Individualized versus conventional ovarian stimulation for in vitro fertilization: a multicenter, randomized, controlled, assessor-blinded, phase 3 noninferiority trial

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Objective: To compare the efficacy and safety of follitropin delta, a new human recombinant FSH with individualized dosing based on serum antimüllerian hormone (AMH) and body weight, with conventional follitropin alfa dosing for ovarian stimulation in women undergoing IVF.

Design: Randomized, multicenter, assessor-blinded, noninferiority trial (ESTHER-1).

Setting: Reproductive medicine clinics.

Patient(s): A total of 1,329 women (aged 18–40 years).

Intervention(s): Follitropin delta (AMH <15 pmol/L: 12 μg/d; AMH $\geq$15 pmol/L: 0.10–0.19 μg/kg/d; maximum 12 μg/d), or follitropin alfa (150 IU/d for 5 days, potential subsequent dose adjustments; maximum 450 IU/d).

Main Outcomes Measure(s): Ongoing pregnancy and ongoing implantation rates; noninferiority margins −8.0%.

Result(s): Ongoing pregnancy (30.7% vs. 31.6%; difference −0.9% [95% confidence interval (CI) −5.9% to 4.1%]), ongoing implantation (35.2% vs. 35.8%; −0.6% [95% CI −6.1% to 4.8%]), and live birth (29.8% vs. 30.7%; −0.9% [95% CI −5.8% to 4.0%]) rates were similar for individualized follitropin delta and conventional follitropin alfa. Individualized follitropin delta resulted in more women with target response (8–14 oocytes) (43.3% vs. 38.4%), fewer poor responses (fewer than four oocytes in patients with AMH <15 pmol/L) (11.8% vs. 17.9%), fewer excessive responses ($\geq$15 or $\geq$20 oocytes in patients with AMH $\geq$15 pmol/L) (27.9% vs. 35.1% and 10.1% vs. 15.6%, respectively), and fewer measures taken to prevent ovarian hyperstimulation syndrome (2.3% vs. 4.5%), despite similar oocyte yield (10.0 ± 5.6 vs. 10.4 ± 6.5) and similar blastocyst numbers (3.3 ± 2.8 vs. 3.5 ± 3.2), and less gonadotropin use (90.0 ± 25.3 vs. 103.7 ± 33.6 μg).

Conclusion(s): Optimizing ovarian response in IVF by individualized dosing according to pretreatment patient characteristics results in similar efficacy and improved safety compared with conventional ovarian stimulation.

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The ovarian response to stimulation with exogenous gonadotropins during IVF is a critical determinant of live birth rates and adverse outcomes (1, 2). Healthcare providers and national guidelines recognize the need for individualization of the starting dose of gonadotropin by using predictive factors related to patient characteristics and diagnostic markers of ovarian reserve to attain an optimal oocyte yield while minimizing the risk of an excessive response and ovarian hyperstimulation syndrome (OHSS) (3, 4). In practice, clinicians are requried to individualize treatment according to their own experience, using subjective preferences for predicitive parameters, because there is not a standard position regarding which factors to take into account or the weight of each factor when determining the dose. The considerable individual heterogeneity in ovarian response to the same dose of gonadotropin, the limited performance of baseline patient characteristics including age, FSH, and antral follicle count (AFC) in predicting ovarian response, and their inconsistent clinical interpretation, as well as the lack of validated dosing algorithms, have limited the generalizability of efficacious and safe ovarian stimulation (3–6). Antimüllerian hormone (AMH), a dimeric glycoprotein produced by granulosa cells of preantral and early antral follicles, can now be measured in serum by robust automated assays at any time of the menstrual cycle and exhibits superior prediction of ovarian response to controlled ovarian stimulation over established alternatives (7, 8).

Follitropin delta is a recombinant FSH (rFSH), uniquely expressed in a human fetal retinal cell line, which owing to differences in glycosylation profile has a lower clearance and induces a higher ovarian response in humans than existing rFSH preparations when administered at equal doses of biological activity (IU) (9). The lack of comparability with existing rFSH preparations combined with the strong clinical need for improved predictability of response merited a novel biomarker-driven dosing strategy to tailor the ovarian stimulation according to each patient's profile (10). Pharmacokinetic and pharmacodynamic simulation facilitated development of an individualized dosing algorithm for follitropin delta incorporating body weight, which influences drug exposure, and pretreatment AMH levels, which predict ovarian response (11). The dosing algorithm is specific for follitropin delta, owing to the unique pharmacokinetic/pharmacodynamic profile of the compound (9), and is designed to maintain ongoing pregnancy rates and reduce the risk of extreme ovarian responses, both hypo- and hyperresponse, and OHSS as compared with current therapeutic dosing strategies. A biomarker-driven strategy also implied that the selected starting dose could be maintained daily throughout stimulation without any obvious need for adjustments. The Evidence-based Stimulation Trial with Human rFSH in Europe and Rest of World (ESTHER-1) trial compared the treatment strategy of individualized follitropin delta dosing with that of conventional follitropin alfa dosing for IVF, with the aim to maintain efficacy (noninferiority) and improve safety. The trial was the first prospective study to test an algorithm incorporating robust pretreatment patient characteristics.

MATERIALS AND METHODS
Study Design

This was a randomized, controlled, assessor-blinded, international, multicenter, noninferiority trial of individualized follitropin delta vs. conventional follitropin alfa dosing. The trial was conducted at 37 investigational sites in 11 countries (Belgium, Brazil, Canada, Czech Republic, Denmark, France, Italy, Poland, Russia, Spain, and United Kingdom). The trial protocol (number 000004) was approved by the local regulatory authorities and the independent ethics committees covering all participating centers. The trial was performed in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and local regulatory requirements. All participants provided written, informed consent.

Study Participants

Women aged 18–40 years undergoing their first IVF/intracytoplasmic sperm injection (ICSI) cycle and diagnosed with unexplained infertility, tubal infertility, endometriosis stage I/II, or with partners diagnosed with male factor infertility, were eligible for the trial. Additional main inclusion criteria were body mass index 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 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. All inclusion/exclusion criteria are listed in Supplemental Table 1 (available online).

Study Randomization and Masking

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 age (<35, 35–37, and 38–40 years) and performed in blocks of four within trial sites. All investigators, embryologists, and central laboratory personnel were blinded to treatment allocation.

Study Procedures

Women randomized to follitropin delta (FE 999049, Ferring Pharmaceuticals) were given a fixed daily SC dose, determined by their serum AMH level at screening by a central laboratory using the automated Elecsys AMH immunoassay (12) (Roche Diagnostics International) and body weight at randomization (AMH <15 pmol/L: 12 μg; AMH ≥15 pmol/L: 0.10–0.19 μg/kg; the maximum daily dose was 12 μg). The follitropin delta dosing algorithm (detailed in Supplemental Table 2) was programmed in the electronic case report form, which calculated the correct dose (all patients had their AMH levels determined centrally at screening, with results uploaded to the electronic case report form, though only used for patients randomized to follitropin delta). The defined target for the follitropin delta dosing regimen was 11 oocytes with a range of 8–14 oocytes.

