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ARTICLE

Individualized follitropin delta dosing reduces OHSS risk in Japanese IVF/ICSI patients: a randomized controlled trial

BIOGRAPHY

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KEY MESSAGE

Through a modulation of the ovarian response, the individualized follitropin delta dosing approach significantly reduced the incidence of ovarian hyperstimulation syndrome and provided a favourable benefit–risk profile in fresh cycles compared with conventional recombinant FSH dosing in Japanese IVF/ICSI patients.

ABSTRACT

Research question: This study aimed to establish the efficacy and safety of ovarian stimulation with a follitropin delta individualized fixed-dose regimen based on serum anti-Müllerian hormone (AMH) concentration and body weight versus conventional follitropin beta dosing in Japanese women.

Design: This randomized, controlled, assessor-blind, multicentre, non-inferiority trial was conducted in 347 Japanese IVF/intracytoplasmic sperm injection patients. They were randomized to individualized follitropin delta (AMH <15 pmol/l: 12 μg/day; AMH ≥15 pmol/l: 0.10–0.19 μg/kg/day; minimum 6 μg/day; maximum 12 μg/day) or conventional follitropin beta (150 IU/day for the first 5 days, with potential subsequent dose adjustments). The primary end-point was the number of oocytes retrieved with a pre-specified non-inferiority margin (−3.0 oocytes).

Results: The primary trial objective was met, as non-inferiority was established for number of oocytes retrieved for individualized follitropin delta dosing compared with conventional follitropin beta dosing (9.3 versus 10.5; lower boundary of 95% confidence interval −2.3). The occurrence of ovarian hyperstimulation syndrome (OHSS) was reduced to approximately half with individualized compared with conventional dosing, with an incidence of 11.2% versus 19.8% (P = 0.021) for OHSS of any grade and 7.1% versus 14.1% (P = 0.027) for moderate/severe OHSS. The live birth rate per started cycle was 23.5% for individualized dosing and 18.6% for conventional dosing.

Conclusions: Dosing with individualized follitropin delta in Japanese women is non-inferior to conventional dosing with follitropin beta for number of oocytes retrieved. The individualized approach shows a favourable benefit–risk profile, providing a statistically significant and clinically relevant reduction in the incidence of OHSS, without compromising live birth rates.

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KEY WORDS

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INTRODUCTION

With the overall objective of obtaining a live birth, ovarian stimulation during an assisted reproductive technology (ART) cycle should be performed in a way that adequate multiple follicular development is obtained with minimum risks for the woman, mainly with respect to ovarian hyperstimulation syndrome (OHSS). Reducing each woman's risk of OHSS, while not compromising her potential for a successful outcome, is one of the major clinical challenges in ovarian stimulation.

In conventional stimulation protocols with transfer of embryo(s)/blastocyst(s) in the fresh cycle, OHSS has been reported to occur at an incidence of 20% or more in Japanese women (*Fujiwara, 2015*; *Ishihara et al., 2020a*). The freeze-all strategy, i.e. elective freezing of embryos/blastocysts and transfer in subsequent cycles, has been shown to reduce the risk of OHSS (*Bosch et al., 2020*; *Roque et al., 2019*). Although fresh cycles are still predominantly used in many countries, the number of freeze-all cycles has increased substantially in Japan since 2007 and they are now used in about 45% of all ovarian stimulation cycles for IVF/intracytoplasmic sperm injection (ICSI) (*EIM et al., 2020*; *Ishihara et al., 2020b*). While pregnancy rates are not compromised, the main objections to the freeze-all strategy are the extended time to pregnancy and the additional patient burden and/or costs (*Bosch et al., 2020*; *Roque et al., 2019*). When shorter time to pregnancy is important and therefore fresh cycle transfer is implemented, ovarian stimulation protocols based on dosing regimens with reduced OHSS risk may be preferable as long as the probability of pregnancy and live birth is not decreased.

Individualization of gonadotrophin dosing in ovarian stimulation is becoming an alternative over the concept of 'one dose fits all' associated with conventional dosing protocols. Stratification of patients based on individual characteristics and/or diagnostic markers of ovarian reserve has been proposed by clinicians, and also recommended by health policy makers in order to individualize doses for ovarian stimulation, minimize OHSS risks and enhance the probability of successful outcomes (*Broer et al., 2014*; *Fauser, 2008*; *Fleming et al., 2013*; *La Marca and Sunkara, 2014*; *National Institute for Health and Care Excellence, 2013*; *Nelson et al., 2009*; *Nelson, 2013*). A few multicentre, randomized, controlled trials (RCT) have explored the dose individualization concept (*Allegra et al., 2017*; *Nyboe Andersen and Nelson et al., 2017*; *Oudshoorn et al., 2017*; *van Tilborg et al., 2017a*, *2017b*). The studies have consistently demonstrated that individualization of gonadotrophin dosing lowers the incidence of OHSS and/or preventive interventions, without compromising pregnancy rates. These effects are achieved by modulating the ovarian response, in terms of reducing the variability of the number of oocytes retrieved or the extreme ovarian responses.

