ORIGINAL ARTICLE: ASSISTED REPRODUCTION

A large, comparative, randomized double-blind trial confirming noninferiority of pregnancy rates for corifollitropin alfa compared with recombinant follicle-stimulating hormone in a gonadotropin-releasing hormone antagonist controlled ovarian stimulation protocol in older patients undergoing in vitro fertilization

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Objective: To compare corifollitropin alfa with recombinant FSH treatment in terms of the vital pregnancy rate in older patients undergoing IVF.
Design: Phase 3 randomized, double-blind, noninferiority trial.
Setting: Multicenter trial.
Patient(s): A total of 1,390 women aged 35–42 years.
Intervention(s): A single injection of 150 μg of corifollitropin alfa or daily 300 IU of recombinant FSH for the first 7 days then daily recombinant FSH until three follicles reach $\geq$17 mm in size. Ganirelix was started on stimulation day 5 up to and including the day of recombinant hCG administration. If available, two good quality embryos were transferred on day 3.
Main Outcome Measure(s): Vital pregnancy rate (PR), number of oocytes, and live birth rate.

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Result(s): Vital PRs per started cycle were 23.9% in the corifollitropin alfa group and 26.9% in the recombinant FSH group, with an estimated difference (95% confidence interval) of -3.0% (−7.4 to 1.4). The mean (SD) number of recovered oocytes per started cycle was 10.7 (7.2) and 10.3 (6.8) in the corifollitropin alfa and the recombinant FSH groups, respectively, with an estimated difference of 0.5 (−0.2 to 1.2). The live birth rates per started cycle were 21.3% in the corifollitropin alfa group and 23.4% in the recombinant FSH group, with an estimated difference (95% confidence interval) −2.3% (−6.5 to 1.9). The incidence of serious adverse events was 0.4% versus 2.7% in the corifollitropin alfa and recombinant FSH groups, respectively, and of ovarian hyperstimulation syndrome (OHSS; all grades) was 1.7% in both groups.

Conclusion(s): Treatment with corifollitropin alfa was proven noninferior to daily recombinant FSH with respect to vital PRs, number of oocytes retrieved, and live birth rates, and was generally well tolerated.

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Key Words: Corifollitropin alfa, recombinant FSH, assisted reproductive technology, GnRH antagonist, women aged 35–42 years

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Corifollitropin alfa is a novel recombinant gonadotropin analogue with FSH activity that has an extended duration of action, enabling it to initiate and sustain multifollicular growth for 7 days (1). This FSH analogue is composed of an α subunit identical to that of human FSH and a hybrid β subunit, consisting of the FSH β unit and the carboxyterminal peptide of hCG β subunit (2). As a result of the extended half-life of this agent, a single injection of corifollitropin alfa replaces 7 days of daily recombinant FSH in an assisted reproductive technology (ART) treatment protocol.

The efficacy and safety of corifollitropin alfa in women $\leq$36 years of age were prospectively studied in two phase 3, double-blind, randomized, controlled studies (3–5). In both studies, treatment with corifollitropin alfa produced a similar therapeutic response compared with treatment with recombinant FSH, and was generally well tolerated (6). The ENGAGE study, which compared 150 μg of corifollitropin alfa to 200 IU of recombinant FSH in a GnRH antagonist protocol in 1,506 IVF patients, demonstrated similar ongoing pregnancy rates (PRs) in both groups (39.0% corifollitropin alfa vs. 38.1% recombinant FSH) (4).

The number of women >35 years of age seeking infertility care continues to increase (7). This older population faces unique challenges with respect to fertility because aging has a major impact on the success of infertility treatments. The decline in ovarian reserve and the reduction in oocyte quality associated with aging (8, 9) result in fewer good quality oocytes available for use in the ART cycle. In 2012, the reported PRs in older women after ART were 26% at age 40 years, 22% at age 41 years, and 17% at age 42 years (7). In addition, the rates of spontaneous abortion increase with aging as a consequence of the decline in oocyte quality, causing even lower live birth rates (18% at age 40 years, 13% at age 41 years, and 9% at age 42 years) (7). These data highlight the importance of evaluating the efficacy and safety of infertility treatments in older women; however, there are no published studies of corifollitropin alfa use in this age cohort. This double-blind, randomized, active-controlled trial compared the efficacy and safety of corifollitropin alfa with recombinant FSH in women $\geq$35 to $\leq$42 years of age seeking treatment for infertility.

