b]	26.8 (13.5)[b]
Follicles ≥12 mm	10.0 (4.8)	16.9 (2.5)[a]	26.4 (4.8)[a]	24.4 (3.0)[a]	14.8 (3.5)[a]
Oestradiol, pmol/l	5810.8 (3267.7)	13650 (9346.3)[a]	11646 (6998.1)[a]	16660 (9361.0)[b]	8006.1 (3645.1)[b]
Inhibin B, pg/ml	811.0 (533.1)	2076.6 (1013.8)[a]	2193.1 (749.4)[a]	2633.2 (815.4)[a]	1484.5 (613.3)[a]
Inhibin A, ng/ml	346.1 (182.8)	755.0 (467.3)[a]	715.7 (322.6)[a]	838.5 (184.3)[a]	474.1 (189.6)[b]
Oocytes retrieved	8.9 (5.3)	16.3 (6.3)[a]	20.4 (8.5)[a]	22.8 (7.5)[a]	15.2 (6.8)[a]

Data are mean (SD); both treatment arms combined. Groups are compared pairwise using Wilcoxon's text.

[a] $P < 0.001$ versus the 'no moderate/severe OHSS or preventive interventions' population.

[b] $P < 0.01$ versus the 'no moderate/severe OHSS or preventive interventions' population.

[c] $P < 0.05$ versus the 'no moderate/severe OHSS or preventive interventions' population.

or late, as well as preventive interventions with or without subsequent OHSS in cycles 1, 2 and 3. The mean AMH levels were significantly higher across all the four groups with moderate/severe OHSS and/or preventive interventions (range, 26.8–42.9 pmol/l) compared with subjects without moderate/severe OHSS or preventive interventions (17.6 pmol/l). Across all three cycles, women with preventive interventions for early OHSS or diagnosed with early moderate/severe OHSS or late moderate/severe OHSS had significantly more oocytes retrieved (all $P < 0.001$) compared with women who did not require preventive interventions nor experienced moderate/severe OHSS. The total number of follicles (≥12 mm) and serum oestradiol, inhibin B and inhibin A at the end of stimulation were also significantly different (all $P < 0.01$) between the women with preventive interventions or moderate/severe OHSS versus those with no actions taken or no moderate/severe OHSS (TABLE 2). Irrespective of the timing of onset of OHSS and thereby the classification of early or late, women with moderate/severe OHSS had significantly larger ovarian and endocrine responses to gonadotrophin treatment compared with women with no OHSS, suggesting that both types of events are related to the degree of ovarian stimulation and can be evaluated as a common consequence of the excessive stimulation. Furthermore, women with preventive interventions for early OHSS had ovarian and endocrine responses at least as high as those observed in women with moderate/severe OHSS, indicating that these events should be viewed as a surrogate for moderate/severe OHSS.

Preventive interventions and OHSS: cumulative data over three cycles

The total number of OHSS cases in cycles 1, 2 and 3 and their severity are presented in **Supplementary TABLE 1**. In each ovarian stimulation cycle, the incidences of moderate/severe OHSS as well as moderate/severe OHSS and/or preventive interventions were numerically lower in the follitropin delta group than in the follitropin alfa group. Overall, moderate/severe OHSS and/or preventive interventions occurred at rates of 4.4% in cycle 1, 1.6% in cycle 2 and 0% in cycle 3 for follitropin delta and at rates of 6.7%, 4.2% and 2.2%, respectively, for follitropin alfa. There were no cases of moderate or severe OHSS in cycles 2 or 3 for women treated with follitropin delta, whereas there were seven cases in cycle 2 and one case in cycle 3 for women treated with follitropin alfa. In comparison to the previous cycle, a starting dose decrease of follitropin alfa was made for only one out of these eight women, whereas six women had no dose adjustment, indicating that their ovarian response in the previous cycle was between 8 and 14 oocytes. For one woman, the dose of follitropin alfa was increased, meaning that fewer than 8 oocytes were retrieved in her previous cycle (**Supplementary TABLE 1**).