Nevertheless, the individualized dosing evidence is mainly based on data from trials primarily conducted in Europe and North and South America (*Allegra et al., 2017*; *Nyboe Andersen and Nelson et al., 2017*; *Oudshoorn et al., 2017*; *van Tilborg et al., 2017a*, *2017b*), with no trials conducted in Asia, where patient characteristics and/or diagnostic markers of ovarian reserve may differ. Furthermore, studies conducted in ART populations in the USA and the UK have identified ethnic disparities in treatment outcomes (*Dhillon et al., 2015*; *Maalouf et al., 2017*; *Quinn and Fujimoto, 2016*), also supporting the need to investigate ovarian response and outcomes to ovarian stimulation across populations from different geographies. The present study compared the ovarian responses associated with individualized follitropin delta dosing versus conventional follitropin beta dosing, and explored the implications on OHSS as well as pregnancy and live birth rates for Japanese women undergoing ovarian stimulation for ART.

MATERIALS AND METHODS

Trial design

This was a randomized, controlled, assessor-blind, multicentre, non-inferiority trial of individualized follitropin delta dosing versus conventional follitropin beta dosing conducted at 17 investigational sites in Japan (Supplemental Table 1). The trial protocol (number 000273) was notified to the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) and approved by the Institutional Review Boards covering all participating centres between 7 July 2017 and 11 September 2018. The trial was performed in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation Guidelines for Good Clinical Practice, Japanese Good Clinical Practice and applicable regulatory requirements. All participants provided written informed consent.

The trial is registered at clinicaltrials.gov, with registration number: NCT03228680.

Trial population

Japanese women aged 20–40 years undergoing their first IVF/ICSI cycle and diagnosed with tubal infertility, unexplained infertility or infertility related to endometriosis stage I/II, or with a partner diagnosed with male factor infertility were eligible for the trial. Additional main inclusion criteria were body mass index (BMI) of 17.5–32.0 kg/m^2, regular menstrual cycles of 24–35 days, presence of both ovaries and early follicular phase FSH serum concentration of 1–15 IU/l. The main exclusion criteria were endometriosis stage III/IV, history of recurrent miscarriage and use of hormonal preparations (except for thyroid medication) during the last menstrual cycle before randomization. There was no eligibility criterion limiting the serum anti-Müllerian hormone (AMH) concentration at screening. All inclusion/exclusion criteria are listed in Supplemental Table 2.

Trial randomization and blinding

Women were randomly assigned in a 1:1 ratio via a central computer-generated randomization sequence, prepared by an independent statistician. Randomization was stratified by centre and according to AMH concentration at screening (<15 pmol/l and ≥15 pmol/l) and performed in blocks of four within the trial sites. All investigators, embryologists and central laboratory personnel were blinded to the treatment allocation throughout the trial.

Trial procedures

Women randomized to follitropin delta (Rekovelle, 72 µg/2.16 ml; Ferring Pharmaceuticals, Switzerland) were assigned to a fixed daily subcutaneous dose, determined by their serum AMH concentration at screening and body weight at randomization (AMH <15 pmol/l: 12 µg; AMH ≥15 pmol/l: 0.10–0.19 µg/kg; the minimum daily dose was

6 µg and the maximum daily dose 12 µg). The follitropin delta dosing regimen was identical to that previously investigated in non-Japanese women (*Nyboe Andersen and Nelson et al., 2017*) with the added establishment of 6 µg as the minimum daily dose to account for the generally lower body weight of the Japanese population. A dose–response trial in Japanese women (*Ishihara et al., 2020a*) followed by modelling and simulation to confirm the appropriateness of the dosing regimen in Japanese women preceded the present trial. The follitropin delta dosing algorithm (Supplemental Table 3) was programmed into the electronic case report form, which calculated the dose. The assigned daily dose was fixed throughout the stimulation period (i.e. no dose adjustments were made during stimulation).

Women randomized to follitropin beta (Follistim, 900 IU/1.08 ml; MSD, Japan) were administered a daily subcutaneous dose of 150 IU (expressed also as 15 µg of follitropin beta; *Puregon, 2020*), which is the lowest approved starting dose in Japan (*Follistim, 2015*) and also in line with international recommendations (*Gianaroli et al., 2012*) for the first 5 days; thereafter, the dose could be adjusted up or down by 75 IU based on the individual response during stimulation as per the investigator's judgement, with 375 IU as the maximum daily dose allowed.

On day 2–3 of the menstrual cycle, the women were randomized to ovarian stimulation with either follitropin delta or follitropin beta. To prevent a premature LH surge, a gonadotrophin-releasing hormone (GnRH) antagonist (Ganirest; MSD, Japan) at a daily dose of 0.25 mg was initiated on day 6 and continued throughout the stimulation period. When ≥3 follicles with a diameter ≥17 mm were observed, triggering of final follicular maturation was performed with 5000 IU urinary human chorionic gonadotrophin (HCG; Fuji Pharma, Japan). In cases of poor ovarian response (≥3 follicles with a diameter ≥17 mm could not be achieved by day 20), the cycle was cancelled. In cases of excessive ovarian response (≥25 follicles with a diameter ≥12 mm), women with 25–35 follicles with a diameter ≥12 mm could either be administered a GnRH agonist (600 µg Suprecur, 600 µg Buserecur and 800 µg Nafarelil, as per local availability and at a dose according to site-specific procedures) or have the cycle cancelled as per the investigator's judgement, while the cycle was cancelled if there were >35 follicles with a diameter ≥12 mm.

Blood samples were collected during the trial for assessment of AMH, FSH, LH, oestradiol, inhibin B, inhibin A and progesterone. The serum concentration of AMH was measured at screening to determine the randomization strata. It was measured at a central laboratory using the automated Elecsys AMH assay from Roche Diagnostics, Switzerland. Serum samples for assessment of endocrine parameters (FSH, LH, oestradiol, inhibin B, inhibin A and progesterone) were collected at the start of stimulation, on stimulation day 6 and at the end of stimulation, and analysed at central laboratories. The sensitivity and precision of the validated methods are presented in Supplemental Table 4.