MATERIALS AND METHODS

Pursue was a phase 3, randomized, double-blind, double-dummy, active-controlled, noninferiority trial conducted at 33 IVF centers in the United States from July 2010 to October 2012. The trial was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. Written informed consent was provided by all subjects.

Study Population

Women aged $\geq$35 to $\leq$42 years with a body weight of $\geq$50 kg and a body mass index (BMI) of $\geq$18 and $\leq$32 kg/m^2 were eligible for enrollment in the study. All subjects had a history of regular spontaneous menstrual cycles (cycle length, 24–35 days), and had access to ejaculatory sperm for IVF or intracytoplasmic sperm injection (ICSI).

Subjects were excluded if they had a history of ovarian hyper-response (including a previous controlled ovarian stimulation [COS] cycle with more than 30 follicles $\geq$11 mm on ultrasound) or a history of ovarian hyperstimulation syndrome (OHSS), a current diagnosis or a history of polycystic ovary syndrome (PCOS) (10), a history of non- or low ovarian response to FSH/hMG treatment (e.g., previous COS cycle cancelled due to insufficient ovarian response or <4 oocytes obtained), more than three unsuccessful COS cycles (i.e., no pregnancy achieved) since the last established ongoing pregnancy (if applicable), or a history of $\geq$3 miscarriages. The following were exclusion criteria: subjects with >20 basal antral follicles on ultrasound (<11 mm, both ovaries combined), or FSH >15 IU/L or LH >12 IU/L in the early follicular phase; current or recent history of alcohol or drug abuse in the past 12 months, contraindications for the use of gonadotropins, a significant endocrine abnormality within the past 3 years, epilepsy,

thrombophilia, diabetes, cardiovascular, gastrointestinal, hepatic, renal, pulmonary, or autoimmune disease requiring regular treatment, or known relevant genetic defects. Only patients with normal thyroid function were included in the study.

Study Design

Pursue was designed as a randomized, double-blind, double-dummy, active-controlled, noninferiority trial to compare the efficacy of a single injection of corifollitropin alfa during the first week of stimulation with seven daily injections of recombinant FSH for inducing and sustaining multifollicular growth during COS. Subjects were randomized in a 1:1 ratio to either treatment group by an interactive web response system and randomized treatment assignments were stratified by center and by age ($\leq$38 and >38 years). The treatment regimen (Fig. 1) is similar to that of the ENGAGE study, a trial evaluating the efficacy of corifollitropin alfa in women aged $\leq$36 years (4). Briefly, cycle day 2 or 3 of a naturally occurring menstrual cycle was stimulation day 1. Subjects randomized to corifollitropin alfa received one injection of 150 μg of corifollitropin alfa (Elonva, Merck & Co., Inc.) on stimulation day 1 and seven injections of placebo recombinant FSH from stimulation days 1–7, and subjects randomized to daily recombinant FSH received one injection of placebo corifollitropin alfa on stimulation day 1 and seven injections of 300 IU of recombinant FSH (Follistim AQ Cartridge, Merck & Co., Inc.) from stimulation days 1–7. All injections were performed by the subject or her delegate (e.g., the subject's partner or study site staff) at approximately the same time each day. On stimulation day 8, treatment was continued in both groups, with open-label daily $\leq$300 IU of recombinant FSH until the criterion to trigger final oocyte maturation was reached and recombinant hCG was administered. Recombinant FSH was not given on the day of recombinant hCG.