Women randomized to follitropin alfa (Gonal-f, EMD Serono) were administered a daily SC standard dose of 150 IU (11 μg) for the first 5 days, in line with labeling and international recommendations (13, 14); thereafter the dose could be adjusted up or down according to follicular response, with 450 IU as the maximum daily dose allowed. Investigators evaluated the need for dose adjustments in a treatment-blinded manner on the basis of follicular development, and requests for dose increases or decreases were implemented as applicable by an unblinded study nurse.

Gonadotropin therapy with either study drug was initiated on day 2–3 of the menstrual cycle. For both treatments, on stimulation day 6, a GnRH antagonist (cetrorelix acetate, Cetrotide, EMD Serono) 0.25 mg/d was initiated and continued throughout the stimulation period. Triggering of final follicular maturation was performed as soon as three or more follicles were ≥17 mm in diameter. For women with <25 follicles ≥12 mm, 250 μg recombinant hCG (choriogonadotropin 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 canceled. For women with >35 follicles ≥12 mm, the cycle was canceled. In the case of poor follicular development, defined as the investigator judging that three or more follicles with a diameter ≥17 mm could not be reached by day 20, the cycle was canceled.

Oocyte retrieval took place 36 ± 2 hours after triggering of final follicular maturation. Oocytes could be inseminated by IVF or ICSI, using ejaculated sperm by either partner or donor. For women receiving GnRH agonist, all blastocysts were cryopreserved. For women who received hCG, a single blastocyst was transferred on day 5 for all women aged ≤37 years and for women aged ≥38 years with a blastocyst grade 3BB or higher available; otherwise two blastocysts were transferred. Surplus blastocysts were cryopreserved for use after trial completion. Vaginal P tablets (Lutinus/Endometrin, Ferring Pharmaceuticals) 100 mg three times daily were provided for luteal phase support from the day after oocyte retrieval for 13–15 days and then discontinued on confirmation of pregnancy by serum hCG. Ultrasound was performed at 5–6 weeks and 10–11 weeks after blastocyst transfer to confirm clinical and ongoing pregnancy, respectively. All pregnancies were followed until 4 weeks after live birth. Adverse events were recorded from signed informed consent until the end-of-trial visit.

Study Outcomes

The co-primary endpoints were ongoing pregnancy rate, defined by at least one intrauterine viable fetus 10–11 weeks after transfer, and ongoing implantation rate, defined as number of intrauterine viable fetuses 10–11 weeks after transfer divided by number of blastocysts transferred.

Prespecified secondary endpoints included pregnancy outcomes and specifically live birth rates (defined as the birth of at least one live-born neonate), targeted ovarian response (8–14 oocytes) and extreme ovarian response (<4, ≥15, or ≥20 oocytes), embryology, safety, and adverse events. The safety endpoints included the proportion of women with early and late OHSS (including OHSS of moderate/severe grade, classified using Golan's system [15]) and/or preventive interventions for early OHSS (i.e., cycle cancellation due to excessive ovarian response, triggering with GnRH agonist, or use of dopamine agonist in women with ≥20 follicles of ≥12 mm).

Statistical Analysis

The primary objective of this trial was to demonstrate noninferiority of an individualized dosing regimen of follitropin delta compared with conventional follitropin alfa dosing on the co-primary endpoints ongoing pregnancy rate and ongoing implantation rate. The noninferiority limit for the risk difference between the two treatments was prespecified at −8.0% for both co-primary endpoints, as agreed with regulatory authorities, and therefore no adjustment for multiplicity was required. On the basis of the results in the present trial, the predefined noninferiority margin of −8.0% would allow a maximum difference in point estimates between the two treatments of −2.7%, and is therefore tight, taking into account variation among clinics. For each co-primary endpoint, a two-sided 95% confidence interval (CI) was established using the Mantel-Haenszel method to combine results across age strata. If the lower limit of the 95% CI was above −8.0% (e.g., if it was −7.9%) for both co-primary endpoints for both the modified intention-to-treat (mITT) and the per-protocol populations, then noninferiority was established. The mITT population excluded three women randomized but not exposed to study drug, whereas the per-protocol population excluded women with major deviations from the protocol impacting the co-primary endpoints.

As planned sensitivity analyses, the homogeneity of risk differences across sites were tested (16), and the treatment comparison was adjusted for factors potentially impacting the co-primary endpoints: insemination method, primary reason for infertility, primary infertility, and smoking status.

Assuming that both primary endpoints, ongoing pregnancy rate and ongoing implantation rate, would equate to 25%–30%, and that <8% of the women would have a major protocol deviation, a total sample size of 1,150 women would have at least 80% power for demonstration of noninferiority.

These assumptions were planned to be evaluated in a blinded manner when the co-primary endpoints were available for approximately 70%–80% of the planned number of participants. On the basis of this blinded review, the sample size was increased to 1,300.

RESULTS

Baseline Characteristics

The trial was conducted between October 8, 2013 and May 11, 2015, with live birth follow-up completed on January 11, 2016. A total of 1,329 eligible women were randomized, of whom 1,326 were exposed to study drug: 665 to individualized follitropin delta and 661 to conventional follitropin alfa. Three women did not receive study drug. The trial and participant flow is shown in Supplemental Figure 1. Demographics and baseline characteristics were comparable between the two treatment groups (Table 1). A total of 1,122 women underwent blastocyst transfer, with 539 (95.9%) of the individualized follitropin delta group and 536 (95.7%) of the conventional follitropin alfa group having a single blastocyst transfer.

Co-primary and Live Birth Endpoints

Outcome data for the randomized and exposed women (mITT population) are displayed in Table 2. The ongoing pregnancy rate was 30.7% in the individualized follitropin delta group and 31.6% in the conventional follitropin alfa group, with a 95% CI for the difference of −5.9% to 4.1%. The ongoing implantation rate was 35.2% in the individualized follitropin delta group and 35.8% in the conventional follitropin alfa group, with a 95% CI for the difference of −6.1% to 4.8%. The lower bound of the 95% CI for both co-primary endpoints was above the prespecified noninferiority limit of −8.0%, and noninferiority of individualized follitropin delta to conventional follitropin alfa on ongoing pregnancy rate and ongoing implantation rate was demonstrated.

There was no difference in the other pregnancy endpoints, including the number of live births and the number of neonates alive at 4 weeks, between individualized follitropin delta and conventional follitropin alfa (Table 2). Similar noninferiority conclusions were obtained with the perprotocol analysis and sensitivity analyses, with no evidence of site heterogeneity.

TABLE 1

Demographic and baseline characteristics.