Oocytes were retrieved 36 h (±2 h) after triggering of final follicular maturation and inseminated by IVF or ICSI, using ejaculated sperm from the woman's partner. The blastocyst with the best quality was transferred on day 5 after oocyte retrieval, while the remaining blastocysts could be cryopreserved. For women who underwent triggering with GnRH agonist, no transfer was performed, and all blastocysts were cryopreserved. All cryopreserved blastocysts could be used by the patient after completion of the trial, in accordance with the declaration by Japan Society of Obstetrics and Gynaecology.

Vaginal progesterone tablets (Lutinus; Ferring Pharmaceuticals, Japan) 100 mg three times daily were provided for luteal phase support from the day after oocyte retrieval until the day of the clinical pregnancy visit, if applicable. A beta-HCG test was performed 13–15 days after blastocyst transfer (earlier assessment was accepted for women experiencing menses). Transvaginal ultrasound was performed 5–6 weeks after blastocyst transfer to assess clinical pregnancy (defined as at least one intrauterine or ectopic gestational sac). All pregnancies were followed until 4 weeks after live birth (defined as the birth of at least one live neonate) for information on pregnancy outcome including ongoing pregnancy (defined as at least one intrauterine viable fetus 10–11 weeks after blastocyst transfer) and neonatal health. Adverse events were recorded from the signed informed consent until the end-of-trial visit. Local tolerability of follitropin delta and follitropin beta following subcutaneous administration were assessed by the woman three times daily, i.e. immediately, 30 min and 24 h after each injection, and recorded in a diary. The injection site reactions (redness, itching, pain, swelling and bruising) were assessed as none, mild, moderate or severe.

Trial outcomes

The primary end-point was the number of oocytes retrieved which is a direct pharmacodynamic parameter of FSH action. The pre-specified efficacy secondary end-points included among others duration of stimulation, total gonadotrophin dose, distribution of number of oocytes retrieved, extreme ovarian response in at-risk populations (defined as <4 oocytes retrieved for women with AMH <15 pmol/l and ≥15 or ≥20 oocytes retrieved for women with AMH ≥15 pmol/l), pregnancy outcomes, including clinical pregnancy as an important secondary end-point, and live birth rates. Safety evaluations included adverse events, early and late OHSS, preventive interventions for early OHSS, cycle cancellation or blastocyst transfer cancellation due to excessive ovarian response/OHSS risk, and local tolerability. All cases of OHSS were categorized by grade (1, 2, 3, 4 or 5) and level (mild, moderate or severe OHSS) according to Golan's classification system (*Golan et al., 1989*). Early OHSS was defined as an onset ≤9 days after triggering of final follicular maturation and late OHSS as an onset >9 days after triggering of final follicular maturation. Preventive interventions included cycle cancellation due to excessive ovarian response, triggering of final follicular maturation with GnRH agonist or administration of dopamine agonist in women with ≥20 follicles of ≥12 mm.

Statistical analysis

The trial was designed to demonstrate non-inferiority in the number of oocytes retrieved for an individualized dosing regimen of follitropin delta versus conventional follitropin beta dosing based on a pre-established non-inferiority margin of −3.0 oocytes for the lower boundary of the two-sided 95% confidence interval (CI) for the mean treatment difference as agreed with the PMDA. The primary end-point and the secondary efficacy end-points were analysed using the full analysis set (FAS),

i.e. all randomized and exposed women, with women analysed according to the actual treatment received (n = 347). The analysis of the primary end-point on the per-protocol analysis set (i.e. all randomized and exposed women, except those excluded as a result of major protocol deviations; n = 337) was considered supportive.

The primary end-point was analysed using an analysis of variance model with treatment and AMH stratum as fixed factors. The two-sided 95% confidence limits for the mean treatment differences were calculated based on the fitted model for the FAS. In addition, subgroup analyses were performed separately for the two AMH strata.

For the analysis of pregnancy and live birth end-points, a two-sided 95% confidence interval was constructed for the difference between rates for follitropin delta and follitropin beta using the Mantel–Haenszel method. Other categorical secondary end-points were compared between treatment groups using a logistic regression model with treatment and AMH stratum as fixed factors, and within each AMH stratum using the chi-squared test. The endocrine parameters were evaluated using analysis of covariance models with the ln-transformed variable as the dependent variable, treatment and AMH stratum as fixed factors, and the ln-transformed baseline value obtained at stimulation day 1 as a covariate. The endocrine data were compared between treatment groups using the F-test. Other continuous secondary end-points were compared between treatment groups using the van Elteren test adjusted for AMH strata. All statistical tests were performed using a two-sided test at a 5% significance level. No adjustments for multiplicity were made. Statistical analyses were performed with SAS software, version 9.4 (SAS Institute Inc., USA).

Assuming the two treatments to be equally effective, a sample size of 155 randomized women per treatment group was calculated to have 90% power to achieve the primary objective for the per-protocol analysis set with a one-sided t-test at a 2.5% significance level.