Treatment with the GnRH antagonist ganirelix (Ganirelix Acetate Injection, Merck & Co., Inc.) (0.25 mg/d) was started on stimulation day 5 and final ovarian maturation was triggered with recombinant hCG (250 μg Ovidrel; Merck Serono) when three follicles $\geq$17 mm were observed by ultrasound scan, or the day thereafter. Oocyte pickup was performed between 34 and 36 hours after recombinant hCG trigger. Luteal phase support with intravaginal P gel (Crinone 8%, 90 mg/d; Merck Serono) was initiated on the day of, or 1 day after, oocyte pickup. Luteal phase support was continued for at least 6 weeks unless there was a negative pregnancy test or a pregnancy loss. A urine pregnancy test was performed at least 18 days after oocyte pickup.

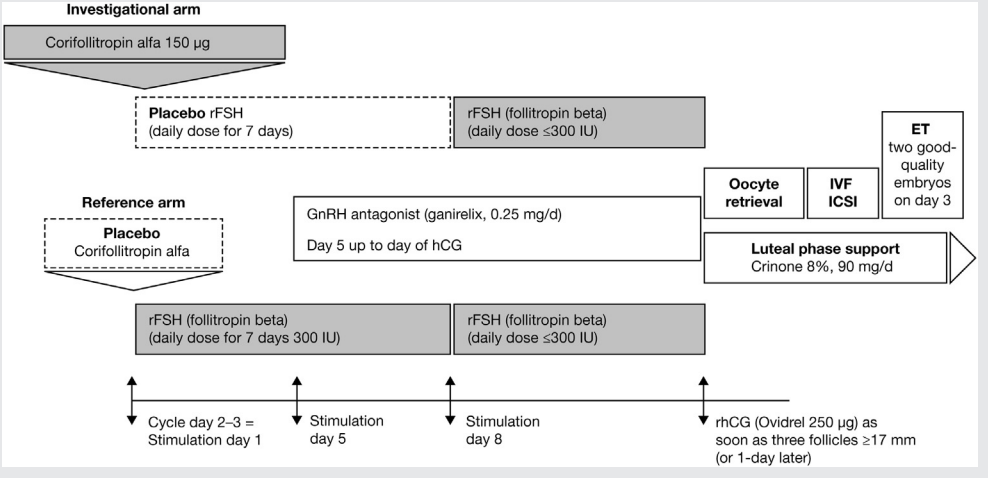
Cycles were cancelled if the investigator deemed the ovarian response to be too low or too high. Likewise, if no follicle $\geq$11 mm was visible on ultrasound on stimulation day 8, the cycle was cancelled. In the case of a risk of OHSS ($\geq$30 follicles $\geq$11 mm), by protocol, recombinant hCG administration was to be withheld and the cycle cancelled. At the investigator's discretion, recombinant FSH administration could be withheld (coasted) for a maximum of 3 days up to and including the day of recombinant hCG. The maximum duration of stimulation permitted per protocol was 19 days.

The embryo transfer (ET) was carried out 3 days after the fertilization procedure, with transfer of no more than two good quality (grades 1 or 2) embryos (or the best quality available). Standard grading guidelines were defined within the protocol and are described later. Subjects who started treatment but did not have ET were noted as cycle cancellations.

Assessments

Blood samples were collected before the start of ovarian stimulation. Before protocol start, all women had a negative serum hCG, and blood samples were obtained for hormone assessments. Subjects returned to the clinic for blood sampling on

FIGURE 1



Treatment regimen. ICSI = intracytoplasmic sperm injection; rFSH = recombinant FSH; rhCG = recombinant hCG.

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stimulation day 3 (FSH levels only) and daily from stimulation days 5–8, as well as on the day of recombinant hCG administration for assessment of endocrine parameters (FSH, LH, E_2, and P). Additional blood samples were collected on the day of ET and 18 days after oocyte pickup. Assessment of antimüllerian hormone was carried out only on baseline samples, using the research-only AMH Gen II ELISA assay from Beckman Coulter, Inc. Immunoassays were performed at a central laboratory to assess serum hormone levels, as previously described (4). Immunogenicity was determined by monitoring for the development of anti-corifollitropin alfa antibodies, as previously described (11). Ultrasound assessments to measure and count visible follicles were performed daily from stimulation day 5 up to and including the day of recombinant hCG administration. Vital signs were recorded throughout the study.