Characteristic	Individualized follitropin delta (n = 665)	Conventional follitropin alfa (n = 661)
Age (y)		
All women	33.4 ± 3.9	33.2 ± 3.9
<35	394 (59.2)	392 (59.3)
35–37	161 (24.2)	167 (25.3)
38–40	110 (16.5)	102 (15.4)
Race (%)		
American Indian or Alaska Native	0	0.2
Asian	3.8	4.4
Black or African American	1.1	1.8
Native Hawaiian or other Pacific Islander	0.5	0
White	94.7	93.6
Body weight (kg)	64.7 ± 10.7	63.4 ± 10.4
Body mass index (kg/m^2)	23.7 ± 3.4	23.3 ± 3.3
Infertility history		
Duration of infertility (mo)	35.3 ± 24.4	34.9 ± 21.7
Primary infertility (%)	70.7	71.3
Primary reason for infertility (%)		
Unexplained	42.3	41.3
Tubal	13.8	14.5
Male factor	40.3	39.3
Endometriosis I/II	3.3	4.4
Other	0.3	0.5
Endometrial thickness (mm)	4.1 ± 1.8	4.1 ± 1.7
Ovarian volume (mL)	6.2 ± 3.2	6.0 ± 3.3
AFC, 2–10 mm (n)	14.7 ± 6.9	14.4 ± 6.8
Endocrine profile		
AMH (pmol/L)	16.3 (9.0–24.8)	16.0 (9.1–25.5)
FSH (IU/L)	7.5 (6.2–9.2)	7.7 (6.5–9.4)
LH (IU/L)	4.5 (3.5–5.8)	4.4 (3.6–5.8)
E$_2$ (pmol/L)	158 (128–199)	162 (130–201)
P (nmol/L)	1.7 (0.8–2.4)	1.7 (0.8–2.3)
Inhibin A (pg/mL)	5.0 (5.0–5.0)	5.0 (5.0–5.0)
Inhibin B (pg/mL)	94 (68–125)	97 (72–121)
TSH (μIU/mL)	1.5 (1.0–2.0)	1.5 (1.1–2.0)
Prolactin (μg/mL)	10.3 (7.4–13.9)	9.8 (7.5–13.6)

Note: Values are mean ± SD, median (interquartile range), or number (percentage), unless stated otherwise.

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TABLE 2

Primary and pregnancy outcomes.

Outcome per started cycle	Individualized follitropin delta (n = 665)	Conventional follitropin alfa (n = 661)	Difference (95% CI)[a]
Primary endpoints			
Ongoing pregnancy[b]	204 (30.7)	209 (31.6)	−0.9% (−5.9% to 4.1%)
Ongoing implantation[c]	206/585 (35.2)	209/584 (35.8)	−0.6% (−6.1% to 4.8%)
Secondary pregnancy endpoints			
Women with live birth[d]	198 (29.8)	203 (30.7)	−0.9% (−5.8% to 4.0%)
Women with live neonate(s) at 4 wk after birth[e]	198 (29.8)	201 (30.4)	−0.6% (−5.5% to 4.3%)
Birth weight (g)[f]	3,186 ± 601	3,168 ± 624	22.8 (−97.2 to 142.8)
Gestational age (d)[f]	272.3 ± 15.6	272.3 ± 16.9	0.1 (−3.1 to 3.3)
Positive hCG[g]	257 (38.6)	266 (40.2)	−1.5% (−6.8% to 3.7%)
Clinical pregnancy[h]	232 (34.9)	241 (36.5)	−1.5% (−6.6% to 3.6%)
Vital pregnancy[i]	211 (31.7)	221 (33.4)	−1.6% (−6.7% to 3.4%)
Implantation[j]	233/585 (39.8)	241/584 (41.3)	−1.4% (−7.0% to 4.2%)
Multiple pregnancy rate	4 (2.0)	8 (3.8)	−2.0% (−5.0% to 1.1%)

Note: Values are mean ± SD or number (percentage), unless stated otherwise.
[a] The noninferiority limit for the risk difference between the two treatments was prespecified at −8.0% for both co-primary endpoints. For each binary endpoint, a two-sided 95% confidence interval was established using the Mantel-Haenszel method to combine results across age-strata. For birth weight and gestational age the two-sided 95% confidence interval was based on a linear model including age-strata as factor.
[b] At least one intrauterine viable fetus 10–11 weeks after transfer.
[c] Number of intrauterine viable fetuses 10–11 weeks after transfer divided by number of blastocysts transferred.
[d] The birth of at least one live neonate.
[e] At least one live neonate 4 weeks after birth.
[f] All live-born neonates.
[g] Positive according to the local laboratory's reference ranges.
[h] At least one gestational sac 5–6 weeks after transfer.
[i] At least one intrauterine gestational sac with fetal heart beat 5–6 weeks after transfer.
[j] Number of gestational sacs 5–6 weeks after transfer divided by number of blastocysts transferred.

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Ovarian Response and Safety

Table 3 shows ovarian response, embryology, and safety data regarding OHSS and preventive measures. There were no significant differences between treatment groups in terms of number of oocytes retrieved. Figure 1A shows that the number of oocytes retrieved increased markedly with increasing AMH values with conventional stimulation, whereas the number of oocytes obtained was more homogeneously distributed with the individualized follitropin delta dosing, with no difference in the number of good-quality blastocysts between the two treatments. In the individualized follitropin delta group, fewer women had an extreme ovarian response (Fig. 1B) despite dose adjustments in 36.8% of the women in the conventional follitropin alfa group, in contrast to none in the individualized follitropin delta group.

Antimüllerian hormone stratification demonstrated a reduction in both poor and excessive responses (Table 3). Among potential hypo-responders (i.e., women with AMH <15 pmol/L), individualized follitropin delta was associated with more oocytes (8.0 vs. 7.0, $P=.004$) as well as a lower ($P=.039$) incidence of women with poor response (fewer than four oocytes) compared with conventional follitropin alfa. Among potential hyper-responders (i.e., women with AMH ≥ 15 pmol/L), individualized follitropin delta was associated with fewer oocytes retrieved (11.6 vs. 13.3, $P=.002$) as well as a lower incidence of patients with ≥ 15 or ≥ 20 oocytes retrieved ($P=.038$ and $P=.030$, respectively) compared with follitropin alfa. The total amount of gonadotropin used was lower ($P<.001$) with individualized follitropin delta despite the similar duration of stimulation. More women reached the target response of 8–14 oocytes with individualized follitropin delta (43.3% vs. 38.4%, $P=.019$, representing a relative increase of 13%).

In the individualized follitropin delta group, fewer women ($P=.005$) required OHSS preventive measures (Table 3). Figure 1C shows that the risk of requiring OHSS preventive interventions or experiencing OHSS increased with increasing AMH and differed between treatments. In the group of patients with polycystic ovaries, the incidence of early moderate/severe OHSS and/or preventive interventions for early OHSS was 7.7% with individualized follitropin delta and 26.7% with conventional follitropin alfa ($P=.001$). Women who received OHSS preventive measures exhibited an ovarian response in excess of those who developed OHSS and presented with a clinically relevant manifestation of symptoms of hyper-response (Supplemental Table 3). In the individualized follitropin delta group, two women were hospitalized because of OHSS, with a mean duration of hospitalization of 4.0 days, compared with six women with a mean duration of 8.7 days in the conventional follitropin alfa group (Table 3).