RESULTS

Baseline characteristics

The trial was conducted between 29 July 2017 and 8 July 2019, with pregnancy follow-up data completed on 20 May 2020. A total of 347 Japanese women were randomized and exposed to ovarian stimulation, of which 170 were treated with individualized follitropin delta dosing and 177 with conventional follitropin beta dosing as shown in the trial participant flow chart in FIGURE 1. The two treatment groups were comparable in terms of age and baseline characteristics (TABLE 1).

Ovarian stimulation

The main ovarian response data are presented in TABLE 2. The daily and total gonadotrophin doses used were lower (both $P < 0.001$) with individualized follitropin delta dosing compared with follitropin beta dosing despite a similar duration of stimulation. As per protocol, the individualized dose of follitropin delta was unchanged throughout the stimulation, while the daily dose was adjusted in 46.3% of the women treated with follitropin beta, with the majority of adjustments being a dose increase on stimulation day 6.

Median serum concentrations of FSH at the end of stimulation were lower ($P < 0.001$) in the individualized follitropin delta group (14.3 IU/l) compared with the follitropin beta group (16.4 IU/l) (TABLE 2). Furthermore, the serum concentrations of oestradiol, inhibin B, inhibin A and progesterone at the end of stimulation were lower ($P = 0.003$, $P = 0.027$, $P < 0.001$ and $P < 0.001$, respectively) with individualized follitropin delta than with follitropin beta.

Dosing with individualized follitropin delta was non-inferior to conventional follitropin beta with respect to the number of oocytes retrieved, as the lower boundary of the 95% confidence interval for the mean treatment difference was above the pre-specified non-inferiority margin of −3.0 oocytes (mean of 9.3 versus 10.5; −1.2 [95% CI −2.3 to −0.1]) (TABLE 2). Overall, there was no difference between the treatment groups in the proportion of women with 8–14 oocytes retrieved (40.8% individualized follitropin delta versus 42.8% follitropin beta). Among women with normal or high ovarian reserve, as reflected by a serum AMH ≥15 pmol/l, the individualized follitropin delta dosing resulted in an average of two oocytes fewer (mean of 10.8 versus 12.9; −2.2 [95% CI −3.9 to −0.5]) compared with follitropin beta (TABLE 2). In this population at risk of excessive ovarian response, the proportion of excessive responders with ≥15 or ≥20 oocytes retrieved was reduced ($P = 0.002$ and $P = 0.021$, respectively) by approximately 50–60% in the follitropin delta group compared with the follitropin beta group (≥15 oocytes retrieved: 22.0% versus 42.0%; ≥20 oocytes retrieved: 8.0% versus 19.0%). Among women with low ovarian reserve, as reflected by a serum AMH <15 pmol/l, there was no difference between the treatment groups in either the number of oocytes retrieved or the proportion of poor responders with <4 oocytes retrieved (TABLE 2).

Clinical outcomes

The incidence of OHSS was lower with individualized follitropin delta than with follitropin beta, including OHSS (early and late combined, 11.2% versus 19.8%, $P = 0.021$), moderate/severe OHSS (7.1% versus 14.1%, $P = 0.027$), OHSS and/or preventive interventions (11.8% versus 22.0%, $P = 0.008$) and moderate/severe OHSS and/or preventive interventions (8.2% versus 17.5%, $P = 0.007$) (TABLE 3). As illustrated in FIGURE 2, the risk of experiencing OHSS and/or requiring preventive interventions for early OHSS increased with increasing serum AMH concentrations and differed between treatment groups. Two women in the follitropin beta group were hospitalized due to OHSS for a duration of 16 days and 33 days, respectively, while there were no hospitalizations in the individualized follitropin delta group.

A lower ($P < 0.001$) number of blastocysts was observed with individualized follitropin delta compared with follitropin beta, with a mean of 3.1 and 4.2 blastocysts, respectively (TABLE 2), while the proportion of women who underwent blastocyst transfer was comparable between treatment groups (79.4% individualized follitropin delta versus 79.7% follitropin beta). Only single blastocyst transfers were performed. Pregnancy and live birth rates per started cycle and per cycle with transfer are presented in TABLE 3. The live birth rate per started cycle was 23.5% for individualized follitropin delta and 18.6% for follitropin beta, while the live birth rate per cycle with transfer was 29.6% and 23.4%, respectively. No women were lost to follow-up and no neonatal deaths occurred between birth and 4 weeks after birth.