Embryo quality was evaluated for all available embryos on day 3 based on the number of blastomeres, degree of fragmentation, blastomere size uniformity, and presence or absence of multinucleation: grade 1, no fragmentation, 6–10 cells, equal blastomere size, taking the impact of cell division into account; grade 2, as in grade 1 but <20% fragmentation; grade 3, 20%–50% fragmentation and/or <6 cells and/or multinucleation. Embryos meeting criteria for grade 1 or grade 2 were considered to be good quality.

Adverse events (AEs) and serious AEs (SAEs) were collected during the study. Three types of AEs were identified as events of clinical interest: [1] OHSS; [2] hypersensitivity reactions; and [3] presence of anti-corifollitropin alfa antibodies. The OHSS cases were categorized as mild (grade I), moderate (grade II), or severe (grade III) based on the investigator's judgment using the World Health Organization guidelines as a reference (12). Subjects were monitored by the clinical staff for potential signs of a hypersensitivity reaction for 30 minutes after the first injection of both (placebo) corifollitropin alfa and (placebo) recombinant FSH.

End Points

The primary end point was the vital PR per started cycle. Vital pregnancy was defined as the presence of at least one fetus with heart activity, as assessed at least 35 days (≥5 weeks) after ET in the COS treatment cycle. Key secondary end points were the number of oocytes retrieved and the live birth rate per started cycle. Prespecified safety end points were the percentage of subjects with moderate or severe OHSS, the cycle cancellations due to SAEs, and the presence of anti-corifollitropin alfa antibodies.

Statistical Analysis

Efficacy analyses were based on the intent-to-treat population, defined as all randomized subjects who received either corifollitropin alfa or recombinant FSH. Analyses of the primary and key secondary end points were carried out per started cycle: treated subjects who did not undergo ET were included in the number of treatment cycles, and counted as not having a vital pregnancy; similarly, treated subjects without oocyte pickup were included with zero oocytes.

The treatment groups were compared with a generalized linear model for vital pregnancy (binary outcome), including covariates for treatment group and age class as stratified (≤38 years vs. >38 years). The identity link function was used in the model to estimate the difference in vital PR between the two treatment groups and associated two-sided 95% likelihood-based confidence interval (CI). The sample size for this trial was determined by the predefined noninferiority margin (i.e., a smaller margin requires a larger sample size to maintain the same power), but was also dependent on the anticipated PR (i.e., a higher PR requires a larger sample size). For the power calculation, the vital PR was assumed to be 30% for subjects aged 35 to 42 years, consistent with the 2006 Assisted Reproductive Technology Report on the success rates of US fertility clinics in this age group. Thus, assuming an overall vital PR of 30% for this population and equal efficacy in the corifollotropin alfa group and the reference group (recombinant FSH), at least 1,380 subjects were required to ensure a power of 90% (i.e., the probability that the lower limit of the two-sided 95% CI is above −8% is 90%). A noninferiority margin of −8% was applied, meaning that corifollitropin alfa treatment would be considered noninferior to the reference treatment (recombinant FSH) if the lower limit of the 95% CI for the treatment difference was >−8%. This margin was selected based on the possible outcome of the PR showing an absolute treatment difference greater than or equal to −5%, which is considered to be clinically relevant. This approach is consistent with the method used in the similarly designed ENGAGE study (4). The same model with the same noninferiority margin of −8% was applied for live birth.

The number of oocytes was compared between treatment groups using analysis of variance (ANOVA), including covariates treatment group, age class as stratified, and center. The estimated difference between the two treatment groups and associated two-sided 95% CI were calculated.

The primary and key secondary end points were tested as part of a confirmatory strategy, taking into account multiplicity using the following sequence of testing: [1] test for noninferiority on vital pregnancy, using a noninferiority margin of −8%; [2] test for noninferiority on the number of oocytes retrieved, using a noninferiority margin of −3 oocytes; and [3] test for noninferiority on the live birth rate, using a noninferiority margin of −8%. With this hierarchical procedure, each of the statistical tests is performed at a type I error (α) rate of 5%; however, testing may only proceed to the next step if the step before succeeds. If not, then no claims can be made for any of the end points lower in the hierarchy.