Apart from OHSS and OHSS preventive measures, there was no difference in other adverse events between the two treatment groups. The most common adverse events observed with individualized follitropin delta and conventional follitropin alfa were headache (14.6% and 13.3%, respectively), procedural pain (7.4% and 7.9%), pelvic pain (6.9% and 6.2%), pelvic discomfort (5.7% and 3.8%), and vomiting in pregnancy (4.5% and 4.5%).

DISCUSSION

Comparing the two treatment strategies of individualized dosing of follitropin delta, based on pretreatment AMH concentrations

TABLE 3

Ovarian response, embryology, and safety secondary endpoints.

Outcome variable	Individualized follitropin delta (n = 665)	Conventional follitropin alfa (n = 661)	P value
Ovarian response endpoints			
Duration of stimulation (d)	8.9 ± 1.9	8.6 ± 1.7	.062[a]
Total dose (μg)	90.0 ± 25.3	103.7 ± 33.6	<.001[a]
Women with investigator-requested gonadotropin dose adjustments[b]	221 (33.2)	243 (36.8)	.178[c]
Women with dose adjustments implemented	0 (0.0)	243 (36.8)	<.001[c]
Poor response leading to cycle cancellation[d]	25 (3.8)	18 (2.7)	.302[e]
Excessive response leading to triggering with GnRH agonist[f]	10 (1.5)	23 (3.5)	.019[e]
Oocytes retrieved[g] (n)	10.0 ± 5.6	10.4 ± 6.5	.692[a]
Target ovarian response[g] (8–14 oocytes retrieved)	275 (43.3)	247 (38.4)	.019[h]
Extreme ovarian response[g]			
<4 or ≥15 oocytes	169 (26.6)	201 (31.3)	.001[h]
<4 or ≥20 oocytes	92 (14.5)	118 (18.4)	.002[h]
Ovarian response stratified by AMH[g]			
Women with AMH <15 pmol/L (at risk of hypo-response) (n)	280	290	
Oocytes retrieved (n)	8.0 ± 4.3	7.0 ± 3.9	.004[i]
Poor responders (<4 oocytes)	33 (11.8)	52 (17.9)	.039[c]
Women with AMH ≥15 pmol/L (at risk of hyperresponse) (n)	355	353	
Oocytes retrieved (n)	11.6 ± 5.9	13.3 ± 6.9	.002[i]
Excessive responders (≥15 oocytes)	99 (27.9)	124 (35.1)	.038[c]
Excessive responders (≥20 oocytes)	36 (10.1)	55 (15.6)	.030[c]
Fertilized oocytes[j] (n)	5.5 ± 3.7	5.9 ± 4.4	.498[a]
Fertilization rate[j] (%)	56.0 ± 24.5	57.0 ± 23.8	.530[a]
Embryos, day 3[j]			
Total (n)	5.4 ± 3.7	5.7 ± 4.3	.590[a]
Good-quality[k] (n)	4.2 ± 3.3	4.5 ± 3.7	.414[a]
Blastocysts, day 5[j]			
Total (n)	3.3 ± 2.8	3.5 ± 3.2	.344[a]
Good-quality[l] (n)	2.0 ± 2.2	2.1 ± 2.4	.580[a]
Cryopreserved (n)	1.9 ± 2.4	2.2 ± 2.6	.262[a]
Women with blastocysts cryopreserved	402 (60.5)	402 (60.8)	.892[c]
Safety outcomes			
Preventive interventions	15 (2.3)	30 (4.5)	.005[m]
Early OHSS[n]			
Any grade	17 (2.6)	20 (3.0)	.291[m]
Moderate/severe	9 (1.4)	9 (1.4)	.644[m]
Any grade and/or preventive intervention	31 (4.7)	41 (6.2)	.046[m]
Moderate/severe and/or preventive intervention	24 (3.6)	34 (5.1)	.019[m]
All OHSS			
Any grade	23 (3.5)	32 (4.8)	.238[m]
Moderate/severe	14 (2.1)	19 (2.9)	.514[m]
Any grade and/or preventive intervention	37 (5.6)	53 (8.0)	.037[m]
Moderate/severe and/or preventive intervention	29 (4.4)	44 (6.7)	.013[m]
Hospitalization due to OHSS	2 (0.30)	6 (0.90)	.108[o]
Mean duration of hospitalization[p] (d)	4.0	8.7	.276[i]
Total duration of hospitalization[p] (d)	8	52	N/A[q]