Cumulatively over three cycles, the individualized follitropin delta dosing regimen was associated with a 50% lower incidence of moderate/severe OHSS versus a conventional dosing approach with follitropin alfa; odds ratio (OR) 0.50 (95% confidence interval [CI]: 0.26–0.97) ($P = 0.036$) (TABLE 3). A similar reduction in the incidence of women requiring preventive interventions was observed with an OR of 0.56 (95% CI: 0.31–0.99] ($P = 0.044$) for follitropin delta versus follitropin alfa. Overall, the proportion of women experiencing moderate/severe OHSS and/or preventive interventions over three cycles was 5.0% with the individualized follitropin delta regimen versus 8.2% for the conventional follitropin alfa regimen, corresponding to an OR of 0.59 [95% CI: 0.38–0.92] ($P = 0.018$) (TABLE 3, **Supplementary FIGURE 1**). There were no differences in cumulative live birth rates between groups after three ovarian stimulation cycles. The cumulative live birth rate over the three cycles was 43.9% and 44.5% for follitropin delta and follitropin alfa, respectively (data from each cycle are included in **Supplementary TABLE 2**).

OHSS and preventive interventions by AMH

The cumulative incidences of moderate/severe OHSS and/or preventive interventions increased significantly with increasing pretreatment serum AMH concentrations, and differed significantly between individualized follitropin delta and conventional follitropin alfa groups (FIGURE 1). The greatest difference between treatment groups was observed in the highest AMH quartile (≥25.35 pmol/l),

TABLE 3 CUMULATIVE INCIDENCE OF MODERATE/SEVERE OHSS AND PREVENTIVE INTERVENTIONS ACROSS THREE OVARIAN STIMULATION CYCLES

Parameter	Follitropin delta in individualized dosing regimen (*n* = 665), *n* (%)	Follitropin alfa in conventional dosing regimen (*n* = 661), *n* (%)	Treatment difference	
			OR (95% CI)	*P*-value
Moderate/severe OHSS	14 (2.1)	27 (4.1)	0.50 (0.26–0.97)	0.036
Preventive interventions	19 (2.9)	33 (5.0)	0.56 (0.31–0.99)	0.044
Moderate/severe OHSS and/or preventive interventions	33 (5.0)	54 (8.2)	0.59 (0.38–0.92)	0.018

OR = odds ratio; 95% CI = two-sided 95% Wald confidence interval *P*-value based on likelihood ratio test.