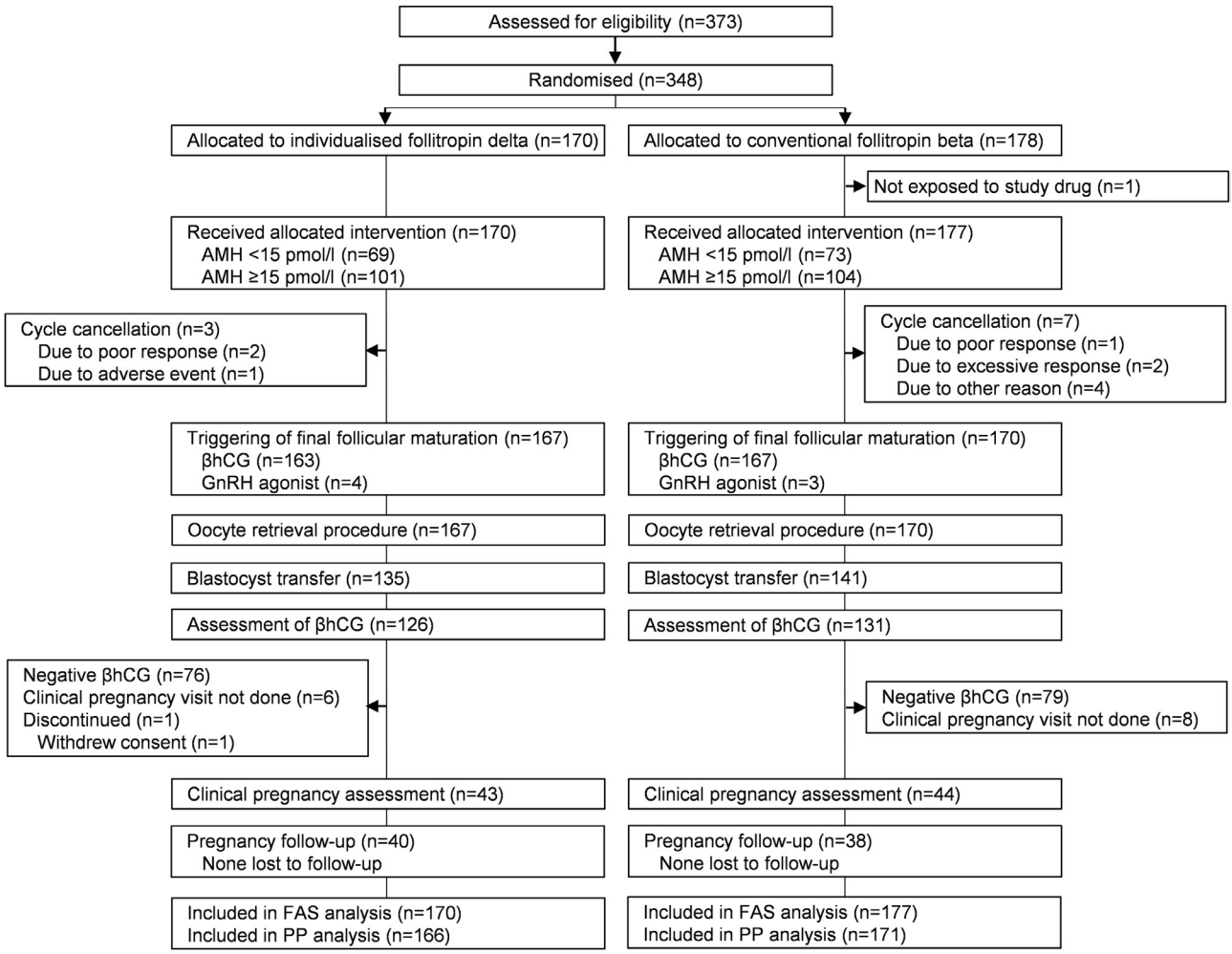

FIGURE 1 Assignment, treatment and analysis of patients. AMH, anti-Müllerian hormone; βhCG, beta unit of human chorionic gonadotrophin; FAS, full analysis set; GnRH, gonadotrophin-releasing hormone; PP, per-protocol.

The proportion of women with adverse drug reactions was 18.8% in the individualized follitropin delta group and 25.4% in the follitropin beta group, with the difference mainly attributed to the higher incidence of OHSS in the latter group. A low incidence of local injection site reactions was reported after subcutaneous administration of either individualized follitropin delta (1.2%) or follitropin beta (3.1%), with the main difference between treatment groups being caused by more reports of pain with follitropin beta (1.8% versus <0.1%).

DISCUSSION

This RCT concluded that dosing with individualized follitropin delta in Japanese women undergoing ovarian stimulation was non-inferior to conventional dosing with follitropin beta in terms of the number of oocytes retrieved. It indicated that selection of the starting gonadotrophin dose according to individual patient parameters results in modulation of the ovarian response, which in at-risk patients could positively influence clinical outcomes, most notably the incidence of OHSS.

Among women with an ovarian reserve indicative of a low response, the individualized dosing approach in the present trial in Japanese IVF/ICSI patients did not increase the mean number of oocytes retrieved compared with the conventional dosing approach, whereas a trial in non-Japanese women found an average of one more oocyte retrieved with individualized dosing (*Nyboe Andersen and Nelson et al., 2017*). On the other hand, among Japanese women with an ovarian reserve indicative of normal to high response, the individualized dosing approach was associated with an average of 10.8 oocytes, corresponding to around two oocytes fewer than the conventional dosing approach, which led to an approximately 50% lower risk of developing hyperresponse and severe hyperresponse. It is well-known that the risk of OHSS increases with oocyte yield, and a drastic rise in frequency has been observed with the retrieval of 15 oocytes or more (*Papanikolaou et al., 2006*; *Steward et al., 2014*). Thus, the individualized dosing approach normalized the ovarian response away from extreme responses, which is in line with previously published results obtained in an RCT in non-Japanese women undergoing IVF/ICSI (*Nyboe Andersen and Nelson et al., 2017*).