Note: Values are mean ± SD or number (percentage), unless stated otherwise. Data are for all women unless otherwise stated.
[a] Van Elteren test stratified by age group.
[b] Investigators were blinded to the trial medication and could request dose adjustment for both treatment groups based on transvaginal ultrasound assessment of follicular response. The follitropin delta dose was, however, fixed throughout stimulation, and no dose adjustments were implemented, whereas the follitropin alfa dose could be adjusted down or up to a maximum of 450 IU.
[c] χ^2 test.
[d] Defined as the investigator judging that three or more follicles with a diameter ≥17 mm could not be reached by stimulation day 20.
[e] Likelihood ratio test based on logistic regression model including age-strata as factor.
[f] For women with 25-35 follicles ≥12 mm, 0.2 mg GnRH agonist (triptorelin acetate, Gonapeptyl, Ferring Pharmaceuticals) was administered.
[g] For women who received triggering of final follicular maturation.
[h] Based on likelihood ratio test comparing nested logistic regression models including AMH and log(AMH) to second order as covariate.
[i] Wilcoxon's test.
[j] For women with oocytes retrieved.
[k] An embryo with six or more blastomers and fragmentation ≤20%.
[l] A blastocyst of grade 3BB or higher.
[m] Based on likelihood ratio test comparing nested logistic regression models including log(AMH) as covariate.
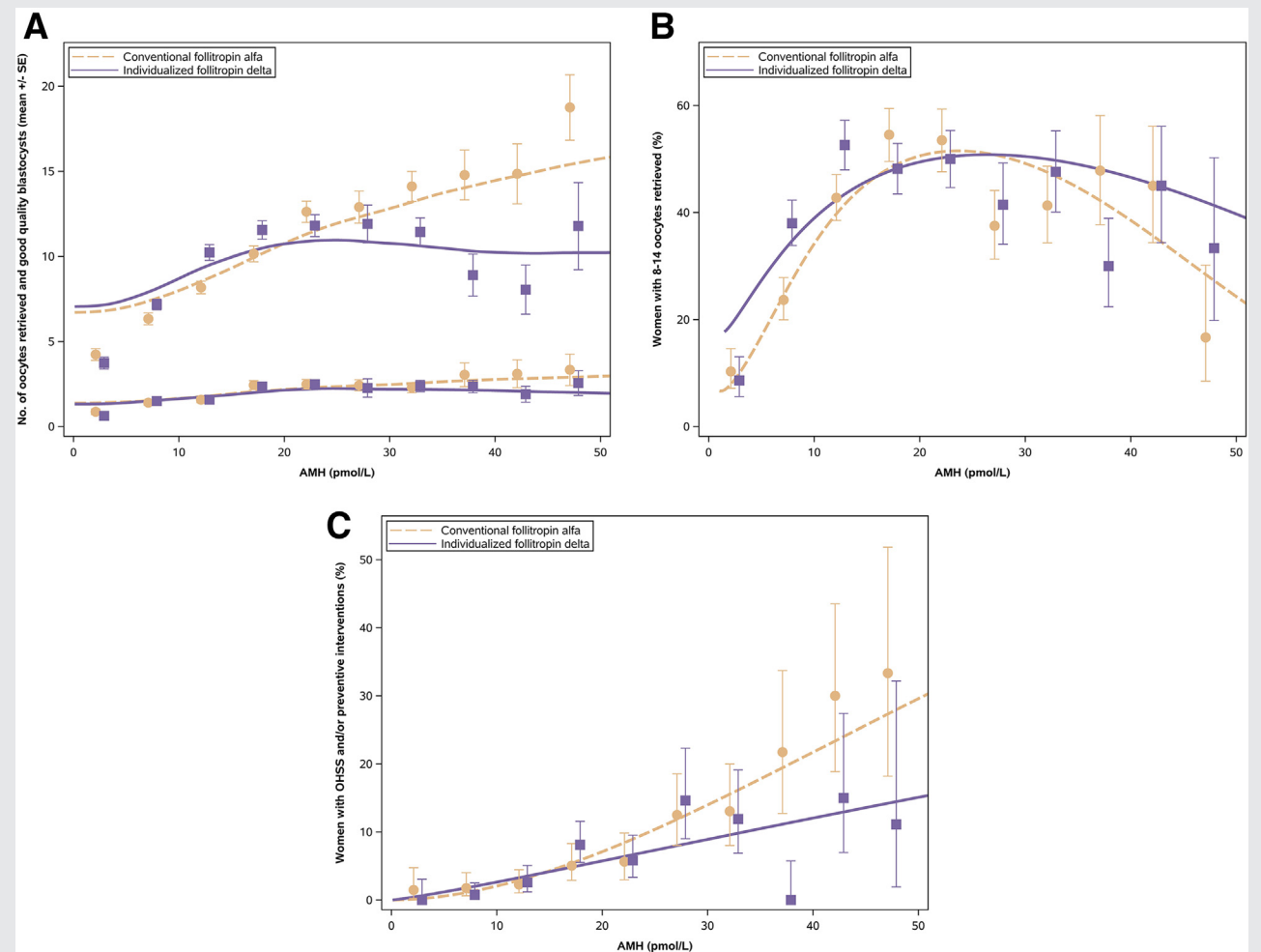[n] Onset ≤9 days after triggering of final follicular maturation.
[o] Fisher's exact test.
[p] For women hospitalized due to OHSS.
[q] The total duration of hospitalization cannot be compared between groups using a statistical test because it is the sum within treatment group.

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FIGURE 1

Ovarian response relative to AMH. (**A**) Number of oocytes retrieved (*two upper curves*) and number of good-quality blastocysts available for transfer (*two lower curves*) by serum AMH levels at screening for the two treatment groups; *circles* (conventional follitropin alfa) and *squares* (individualized follitropin delta) illustrate the observed number ± 1 SE; trend lines are penalized B-splines of degree 1. (**B**) Proportion of women achieving the target number of oocytes retrieved (8–14) by serum AMH levels at screening for the two treatment groups; *circles* (conventional follitropin alfa) and *squares* (individualized follitropin delta) illustrate the observed proportion ± 1 SE; the lines are based on a logistic regression model with treatment, AMH and log(AMH)^2, and corresponding interactions in the linear predictor; the likelihood ratio test of treatment difference indicates evidence of a treatment difference ($P=.037$). (**C**) Proportion of women requiring OHSS preventive interventions and/or experiencing OHSS by AMH levels for the two treatment groups; *circles* (conventional follitropin alfa) and *squares* (individualized follitropin delta) illustrate the observed proportion ± 1 SE; the lines are based on a logistic regression model with treatment and log(AMH) and an interaction term in the linear predictor; the likelihood ratio test of treatment difference indicates evidence of a treatment difference ($P=.037$).

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and body weight, and conventional dosing of follitropin alfa, individualized follitropin delta was noninferior to conventional follitropin alfa for the primary efficacy endpoints of ongoing pregnancy and ongoing implantation rates in women undergoing ovarian stimulation for IVF. Without any dose adjustments during stimulation, individualized follitropin delta dosing resulted in more women within the prespecified targeted ovarian response of 8–14 retrieved oocytes, with fewer clinically relevant cases of both poor and excessive ovarian responses, and a reduced need for OHSS preventive measures.

Ovarian hyperstimulation syndrome remains the most critical safety concern associated with the use of gonado-

tropin preparations [17–19]. In clinical practice, clinicians need to act on increased risk of OHSS or symptoms of hyperstimulation. Therefore, the trial design included a composite endpoint of early OHSS and/or preventive interventions for early OHSS (according to protocol-defined criteria), because recordings of only OHSS cases might lead to an underestimation of hyperstimulation caused by gonadotropins.

Large-scale population data have observed a positive linear relationship between oocyte yield and live birth rates up to 15 oocytes using conventional ovarian stimulation [1, 2]. Beyond 15 oocytes there is no increase in live birth

rates, but the risk of OHSS increases exponentially (1), prompting international guidance for implementation of less aggressive stimulation while maintaining an adequate oocyte yield (14). Although a target of 8–14 oocytes may be potentially perceived as low, setting a higher oocyte target would have been accompanied by an increased risk of OHSS, because 1 standard deviation above the observed mean oocyte yield was >15 oocytes in both treatment arms. Furthermore, an oocyte yield of 15 or more was associated with an increase in abdominal discomfort as determined by visual analogue scale assessments made by the patients. Because live birth rates from fresh blastocyst transfer cycles were similar for those with the highest oocyte yield and equivalent numbers of good-quality blastocysts were available for cryopreservation for both treatment arms, any numeric difference in oocyte yield is unlikely to be advantageous and only incurs risk. In that respect, the strict cycle criteria for implementing OHSS preventive interventions combined with the efficacy of these preventive interventions may have attenuated treatment differences in the incidence as well as the severity of OHSS.

Consistent and predictable attainment of an optimized ovarian response has previously not been feasible. The present trial demonstrates that pretreatment characteristics can predict the overall ovarian response profile for a population and be used to accurately estimate the frequency of a given target response. Inevitably the proportion of women capable of achieving a target of 8–14 oocytes will be primarily determined by the actual population undergoing ovarian stimulation. In the present study, which used wide inclusion criteria, it was predicted at trial enrolment that 42% of the individualized dosing group would yield an average of 8–14 oocytes, and this prediction was validated, with 43% attaining the predicted target yield (11). Future trials could examine alternative patient groups and predicted response profiles.