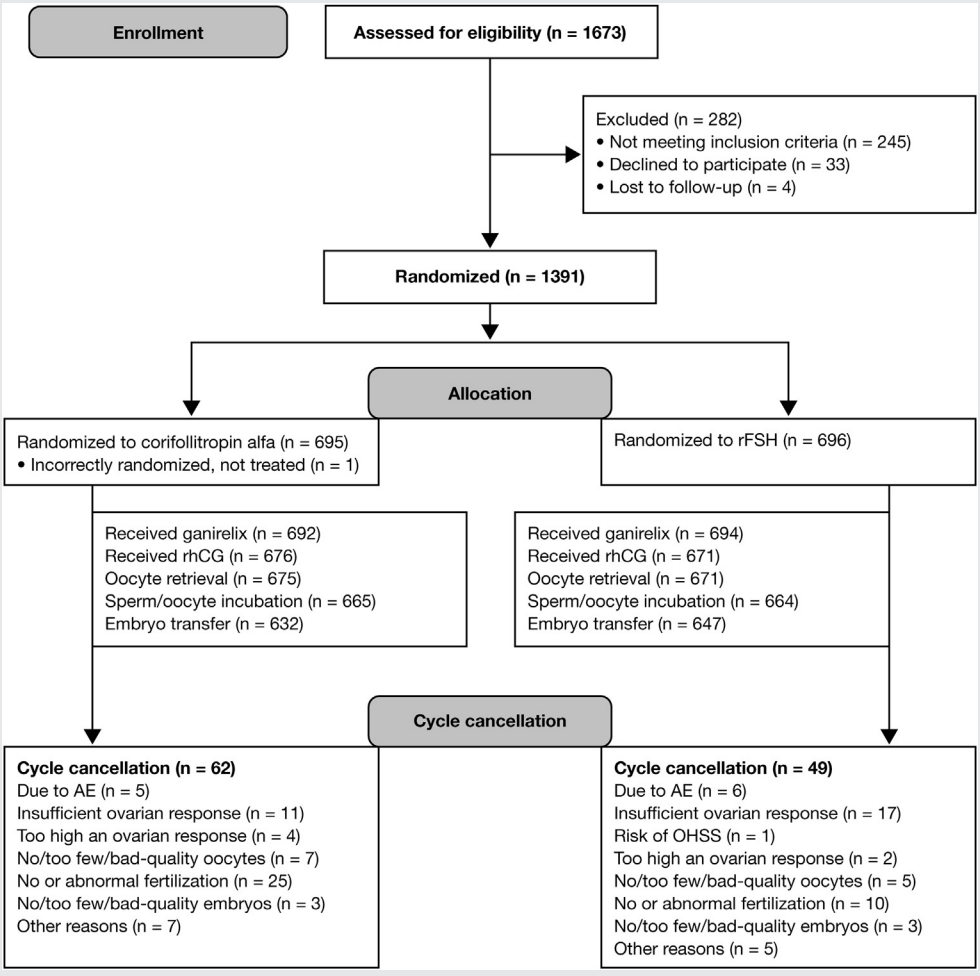
Safety analyses were based on all subjects treated. The percentage of subjects with moderate or severe OHSS and the percentage of subjects who cancelled the treatment cycle due to an SAE were compared between the treatment groups using the Fisher's exact test.

RESULTS

Patient Disposition and Baseline Characteristics

A total of 1,391 women were randomized to the corifollitropin alfa or recombinant FSH (n = 695 and 696, respectively). One woman who did not meet inclusion criteria

FIGURE 2



Disposition of subjects. AE = adverse event; OHSS = ovarian hyperstimulation syndrome; rFSH = recombinant FSH; rhCG = recombinant hCG.

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was inadvertently randomized to the corifollitropin alfa group but never started treatment, resulting in 694 women receiving corifollitropin alfa and 696 receiving recombinant FSH. The disposition of subjects is shown in Figure 2. Of all subjects who were randomized and treated, 62 (8.9%) subjects in the corifollitropin alfa group and 49 (7.0%) subjects in the rFSH group did not have ET (cycle cancellations). None of the subjects with a vital pregnancy was lost to follow-up before delivery.