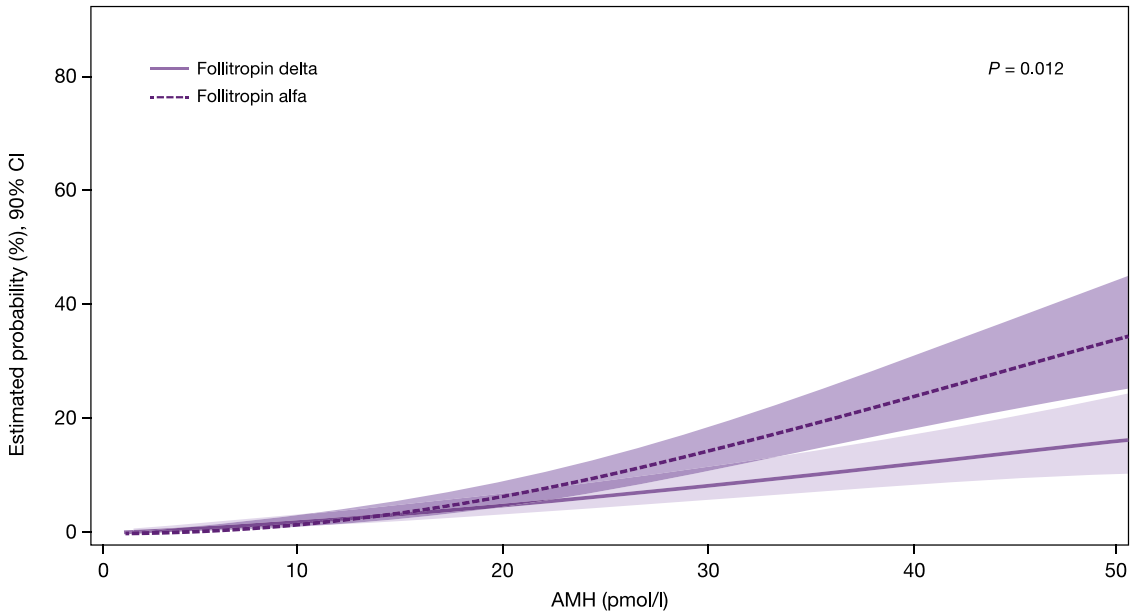

FIGURE 1 Estimated risk of moderate/severe ovarian hyperstimulation syndrome and/or preventive interventions across three ovarian stimulation cycles. AMH = anti-Müllerian hormone. The lines are based on a logistic regression model with treatment and log (AMH) and interaction term in the linear predictor. The *P*-value is based on a likelihood ratio test comparing nested logistic regression models including log (AMH) as a covariate.

where 11.8% of the women undergoing stimulation according to the individualized follitropin delta dosing regimen had experienced moderate/severe OHSS and/or preventive interventions compared with 22.1% in the conventional follitropin alfa dosing group, corresponding to a significant reduction and an OR of 0.47 (95% CI: 0.26–0.86) (*P* = 0.012) (FIGURE 2). Among women in the highest AMH quartile, the cumulative incidence of moderate/severe OHSS was 4.3% with the individualized follitropin delta dosing regimen versus 9.3% with the conventional follitropin alfa dosing regimen (OR 0.44; 95% CI: 0.18–1.11; *P* = 0.071), and the cumulative incidence of preventive interventions was 7.5% versus 15.7% (OR 0.43; 95% CI: 0.21–0.89; *P* = 0.018), respectively (FIGURE 2). The observed increased risk of OHSS from the lowest AMH quartile to the highest AMH quartile was in good agreement with the increasing ovarian response as the mean (SD) number of oocytes was 5.5 (3.6), 8.9 (4.4), 11.3 (5.2) and 12.3 (7.1) in quartiles 1, 2, 3 and 4, respectively.

OHSS leading to hospital admission

Hospitalization due to OHSS over the three cycles occurred in two women in the individualized follitropin delta group and in eight women in the conventional follitropin alfa group. The two admissions in the follitropin delta group happened in cycle 1, with no further hospitalizations due to OHSS in the subsequent cycles. For follitropin alfa, hospitalizations because of OHSS occurred in all three cycles: six in cycle 1 and one in each additional cycle. The mean duration of hospital stay due to OHSS was 4.0 days in the follitropin delta group and 8.4 days in the follitropin alfa group, with total durations of hospitalization of 8 and 57 days, respectively.

GnRH agonist for triggering of final follicular maturation

The proportion of women undergoing preventive interventions for early OHSS cumulatively over all three cycles was significantly lower in the individualized follitropin delta group compared with the conventional follitropin alfa group (19 versus 33; *P* = 0.044). In this analysis, three women in the follitropin alfa group, who had preventive interventions in two of three ovarian stimulation cycles, were counted once. Moderate OHSS was reported in 11% (five events in 46 cases) of women who received GnRH agonist triggering, distributed as one in 15 women with follitropin delta and four in 31 women with follitropin alfa. It is noted that these five cases came from five different IVF units in four countries, and that all were classified as moderate OHSS due to ultrasound evidence of ascites. None of these women had fresh