In the individualized dosing approach, the daily dose was fixed for the duration of stimulation while requests for a dose change were implemented for follitropin alfa after the first 5 days of stimulation. Although some may consider an initial starting dose of 150 IU/d of follitropin alfa inadequate, particularly for older women, it is consistent with prescribing guidance, and we observed adverse events even at this dose level. The differential effects on excessive response or OHSS risk management may have been even greater if the conventional follitropin alfa initial dose was higher than 150 IU. That approximately one-third of the women in both treatment groups had a request by the fertility specialist for their dose to be altered, and predominantly that it be increased, may reflect the common belief that higher doses of FSH are beneficial. However, a meta-analysis of 10 trials (n = 1,952 IVF cycles) found no benefit of FSH doses above 200 IU/d (20), and analysis of 658,519 IVF cycles demonstrated a reduced live birth rate with FSH doses above 300 IU/d independent of the age of the woman, the number of oocytes retrieved, or underlying diagnosis (21). The present trial showed that a fixed dose regimen of follitropin delta, without any implementation of requested dose adjustments (the majority of which were requests for

dose increases), resulted in more women reaching the targeted response. The fixed dosing regimen of follitropin delta might prove beneficial to patients, in terms of simpler dosing instructions as well as potential reduced monitoring needs.

Previous trials (n = 200–262) assessing individualization of FSH doses by incorporating routinely available pretreatment characteristics, but not AMH, were statistically inferior for their primary outcome of oocyte yield (22) or have not been adopted clinically owing to concerns regarding reproducibility, especially of the ultrasound measurements (23). In randomized, controlled trials, AMH exhibits superior prediction of ovarian response compared with age, FSH, and AFC, with their inclusion in multivariate prediction models not improving performance (8). Serum concentrations of exogenous FSH are inversely associated with body weight, and the clinical impact is particularly evident when low gonadotropin doses are applied (10, 11, 24, 25). The present trial substantially extends both these initial observations, by combining a human cell line follitropin delta with a robust automated AMH assay and body weight to individualize the FSH dose. It may also be possible to develop and validate biomarker-driven dosing strategies for other gonadotropins, utilizing a similar modeling approach that was used for development of the individualized follitropin delta algorithm.

Although this study has substantial strengths, including its design, size, broad eligibility criteria, generalizability, and the introduction of the biomarker AMH to guide dosing, we acknowledge some limitations. The present study used AMH analysis at a central laboratory, but the intra- and interassay coefficients of variation of the automated AMH assay have been reported to be low across multiple platforms and sites (26). Cumulative live-birth rates accounting for the transfer of all fresh and frozen embryos are not available, because some women proceeded directly to a further fresh cycle. For both cumulative live birth and infant number, we do not anticipate treatment differences, because both treatment groups had an equivalent number of blastocysts available for vitrification (20). A quality-of-life evaluation was not undertaken, and whether fewer complications observed for follitropin delta would be associated with a reduction in treatment discontinuation is uncertain. Women diagnosed with anovulatory polycystic ovarian syndrome were not included. Nevertheless, in this trial the biggest difference in safety was observed in women with high AMH, many of whom would have polycystic ovaries (27), but all were ovulatory. Because women with polycystic ovarian syndrome are at greatest risk of OHSS, the treatment differences in safety may be expected to be larger, but this requires confirmation.

CONCLUSION

Pretreatment risk stratification and biomarker-driven treatment modification have been proposed as a means of improving patient outcomes (28, 29). The present trial demonstrates that an individualized follitropin delta dosing is noninferior to conventional follitropin alfa with

respect to ongoing pregnancy rate, ongoing implantation rate, and also live births, with a concomitant reduction in iatrogenic complications, including preventive interventions of OHSS.

ESTHER-1 STUDY GROUP
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REFERENCES

1. Steward RG, Lan L, Shah AA, Yeh JS, Price TM, Goldfarb JM, et al. Oocyte number as a predictor for ovarian hyperstimulation syndrome and live birth: an analysis of 256,381 in vitro fertilization cycles. Fertil Steril 2014;101: 967–73.
2. Sunkara SK, Rittenberg V, Raine-Fenning N, Bhattacharya S, Zamora J, Coomarasamy A. Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles. Hum Reprod 2011;26:1768–74.
3. Boothroyd C, Karia S, Andreadis N, Rombauts L, Johnson N, Chapman M. Consensus statement on prevention and detection of ovarian hyperstimulation syndrome. Aust N Z J Obstet Gynaecol 2015;55:523–34.
4. Corbett S, Shmorgun D, Claman P, Healey S, Gysler M. The prevention of ovarian hyperstimulation syndrome. J Obstet Gynaecol Can 2014;36: 1024–36.
5. Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF outcome. Hum Reprod Update 2006;12:685–718.
6. Fauser BC, Diedrich K, Devroey P, Evian Annual Reproduction Workshop Group 2007. Predictors of ovarian response: progress towards individualized treatment in ovulation induction and ovarian stimulation. Hum Reprod Update 2008;14:1–14.
7. Dewailly D, Andersen CY, Balen A, Broekmans F, Dilaver N, Fanchin R, et al. The physiology and clinical utility of anti-Müllerian hormone in women. Hum Reprod Update 2014;20:370–85.
8. Iliodromiti S, Anderson RA, Nelson SM. Technical and performance characteristics of anti-Müllerian hormone and antral follicle count as biomarkers of ovarian response. Hum Reprod Update 2015;21:698–710.
9. Olsson H, Sandström R, Grundemar L. Different pharmacokinetic and pharmacodynamic properties of recombinant follicle-stimulating hormone (rFSH) derived from a human cell line compared with rFSH from a non-human cell line. J Clin Pharmacol 2014;54:1299–307.
10. Arce J-C, Nyboe Andersen A, Fernandez-Sanchez M, Visnova H, Bosch E, García-Velasco JA, et al. Ovarian response to recombinant human follicle-stimulating hormone: a randomized, antimüllerian hormone-stratified, dose-response trial in women undergoing in vitro fertilization/intracytoplasmic sperm injection. Fertil Steril 2014;102:1633–40.e5.
11. Arce J-C, Klein BM, Erichsen L. Using AMH for determining a stratified gonadotropin dosing regimen for IVF/ICSI and optimizing outcomes. In: Seifer DB, Tal R, editors. Anti-Müllerian hormone: biology, role in ovarian function and clinical significance. Hauppauge, NY: Nova Science Publishers; 2016:83–102.
12. Gassner D, Jung R. First fully automated immunoassay for antimüllerian hormone. Clin Chem Lab Med 2014;52:1143–52.
13. EMD Serono. Gonal-f RFF Redi-ject: highlights of prescriber information. Available at: www.emdserono.com/ms.country.us/en/images/Gonal-f_RFF_Redi-ject_PI_tcm115_140008.pdf. Accessed August 30, 2016.
14. Gianaroli L, Racowsky C, Geraedts J, Cedars M, Makrigiannakis A, Lobo RA. Best practices of ASRM and ESHRE: a journey through reproductive medicine. Fertil Steril 2012;98:1380–94.
15. Golan A, Ron-El R, Herman A, Soffer Y, Weinraub Z, Caspi E. Ovarian hyperstimulation syndrome: an update review. Obstet Gynecol Surv 1989;44: 430–40.
16. Lipsitz SR, Dear KB, Laird NM, Molenberghs G. Tests for homogeneity of the risk difference when data are sparse. Biometrics 1998;54:148–60.