Subjects were well matched between treatment groups in their baseline characteristics, including age, BMI, weight, and infertility characteristics (Table 1). In both treatment groups, the most frequent cause of infertility was unexplained infertility (42.2% and 42.0%, corifollitropin alfa and recombinant FSH, respectively) and the second most frequent cause was male factor (31.8% and 30.5%, corifollitropin alfa and recombinant FSH, respectively). Serum FSH and antimüllerian hormone levels, and the antral follicle count on stimulation day 1 were similar between groups (Table 1).

Primary End Point

Vital PRs per started cycle were 23.9% (166/694) in the corifollitropin alfa treatment arm and 26.9% (187/696) in the recombinant FSH arm (Table 2). The estimated difference (95% CI) between treatments was −3.0% (−7.4 to 1.4), confirming the noninferiority of corifollitropin alfa to daily recombinant FSH with respect to vital PRs (primary hypothesis). Vital PRs per ET were 26.3% and 28.9% in the corifollitropin alfa and recombinant FSH groups, respectively. The estimated difference (95% CI) between treatments was −2.7% (−7.4 to 2.0).

Secondary End Points

Number of oocytes retrieved. The mean (SD) number of recovered oocytes per started cycle was similar in the two treatment groups: 10.7 (7.2) and 10.3 (6.8) in the corifollitropin alfa and recombinant FSH groups, respectively (Table 2). The estimated difference between treatments was 0.5 (-0.2 to 1.2) oocytes. The mean (SD) number of oocytes retrieved per

TABLE 1

Baseline characteristics, clinical parameters, and clinical outcomes (intent-to-treat population).

Variable	Corifollitropin alfa (n = 694)	Recombinant FSH (n = 696)
Baseline characteristics, mean (SD)		
Age (y)	38.0 (2.2)	38.0 (2.2)
Frequency[a]		
35–37	316	319
38–40	265	253
41–42	110	122
BMI (kg/m^2)	25.1 (3.6)	24.7 (3.5)
Range	18.1–32.8	18.0–32.2
Weight (kg)	67.8 (10.7)	66.6 (10.8)
Infertility characteristics		
Primary infertility	33.7%	35.1%
Duration of infertility (y)	2.9 (2.8)	2.8 (2.8)
AFC on stimulation day 1 (<11 mm)	10.8 (4.0)	10.6 (3.8)
AMH on stimulation day 1 (ng/mL)	1.8 (1.4)	1.8 (1.5)
FSH on stimulation day 1 (IU/L)	7.5 (2.8)	7.5 (2.6)
Stimulation characteristics, median (range)[b]		
Total dose of recombinant FSH (IU)	300 (0–2,700)	2,400 (0–4,200)
Total dose of recombinant FSH from day 8 (IU)	300 (0–2,700)	300 (0–2,100)
Total duration of stimulation (d)	9.0 (6–17)	9.0 (6–15)
Follicles ≥11 mm on day of hCG	11.9 (6.0)	10.9 (5.5)
Serum hormones on day of hCG, median (P5, P95)		
FSH (IU/L)	17.1 (10.1, 26.2)	19.1 (12.8, 26.9)
LH (IU/L)	2.0 (0.3, 7.9)	2.3 (0.3, 7.4)
E_2 (pmol/L)	4,844 (1,688, 12,845)	4,991 (1,659, 12,368)
P (nmol/L)	3.7 (1.5, 7.7)	4.0 (1.9, 7.2)
Clinical outcome, mean (SD)		
Metaphase II oocytes (ICSI only)[c]	8.0 (5.5)	7.5 (4.8)
Embryos obtained	6.4 (4.6)	6.2 (4.2)
Good quality embryos obtained[d]	2.9 (3.1)	2.8 (2.8)
Embryos transferred	1.9 (0.3)	1.9 (0.2)
Good quality embryos transferred	1.4 (0.8)	1.4 (0.8)
Subjects with embryos cryopreserved, % (n/N)	42.4 (282/665)	43.1 (286/664)
Embryos cryopreserved[e]	3.6 (3.0)	3.3 (2.5)
Implantation rate[f]	19.1%	20.8%
Miscarriage rate per clinical pregnancy, % (n/N)	16.8 (31/185)	20.9 (44/211)
Ongoing pregnancy rate[g] per started cycle, % (n/N)	22.2 (154/694)	24.0 (167/696)