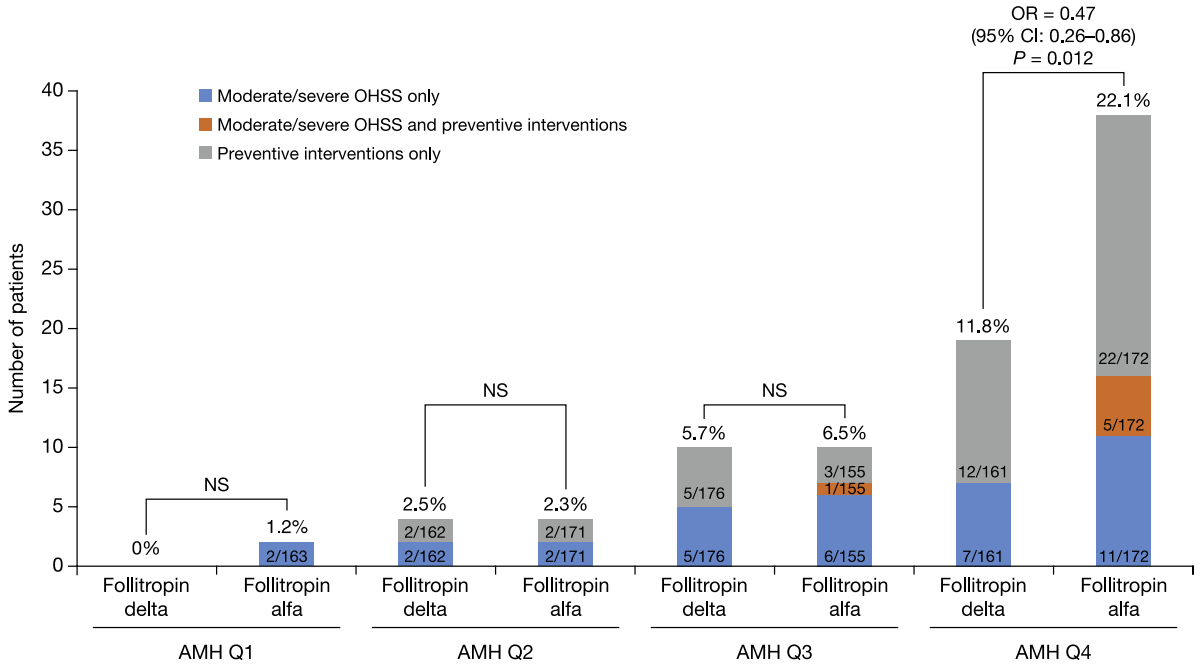

FIGURE 2 Incidence of moderate/severe OHSS and/or preventive interventions by AMH levels at screening in cycle 1. AMH quartiles. Q1: AMH <8.99 pmol/l, Q2: AMH 8.99 to <16.14 pmol/l, Q3: AMH 16.14 to <25.35 pmol/l, Q4: AMH ≥25.35 pmol/l. AMH = anti-Müllerian hormone; NS = non-significant; OHSS = ovarian hyperstimulation syndrome.

embryo transfer. It was documented that 37 women (11 in the individualized follitropin delta group and 26 in the conventional follitropin alfa group) had GnRH agonist administered according to the protocol prespecified criteria, i.e. 25 to 35 follicles ≥12 mm at the end of stimulation, and that nine women (four in the individualized follitropin delta group and five in the conventional follitropin alfa group) had GnRH agonist administered based on the investigator's criteria. When following the protocol criteria for GnRH agonist administration, none of the 11 women in the individualized follitropin delta group developed early moderate/severe OHSS, while four of the 26 women in the conventional follitropin alfa group developed moderate/severe OHSS (P = 0.022). Among women who received GnRH agonist triggering despite not fulfilling the criterion, only one in the follitropin delta group developed moderate OHSS. The characteristics of all five women who developed moderate OHSS after GnRH agonist triggering are presented in **Supplementary TABLE 3**.