17. American Society of Reproductive Medicine. Ovarian hyperstimulation syndrome. Fertil Steril 2008;90(Suppl 3):S188–93.

18. Kupka MS, Ferraretti AP, de Mouzon J, Erb K, D'Hooghe T, Castilla JA, et al. Assisted reproductive technology in Europe, 2010: results generated from European registers by ESHRE. Hum Reprod 2014;29:2099–113.

19. Kol S, Humaidan P. GnRH agonist triggering: recent developments. Reprod Biomed Online 2013;26:226–30.

20. Sterrenburg MD, Veltman-Verhulst SM, Eijkemans MJ, Hughes EG, Macklon NS, Broekmans FJ, et al. Clinical outcomes in relation to the daily dose of recombinant follicle-stimulating hormone for ovarian stimulation in in vitro fertilization in presumed normal responders younger than 39 years: a meta-analysis. Hum Reprod Update 2011;17:184–96.

21. Baker VL, Brown MB, Luke B, Smith GW, Ireland JJ. Gonadotropin dose is negatively correlated with live birth rate: analysis of more than 650,000 assisted reproductive technology cycles. Fertil Steril 2015;104:1145–52.e5.

22. Olivennes F, Trew G, Borini A, Broekmans F, Arriagada P, Warne DW, et al. Randomized, controlled, open-label, non-inferiority study of the CONSORT algorithm for individualized dosing of follitropin alfa. Reprod Biomed Online 2015;30:248–57.

23. Popovic-Todorovic B, Loft A, Bredkjaeer HE, Bangsbøll S, Nielsen IK, Nyboe Andersen A. A prospective randomized clinical trial comparing an individual dose of recombinant FSH based on predictive factors versus a 'standard' dose of 150 IU/day in 'standard' patients undergoing IVF/ICSI treatment. Hum Reprod 2003;18:2275–82.

24. Verberg MF, Eijkemans MJ, Macklon NS, Heijnen EM, Fauser BC, Broekmans FJ. Predictors of low response to mild ovarian stimulation initiated on cycle day 5 for IVF. Hum Reprod 2007;22:1919–24.

25. Macklon NS, Stouffer RL, Giudice LC, Fauser BC. The science behind 25 years of ovarian stimulation for in vitro fertilization. Endocr Rev 2006;27:170–207.

26. Anckaert E, Oktem M, Thies A, Cohen-Bacrie M, Daan NM, Schiettecatte J, et al. Multicenter analytical performance evaluation of a fully automated anti-Müllerian hormone assay and reference interval determination. Clin Biochem 2016;49:260–7.

27. Pigny P, Gorisse E, Ghulam A, Robin G, Catteau-Jonard S, Duhamel A, et al. Comparative assessment of five serum antimüllerian hormone assays for the diagnosis of polycystic ovary syndrome. Fertil Steril 2016;105:1063–9.e3.

28. Hamburg MA, Collins FS. The path to personalized medicine. N Engl J Med 2010;363:301–4.

29. Mega JL, Sabatine MS, Antman EM. Population and personalized medicine in the modern era. JAMA 2014;312:1969–70.

SUPPLEMENTAL TABLE 1

Inclusion/exclusion criteria.

Inclusion criteria
1. Informed consent documents signed before screening evaluations.
2. In good physical and mental health.
3. Premenopausal women between the ages of 18 and 40 y. The subjects must be at least 18 y (including the 18th birthday) when they sign the informed consent and no more than 40 y (up to the day before the 41st birthday) at the time of randomization.
4. Infertile women diagnosed with tubal infertility, unexplained infertility, endometriosis stage I/II or with partners diagnosed with male factor infertility, eligible for IVF and/or intracytoplasmic sperm injection (ICSI) using fresh or frozen ejaculated sperm from male partner or sperm donor.
5. Infertility for at least 1 y before randomization for subjects aged ≤37 y or for at least 6 mo for subjects aged ≥38 y (not applicable in case of tubal or severe male factor infertility).
6. The trial cycle will be the subject's first controlled ovarian stimulation cycle for IVF/ICSI.
7. Regular menstrual cycles of 24–35 d (both inclusive), presumed to be ovulatory.
8. Hysterosalpingography, hysteroscopy, saline infusion sonography, or transvaginal ultrasound documenting a uterus consistent with expected normal function (e.g., no evidence of clinically interfering uterine fibroids defined as submucous or intramural fibroids larger than 3 cm in diameter, no polyps, and no congenital structural abnormalities that are associated with a reduced chance of pregnancy) within 1 y before randomization.
9. Transvaginal ultrasound documenting presence and adequate visualization of both ovaries, without evidence of significant abnormality (e.g., no endometrioma greater than 3 cm or enlarged ovaries that would contraindicate the use of gonadotropins) and normal adnexa (e.g., no hydrosalpinx) within 1 y before randomization. Both ovaries must be accessible for oocyte retrieval.
10. Early follicular phase (cycle day 2–4) serum levels of FSH between 1 and 15 IU/L (results obtained within 3 mo before randomization).
11. Negative serum hepatitis B surface antigen, hepatitis C virus, and human immunodeficiency virus antibody tests within 2 y before randomization.
12. Body mass index between 17.5 and 32.0 kg/m^2 (both inclusive) at screening.
13. If aged ≤37 y willing to accept single blastocyst transfer. If aged ≥38 y willing to accept transfer of a single good-quality blastocyst or double blastocyst transfer if no good-quality blastocyst is available.
14. Willing to accept transfer of maximum two blastocysts in cryopreserved cycles with blastocysts originating from the trial cycle and conducted within 1 y after randomization.

Exclusion criteria
1. Known endometriosis stage III–IV.
2. One or more follicles ≥10 mm observed on the transvaginal ultrasound before randomization on stimulation day 1.
3. Known history of recurrent miscarriage (defined as three consecutive losses after ultrasound confirmation of pregnancy (excluding ectopic pregnancy) and before week 24 of pregnancy).
4. Known abnormal karyotype of subject or of her partner/sperm donor, as applicable, depending on source of sperm used for insemination in this trial. In case partner sperm will be used and the sperm production is severely impaired (concentration <1 × 10^6/mL), normal karyotype, including no Y-chromosome microdeletion, must be documented.
5. Any known clinically significant systemic disease (e.g., insulin-dependent diabetes).
6. Known inherited or acquired thrombophilia disease.
7. Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events.
8. Known porphyria.
9. Any known endocrine or metabolic abnormalities (pituitary, adrenal, pancreas, liver or kidney) that can compromise participation in the trial with the exception of controlled thyroid function disease.
10. Known presence of anti-FSH antibodies (based on the information available in the subject's medical records; i.e., not based on the anti-FSH antibody analyses conducted in the trial).
11. Known tumors of the ovary, breast, uterus, adrenal gland, pituitary, or hypothalamus that would contraindicate the use of gonadotropins.
12. Known moderate or severe impairment of renal or hepatic function.
13. Currently breast-feeding.
14. Undiagnosed vaginal bleeding.
15. Known abnormal cervical cytology of clinical significance observed within 3 y before randomization (unless the clinical significance has been resolved).
16. Findings at the gynecologic examination at screening that preclude gonadotropin stimulation or are associated with a reduced chance of pregnancy (e.g., congenital uterine abnormalities or retained intrauterine device).
17. Pregnancy (negative urinary pregnancy tests must be documented at screening and before randomization) or contraindication to pregnancy.
18. Known current active pelvic inflammatory disease.
19. Use of fertility modifiers during the last menstrual cycle before randomization, including DHEA or cycle programming with oral contraceptives, progestogen, or estrogen preparations.
20. Use of hormonal preparations (except for thyroid medication) during the last menstrual cycle before randomization.
21. Known history of chemotherapy (except for gestational conditions) or radiotherapy.
22. Current or past (1 y before randomization) abuse of alcohol or drugs, and/or current (last month) intake of more than 14 units of alcohol per week.
23. Current or past (3 mo before randomization) smoking habit of more than 10 cigarettes per day.
24. Hypersensitivity to any active ingredient or excipients in the medicinal products used in the trial.
25. Previous participation in the trial.
26. Use of any nonregistered investigational drugs during the last 3 mo before randomization.