Note: mean (SD). AFC = antral follicle count; AMH = antimüllerian hormone; ISCI = intracytoplasmic sperm injection; P5, P95 = 5th and 95th percentiles.
[a] Excludes two 34-year olds (one in each arm) and three 43-year olds (two in corifollitropin alfa and one in recombinant FSH arm).
[b] Restricted to subjects who received hCG.
[c] n = 474 and n = 451 in corifollitropin alfa and recombinant FSH arms, respectively.
[d] Good quality embryo grade 1 and 2.
[e] Restricted to subjects with one or more embryos cryopreserved.
[f] Restricted to subjects with ET.
[g] Vital fetus at least 10 wk after ET or live birth.

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oocyte pickup was also similar: 10.7 (7.2) in the corifollitropin alfa group and 10.3 (6.8) in the recombinant FSH group. The estimated difference between treatments was 0.4 (−0.3 to 1.1) oocytes.

Live birth rate. Similar live birth rates per started cycle were observed: 21.3% and 23.4% in the corifollitropin alfa and recombinant FSH arms, respectively, with an estimated treatment difference of −2.3% (−6.5 to 1.9) (Table 2). Of the 148 live births in the corifollitropin alfa group, 113 were singleton and 35 were multiple. Of the 163 live births in the recombinant FSH group, 129 were singleton and 34 were multiple.

Exploratory Analyses

Two exploratory analyses were conducted to examine differences in vital PRs and number of oocytes retrieved in younger (≤38 years) versus older (>38 years) women. Vital PRs per started cycle were higher in younger relative to older women in both treatment groups, with a similar difference in both groups: in the corifollitropin alfa group, 30.4% (122/401) and 15.0% (44/293) for subjects ≤38 years and >38 years, respectively; in the recombinant FSH group, 33.2% (134/404) and 18.2% (53/292) for subjects ≤38 years and >38 years, respectively (Table 2). The mean (SD) number of oocytes retrieved per started cycle was also higher in younger relative to older women in both groups, with a similar difference in both groups: in the corifollitropin alfa group, 11.6 (7.1) and 9.6 (7.1) for subjects ≤38 years and >38 years, respectively; in the recombinant FSH group, 11.4 (7.2) and 8.7 (5.9) for subjects ≤38 years and >38 years, respectively (Table 2).

Other Clinical Parameters

The median duration of stimulation was 9 days in each treatment arm, and the median total dose of recombinant FSH given from day 8 until the day of hCG trigger was 300 IU in

TABLE 2

Vital pregnancy rates, mean (SD) number of oocytes retrieved, and live birth rates (intent-to-treat population).

Variable	Corifollitropin alfa N	Corifollitropin alfa n (%)	Recombinant FSH N	Recombinant FSH n (%)	Estimated treatment difference (95% CI)
Vital PRs					
Per started cycle, n (%)	694	166 (23.9)	696	187 (26.9)	−3.0 (−7.4 to 1.4)
≤38 y	401	122 (30.4)	404	134 (33.2)	
>38 y	293	44 (15.0)	292	53 (18.2)	
Per ET, n (%)	632	166 (26.3)	647	187 (28.9)	−2.7 (−7.4 to 2.0)
Number of oocytes retrieved					
Per started cycle, mean (SD)	694	10.7 (7.2)	696	10.3 (6.8)	0.5 (−0.2 to 1.2)
≤38 y	401	11.6 (7.1)	404	11.4 (7.2)	
>38 y	293	9.6 (7.1)	292	8.7 (5.9)	
Per oocyte pickup, mean (SD)	675	10.7 (7.2)	671	10.3 (6.8)	0.4 (−0.3 to 1.1)
Live birth rates					
Per started cycle, n (%)	694	148 (21.3)	696	163 (23.4)	−2.3 (−6.5 to 1.9)
≤38 y	401	112 (27.9)	404	118 (29.2)	
>38 y	293	36 (12.3)	292	45 (15.4)	

Note: CI = confidence interval; PR = pregnancy rate.