The differential modulation of ovarian response between treatment groups in patients at risk of excessive response impacted the overall OHSS rates. In the present trial, conventional dosing was

TABLE 1 PATIENT CHARACTERISTICS

Characteristic	Treatment group	
	Individualized follitropin delta (*N* = 170)	Conventional follitropin beta (*N* = 177)
Age		
All patients (years)	34.2 ± 3.5	34.0 ± 3.4
<35	88 (51.8)	93 (52.5)
35–37	51 (30.0)	55 (31.1)
38–40	31 (18.2)	29 (16.4)
Weight (kg)	54.5 ± 7.5	54.3 ± 7.5
BMI (kg/m^2)	21.4 ± 2.7	21.6 ± 2.8
Infertility history		
Duration of infertility (months)	34.3 ± 26.0	31.6 ± 18.2
Primary infertility	109 (64.1)	117 (66.1)
Reason for infertility		
Unexplained infertility	81 (47.6)	88 (49.7)
Tubal infertility	28 (16.5)	37 (20.9)
Male factor	56 (32.9)	50 (28.2)
Endometriosis stage I/II	4 (2.4)	2 (1.1)
Other	1 (0.6)	0
Endometrial thickness (mm)	5.3 ± 2.0	5.3 ± 2.0
Ovarian volume (cm^3)	4.6 ± 2.1	4.8 ± 2.1
AFC[a]	11.5 ± 6.9	11.4 ± 6.9
Endocrine profile[b]		
AMH (pmol/l)[c]	18.2 (11.0–28.2)	16.7 (11.3–27.4)
FSH (IU/l)	8.2 (7.0–9.6)	8.2 (6.8–9.7)
LH (IU/l)	3.7 (2.8–4.6)	3.8 (3.0–4.7)
Oestradiol (pmol/l)	165.0 (133.3–209.2)	162.8 (127.8–194.1)
Inhibin B (ng/l)	83.0 (65.0–105.0)	80.0 (60.0–101.0)
Inhibin A (ng/l)	5.8 (4.3–7.5)	5.5 (4.5–7.3)
Progesterone (nmol/l)	0.8 (0.8–2.0)	1.6 (0.8–2.1)

Values are mean ± SD, median (25th–75th percentiles) or *n* (%). Data are for all patients unless otherwise stated.

[a] This measurement reports the total number of antral follicles with a diameter of ≥2 mm for both ovaries combined, assessed by transvaginal ultrasound on the day of starting ovarian stimulation.

[b] The AMH values are based on the screening samples, while the remaining endocrine parameters are based on the samples taken on stimulation day 1 before first exposure to the trial drug.

[c] The serum concentration of AMH was assessed by a central laboratory using the Elecsys AMH assay from Roche Diagnostics.

AFC, antral follicle count; AMH, anti-Müllerian hormone; BMI, body mass index; *N*, total number of patients; *n*, number of patients with observation.

associated with an incidence of 19.8% for OHSS and 14.1% for moderate/severe OHSS. This is consistent with previous clinical trials in Japan reporting OHSS rates of 20–22% (*Fujiwara, 2015*; *Ishihara et al., 2020a*). The 50% reduction in occurrence of OHSS (11.2%) and moderate/severe OHSS (7.1%) with the individualized dosing approach is therefore clinically relevant and a major improvement for the women's safety. The treatment option of personalized dosing associated with a safer OHSS profile is especially valuable considering the high risk of OHSS with conventional therapy in Japanese IVF/ICSI patients even when using the lowest recommended starting dose of 150 IU/day and despite the investigator's option to decrease the dose during stimulation.

While the OHSS rate observed with conventional dosing in this trial is in line with previous Japanese data, it is acknowledged that the OHSS rate for both dosing approaches is higher than in non-Japanese IVF/ICSI patients (*Nyboe Andersen and Nelson et al., 2017*). There are several risk factors associated with the development of OHSS, including low BMI, polycystic ovary syndrome, high or rapidly rising oestradiol concentrations after ovarian stimulation and a high number of follicles and oocytes retrieved (*Alper et al., 2009*), but specific reasons for differences in OHSS rate between trials or regions have not been fully elucidated. It is noteworthy that the incidence of preventive interventions for early OHSS was much lower than the incidence of early OHSS, which may suggest that follicular development alone is an insufficient indicator for risk of OHSS in the Japanese population and

TABLE 2 OVARIAN RESPONSE OUTCOMES

Outcome variable	Treatment group		
	Individualized follitropin delta (*N* = 170)	Conventional follitropin beta (*N* = 177)	Difference (95% CI) or *P*-value
Duration of stimulation (days)	8.9 ± 1.9	8.8 ± 1.7	0.694[a]
Total dose (µg)[b]	83.5 ± 28.9	149.9 ± 51.4 (1499 ± 514 IU)	<0.001[a]
Daily dose (µg/day)[b]	9.4 ± 2.5	16.7 ± 2.5 (167 ± 25 IU/day)	<0.001[a]
FSH (IU/l)[c]	14.3 (11.6–19.7)	16.4 (13.5–20.4)	<0.001[d]
LH (IU/l)[c]	1.6 (1.0–2.5)	1.4 (0.9–2.3)	0.057[d]
Oestradiol (pmol/l)[c]	6517.0 (4465.3–9033.4)	7438.8 (5363.6–10,283.1)	0.003[d]
Inhibin B (ng/l)[c]	686.0 (461.0–1057.0)	734.5 (492.5–1120.5)	0.027[d]
Inhibin A (ng/l)[c]	323.8 (222.1–458.8)	390.3 (301.0–551.1)	<0.001[d]
Progesterone (nmol/l)[c]	2.5 (1.9–3.5)	3.1 (2.3–4.3)	<0.001[d]
Oocytes retrieved	9.3 ± 5.4	10.5 ± 6.1	−1.2 (−2.3 to −0.1)[e]
Ovarian response stratified by AMH			
Women with AMH <15 pmol/l (at risk of hyporesponse)	69 (40.6)	73 (41.2)	
Oocytes retrieved	7.2 ± 3.7	7.0 ± 3.4	0.1 (−1.0 to 1.3)[f]
Poor responders (<4 oocytes)[g]	8 (11.6)	9 (12.3)	0.893[h]
Women with AMH ≥15 pmol/l (at risk of hyperresponse)	101 (59.4)	104 (58.8)	
Oocytes retrieved	10.8 ± 5.9	12.9 ± 6.4	−2.2 (−3.9 to −0.5)[f]
Excessive responders (≥15 oocytes)[g]	22 (22.0)	42 (42.0)	0.002[h]
Excessive responders (≥20 oocytes)[g]	8 (8.0)	19 (19.0)	0.021[h]
Poor response leading to cycle cancellation[i]	2 (1.2)	1 (0.6)	0.535[j]
Excessive response leading to cycle cancellation[k]	0	2 (1.1)	0.100[j]
Excessive response/OHSS risk leading to blastocyst transfer cancellation[l]	13 (7.6)	20 (11.3)	0.244[j]
Blastocysts, day 5[m]	3.1 ± 2.7	4.2 ± 3.4	<0.001[a]