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SUPPLEMENTAL TABLE 2

Individualized follitropin delta dosing regimen.

Serum AMH concentration (pmol/L)	Daily dose[a] (fixed throughout stimulation)
<15	12 μg
15–16	0.19 μg/kg
17	0.18 μg/kg
18	0.17 μg/kg
19–20	0.16 μg/kg
21–22	0.15 μg/kg
23–24	0.14 μg/kg
25–27	0.13 μg/kg
28–32	0.12 μg/kg
33–39	0.11 μg/kg
≥40	0.10 μg/kg

[a] Maximum daily dose is 12 μg.

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SUPPLEMENTAL TABLE 3

Risk profile of patients with preventive interventions for early OHSS.

Parameter	No OHSS or preventive interventions (n = 1,236)	Late OHSS (n = 18)	Early OHSS and no preventive interventions (n = 27)	Preventive interventions and no early OHSS (n = 35)	Preventive interventions and early OHSS (n = 10)
Oocytes retrieved	9.2 (5.6)	14.4 (6.8)[a]	15.7 (6.0)[a]	20.5 (7.1)[a]	26.9 (10.4)[a]
E_2 (pmol/L)	5,856 (3,381)	7,450 (3,943)[b]	11,530 (6,632)[a]	10,552 (6,656)[a]	16,392 (9,274)[a]
Inhibin B (pg/mL)	849 (545)	1,346 (664)[a]	1,773 (822)[a]	2,120 (659)[a]	2,794 (1,021)[a]
Inhibin A (pg/mL)	347 (184)	442 (201)[b]	663 (404)[a]	653 (271)[a]	998 (411)[a]

Note: Data are mean (SD); both treatment groups combined. Groups are compared pairwise using Wilcoxon's test.
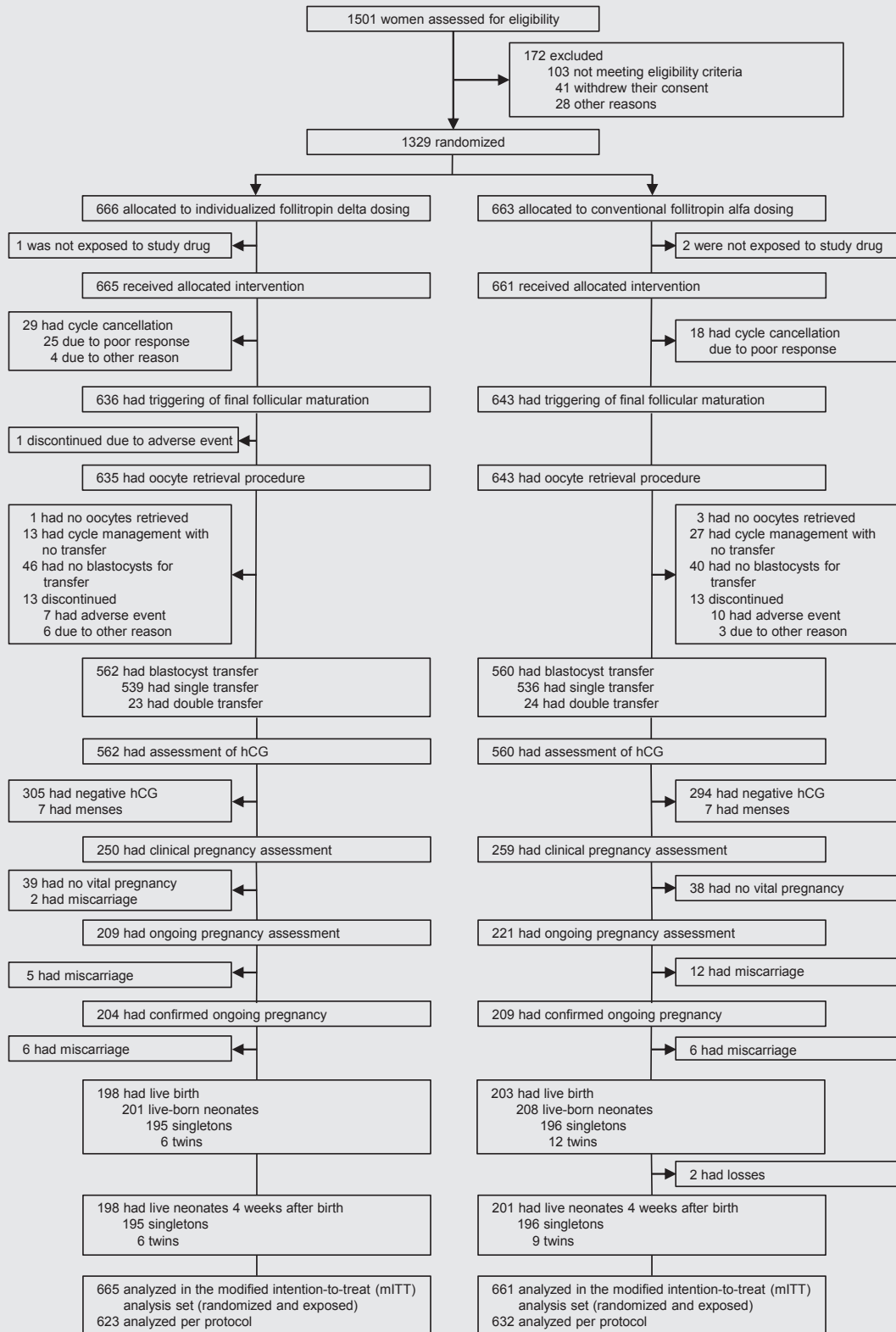[a] $P < .001$ vs. the "no OHSS or preventive interventions" population.
[b] $P < .05$ vs. the "no OHSS or preventive interventions" population.

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SUPPLEMENTAL FIGURE 1

Trial and participant flow.

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