DISCUSSION

Prevention of OHSS starts by administering the appropriate starting gonadotrophin dose to women at risk for excessive ovarian response. Pretreatment serum AMH levels allow the identification of patients at risk, and this parameter was therefore incorporated in the follitropin delta individualized dosing regimen. The present investigation provides additional data on the impact of the individualized follitropin delta dosing approach on OHSS risk beyond the findings reported from a single ovarian stimulation cycle (*Nyboe Andersen and Nelson et al., 2017*). Analysing the data from up to three ovarian stimulation cycles, the individualized follitropin delta dosing regimen is associated with an overall decrease in risk of moderate/severe OHSS as well as the need for additional preventive interventions compared with a conventional follitropin alfa regimen.

Mild OHSS develops in many IVF cycles, but the subjective, unspecific and diverse nature of mild symptoms constitute a confounding factor in the evaluation of OHSS risk by different dosing approaches. The more relevant clinical implications associated with presence of ascitic fluid in the abdomen, which can be evidenced objectively by ultrasound or more importantly assessed by clinical signs, stress the importance of evaluating moderate and severe OHSS (*Nelson, 2017*). Data from this study continue to indicate that early OHSS and late OHSS, despite differences in timing and pathophysiology, are closely linked to the degree of ovarian response to stimulation (*Nyboe Andersen and Nelson et al., 2017*) and can be evaluated together as a common consequence of excessive stimulation. Furthermore, the ovarian and endocrine responses in women with preventive interventions was at least as high as those observed in women with moderate/severe OHSS, indicating that these events should be viewed as a surrogate for moderate/severe OHSS and justifying the combined endpoint. Therefore, the present investigation focuses on moderate/severe OHSS, independent of the timing of onset of the OHSS, as well as preventive interventions with or without associated moderate/severe OHSS.

The additional moderate/severe OHSS cases in cycles 2 and 3 continued to expand the difference in incidence rates between the individualized follitropin delta and conventional follitropin alfa groups. This is an interesting, novel finding as the dosing in these two additional cycles was based on ovarian response in the previous cycle, with similar cycle-to-cycle dose adjustment approach for both treatment groups. Furthermore, patients with severe OHSS in previous cycles were excluded from subsequent cycles. It is postulated that maintaining or adjusting the dose according to the ovarian response in a previous cycle in which the fixed daily

dose was determined on the basis of serum AMH is more reliable and appropriate than if based on the ovarian response to a standard starting dose and with dose adjustments mid-cycle. Intercycle variability in ovarian response to identical doses of gonadotrophins is a recognized phenomenon (*Rombauts et al., 2015*) and represents the naturally occurring variability in ovarian response. Therefore, cycle-to-cycle adjustments based on the ovarian response to a dose initially selected according to a robust biomarker of ovarian response should have advantages in preventing OHSS versus cycle-to-cycle adjustments made in response to a standard dose, which is somewhat arbitrary and which may not uncover the true potential of the ovary.

Breakdown of the study population by pretreatment AMH quartiles provides evidence that the difference between dosing strategies with respect to moderate/severe OHSS as well as moderate/severe OHSS and/or preventive interventions is mainly driven by the highest AMH quartile (i.e. women with serum AMH ≥25.35 pmol/l at screening). After three cycles, patients in the highest AMH quartile had an incidence of moderate/severe OHSS of 4.3% in the individualized follitropin delta group compared with 9.3% in the conventional follitropin alfa group, and when considering also the preventive interventions, the incidence of moderate/severe OHSS and/or preventive interventions was 11.8% for the individualized follitropin delta group versus 22.1% for the conventional follitropin alfa treatment. These incidence rates cannot be considered negligible or low, and reflect the clinical implications for some patients undergoing repeated ovarian stimulation cycles, with a risk above 20% for moderate/severe OHSS in potential high responders with conventional dosing. Interestingly, despite relatively high doses of follitropin delta administered to patients in the lower pretreatment serum AMH quartiles, the incidence of moderate/severe OHSS or preventive interventions is not increased compared with the conventional follitropin alfa group. Although women in the lowest AMH quartile received the highest possible follitropin delta dose of 12 µg in cycle 1, with the option of increasing the dose up to 24 µg in cycle 3, there were no cases of moderate/severe OHSS or preventive interventions in this treatment group during cycles 2 or 3. Therefore, it appears that patient stratification based on AMH allows for dosing recommendations with follitropin delta that decrease the rate of moderate/severe OHSS in patients with higher AMH levels compared with conventional follitropin alfa. Moreover, this strategy does not increase this risk of OHSS in populations with lower AMH despite the use of relatively higher gonadotrophin doses in subsequent cycles.