Values are mean ± SD, median (25th–75th percentiles) or *n* (%), unless otherwise stated. Data are for all patients unless otherwise stated.

[a] The *P*-value is based on a van Elteren test adjusted for AMH strata.

[b] Follitropin beta is dosed in IU and the approved Follistim labelling in Japan does not include any information on conversion (*Follistim, 2015*). A dose of 150 IU is equal to 15 µg for follitropin beta according to the approved Puregon labelling in Europe (*Puregon, 2020*).

[c] At end of stimulation.

[d] The *P*-value corresponds to an F-test for testing of no treatment difference.

[e] The overall comparison is based on an ANOVA with treatment and AMH stratum as fixed factors. The non-inferiority margin for the difference between the two treatments was pre-specified at −3.0 for the primary end-point.

[f] The comparison within each AMH stratum is based on an ANOVA fitted to each AMH stratum with treatment as the fixed factor.

[g] *N* represents the number of patients with oocytes retrieved and patients with cycle cancellation due to poor or excessive ovarian response, i.e. 169 in the follitropin delta group (69 with AMH <15 pmol/l and 100 with AMH ≥15 pmol/l) and 173 in the follitropin beta group (73 with AMH <15 pmol/l and 100 with AMH ≥15 pmol/l).

[h] The *P*-value is based on a likelihood ratio chi-squared test.

[i] Defined as the investigator judging that ≥3 follicles with a diameter ≥17 mm could not be achieved by stimulation day 20.

[j] The *P*-value is based on a likelihood ratio test.

[k] Defined as ≥25 follicles with a diameter ≥12 mm.

[l] Defined as adverse events such as the MedDRA preferred terms 'ovarian hyperfunction', 'ovarian enlargement', 'ovarian hyperstimulation syndrome' and 'high progesterone' in patients with blastocysts available for transfer.

[m] For women with oocytes retrieved.

ANOVA, analysis of variance; AMH, anti-Müllerian hormone; MedDRA, Medical Dictionary for Regulatory Activities; *N*, total number of patients; *n*, number of patients with observation; OHSS, ovarian hyperstimulation syndrome.

that the impact of other variables, such as oestradiol, could be investigated.

Ovarian hyperstimulation is a preventable life-threatening risk, and it furthermore affects efficacy in the fresh cycle because of either endometrial advancement due to exaggerated hormonal ovarian response or postponement of embryo/blastocyst transfer to a subsequent frozen cycle, delaying the time to pregnancy and potentially compromising the chances of having a child. In line with the RCT conducted outside Japan (*Nyboe Andersen and Nelson et al., 2017*), the present trial also showed that efficacy in terms of pregnancy and live birth rates was not compromised with individualized dosing. The live birth rates of 23.5% for individualized dosing and 18.6% for conventional dosing in Japanese IVF/ICSI patients are in line with the observations made in previous clinical trials conducted in Japan (*Follistim, 2015*; *Ishihara et al., 2020a*) and also with what is reported from clinical practice in Japan (*Ishihara et al., 2020b*).

TABLE 3 CLINICAL OUTCOMES

Outcome variable	Treatment group		
	Individualized follitropin delta (*N* = 170)	Conventional follitropin beta (*N* = 177)	Percentage difference (95% CI) or *P*-value
Preventive interventions	2 (1.2)	6 (3.4)	0.152[a]
Early OHSS[b]			
Any grade	17 (10.0)	33 (18.6)	0.017[a]
Moderate/severe	11 (6.5)	23 (13.0)	0.035[a]
Any grade and/or preventive intervention	18 (10.6)	37 (20.9)	0.006[a]
Moderate/severe and/or preventive intervention	13 (7.6)	29 (16.4)	0.009[a]
Total (early and late[c]) OHSS			
Any grade	19 (11.2)	35 (19.8)	0.021[a]
Moderate/severe	12 (7.1)	25 (14.1)	0.027[a]
Any grade and/or preventive intervention	20 (11.8)	39 (22.0)	0.008[a]
Moderate/severe and/or preventive intervention	14 (8.2)	31 (17.5)	0.007[a]
Clinical pregnancy[d]			
Per started cycle	43 (25.3)	42 (23.7)	1.6 (−7.5 to 10.6)[e]
Per cycle with transfer[f]	43 (31.9)	42 (29.8)	1.9 (−8.9 to 12.8)[e]
Ongoing pregnancy[g]			
Per started cycle	40 (23.5)	34 (19.2)	4.3 (−4.3 to 12.9)[e]
Per cycle with transfer[f]	40 (29.6)	34 (24.1)	5.3 (−5.1 to 15.7)[e]
Women with live birth[h]			
Per started cycle	40 (23.5)	33 (18.6)	4.9 (−3.7 to 13.4)[e]
Per cycle with transfer[f]	40 (29.6)	33 (23.4)	6.0 (−4.3 to 16.4)[e]

Values are *n* (%), unless otherwise stated. Data are for all patients unless otherwise stated.