Once the cycle is initiated and after detecting that the ovarian response is too high, preventive interventions are utilized in order to reduce the likelihood of OHSS (*Humaidan et al., 2010*). The most frequent preventive action at the end of the stimulation phase in a GnRH antagonist cycle is the use of a GnRH agonist for triggering of final maturation combined with freezing of all embryos and no fresh transfer, as this strategy has been suggested to be effective in significantly reducing the risk of OHSS (*Devroey et al., 2011*). However, there have been reports of the occurrence of OHSS despite the preventive intervention of GnRH agonist triggering and a freeze-all strategy in a GnRH antagonist protocol (*Fatemi et al., 2014; Gurbuz et al., 2014; Ling et al., 2014; Santos-Ribeiro et al., 2015*). These case studies suggest that there may be a possible AMH level threshold whereby GnRH agonist triggering may not be effective in eliminating OHSS (*Ling et al., 2014; Santos-Ribeiro et al., 2015*). In the present investigation, an 11% incidence of moderate OHSS was observed in patients who received GnRH agonist triggering; this is a relatively high percentage, although a case review indicated only small amounts of ascites visible on ultrasound. These observations suggest that GnRH agonist triggering can reduce but not eliminate the risk of OHSS, and at the same time, compromises the ability to undergo a fresh transfer. Less need for GnRH agonist triggering allows more women to undergo fresh embryo transfer, thereby potentially reducing the time to pregnancy and the retained risk of OHSS following GnRH agonist triggering.

Women who underwent subsequent cycles represent a subset of the initial study population included in cycle 1. Patients who discontinued after cycle 1 included patients who became pregnant or suffered from severe OHSS, which was an exclusion criterion for subsequent treatment cycles. As the previous cycle response was being considered for subsequent cycles, the risk of OHSS was lower in cycle 2 than in cycle 1 and lower in cycle 3 than in cycle 2. Importantly, although the value of large controlled studies and the collection of cumulative cycle information is to be recognized, this data set is of limited magnitude for fully demonstrating the public issues of increased hospitalizations and use of emergency care admissions associated with OHSS resulting from IVF treatment. The number of hospitalizations due to OHSS across the three cycles for individualized dosing (two women) compared with conventional dosing (eight women) further points toward individualization of gonadotrophin dosing based on biomarkers being a step in the right direction. Although there are distinct pharmacokinetic and dynamic properties, the concept of individualization should be considered in IVF treatment. The specific individualized dosing algorithm applied is unique for follitropin delta and cannot be extrapolated to other FSH preparations. Real-world evidence will provide further insight into the role of individualized dosing on OHSS prevention and cost reduction (*van Tilborg et al., 2017*).

The analysis of up to three ovarian stimulation cycles demonstrates that an individualized follitropin delta dosing regimen, determined by serum AMH levels and body weight, reduces the incidence of moderate/severe OHSS and the need for preventive interventions beyond the initial stimulation cycle. An analysis per AMH quartile indicated that these statistically significant differences are driven mainly by patients with the highest pretreatment AMH levels.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.rbmo.2018.12.032.

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