In the follitropin beta group, there were two cases of OHSS during the trial that led to hospitalization for a duration of 16 days and 33 days, respectively.

[a] The *P*-value is based on a likelihood ratio chi-squared test.

[b] Onset ≤9 days after triggering of final follicular maturation.

[c] Onset >9 days after triggering of final follicular maturation.

[d] At least one intrauterine or ectopic gestational sac 5–6 weeks after transfer.

[e] The overall comparison is adjusted for AMH strata by using the Mantel–Haenszel method to combine the risk differences obtained within each AMH stratum.

[f] *N* represents the number of patients with blastocyst transfer, i.e. 135 in the follitropin delta group and 141 in the follitropin beta group.

[g] At least one intrauterine viable fetus 10–11 weeks after transfer.

[h] The birth of at least one live neonate.

AMH, anti-Müllerian hormone; *N*, total number of patients; *n*, number of patients with observation; OHSS, ovarian hyperstimulation syndrome.

The individualized dosing regimen was associated with a 44% reduced exposure to recombinant FSH compared with conventional dosing and contributed to explain the outcomes, primarily the safety. Interestingly, the use of lower gonadotrophin doses has been associated with higher chances of a live birth, potentially by oocyte selection or reduced probability of a detrimental impact on oocyte development and embryo quality (*Baker et al., 2015*; *Gerber et al., 2020*; *Munch et al., 2017*; *Shaia et al., 2020*).

An increasing number of women of advanced age seek fertility treatment in developed countries. The present study included women with a maximum age of 40 years; in Japan the average age for women undergoing ART is 38 years and approximately one-third of cycles are performed in women older than 40 years (*Ishihara et al., 2020b*). The contribution of frozen cycles to cumulative live birth rate was not investigated in this trial, but both dosing approaches were associated with supernumerary blastocysts after stimulation and transfer in the fresh cycle. Knowledge of patients' preferences and experiences, including the reasons for not pursuing further care or cycles, is important for meeting the patients' needs, and time to pregnancy plays a critical role in this context (*Roque and Simon, 2020*; *Stormlund et al., 2020*).

In conclusion, this trial demonstrates that individualized dosing with follitropin delta is non-inferior to conventional stimulation with respect to the number of oocytes retrieved in Japanese women. Furthermore, the individualized dosing approach reduces the incidence of OHSS and total dose of recombinant FSH, without compromising pregnancy or live birth rates. Overall, the personalized dosing regimen leads to a favourable benefit–risk profile in Japanese women as already observed in non-Japanese women (*Nyboe Andersen and Nelson et al., 2017*). Consideration should be given to individualized ovarian stimulation with follitropin delta when time to pregnancy is an important factor, as it reduces the risk of OHSS associated

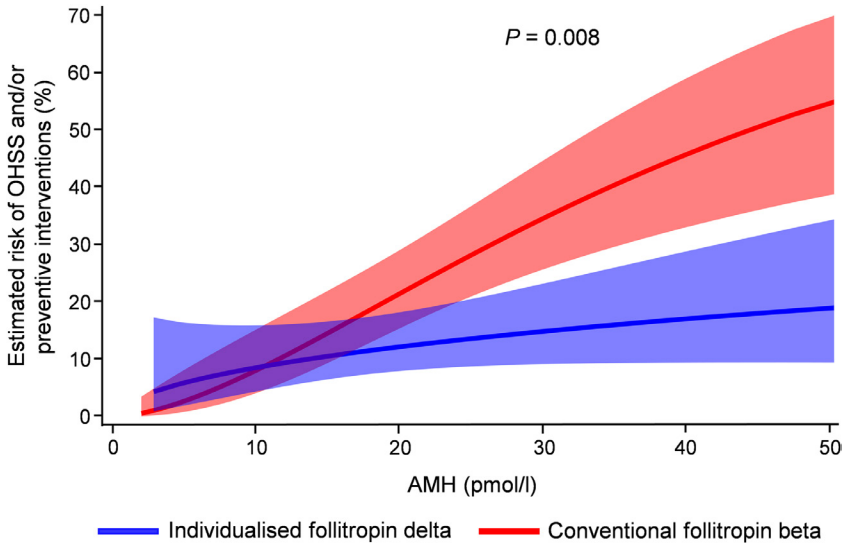

FIGURE 2 Estimated risk of OHSS (any grade) and/or preventive interventions for early OHSS relative to AMH. The solid blue (individualized follitropin delta dosing) and red (conventional follitropin beta dosing) lines are based on a logistic regression model with treatment and log(AMH), and an interaction term in the linear predictor. The shadings represent 90% CIs for the estimated risks. The likelihood ratio test of treatment difference indicates evidence of a benefit of follitropin delta over follitropin beta (P = 0.008). AMH, anti-Müllerian hormone; OHSS, ovarian hyperstimulation syndrome.

with the use of conventional dosing and transfer in a fresh cycle.

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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.2021.01.023.

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