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each group (Table 1). The percent of subjects reaching hCG criteria (3 follicles ≥17 mm) before or on stimulation day 8 was 34.0% and 40.5% for the corifollitropin alfa and recombinant FSH groups, respectively.

The number of follicles ≥11 mm on the day of recombinant hCG was similar in the two treatment arms, as were the serum hormone levels (FSH, LH, E_2, and P) on the day of recombinant hCG (Table 1). There were no differences between treatment groups in oocyte maturity assessed before ICSI. The number of metaphase II oocytes as a percentage of the total was 72.5% and 72.7% in the corifollitropin alfa and recombinant FSH groups, respectively (Table 1). The overall fertilization rates were 68.0% in the corifollitropin alfa group and 69.5% in the recombinant FSH group.

The total number of embryos and the number of good quality embryos (i.e., grade 1 or 2) obtained and transferred were similar between treatment groups (Table 1). The mean (SD) number of good quality embryos transferred was 1.4 (0.8) in each group. In subjects with ET, 93.4% and 94.3% (corifollitropin alfa and recombinant FSH, respectively) had two embryos transferred and, in this group, 63.7% and 62.3% (corifollitropin alfa vs. recombinant FSH, respectively) of the patients had two good quality embryos transferred. A similar number of embryos were cryopreserved in both treatment groups.

The ongoing PRs per started cycle were 22.2% and 24.0% in the corifollitropin alfa and recombinant FSH groups, respectively (Table 1), with an estimated treatment difference (95% CI) of −1.9% (−6.1 to 2.3). The multiple PRs per ongoing pregnancy were 22.7% (35/154) in the corifollotropin alfa group and 21.6% (36/167) in the recombinant FSH group.

Safety

There was no meaningful difference in the incidence of AEs between corifollitropin alfa and recombinant FSH (57.8% vs. 58.6%, respectively). Adverse events assessed by the investigator as drug-related occurred in 20.7% of women in the corifollitropin alfa group and 18.8% of women in the recombinant FSH group. The most common drug-related AEs in the corifollitropin alfa and recombinant FSH groups, respectively, were headache (6.1% and 5.7%), pelvic discomfort (5.8% and 5.9%), nausea (3.9% and 2.4%), breast tenderness (2.6% and 1.1%), fatigue (1.9% and 2.0%), OHSS (1.7% and 1.4%), pelvic pain (1.6% and 1.6%), injection site pain (1.2% and 0.6%), and dizziness (0.6% and 1.1%). Serious adverse events occurred in 3 subjects (0.4%) in the corifollitropin alfa group and in 19 (2.7%) subjects in the recombinant FSH group. Ectopic pregnancy was reported as an SAE in three (0.4%) and eight (1.1%) women in the corifollitropin alfa and recombinant FSH groups, respectively.

The overall incidence of OHSS (all grades), regardless of the investigator's assessment of relationship to the study drug, was 1.7% in each treatment arm (12/692 and 12/698 in the corifollitropin alfa and recombinant FSH arms, respectively). The incidence of moderate/severe OHSS was 0.7% (5/692) and 1.4% (10/698) in the corifollitropin alfa and recombinant FSH arms, respectively (P=.30, Fisher's exact test). Early onset of OHSS (<10 days after recombinant hCG administration) was noted in 10 of 12 subjects in the corifollitropin alfa group and 6 of 12 subjects in the recombinant FSH group. No cases of severe OHSS were reported in the corifollitropin alfa group, and 6 (0.9%) cases were reported in the recombinant FSH group. Two subjects with severe OHSS in the recombinant FSH group had paracentesis. None of the OHSS cases in the corifollitropin alfa group were reported as an SAE or required hospitalization. Five of the six severe OHSS cases in the recombinant FSH group were reported as an SAE, of which two subjects (0.3%) were hospitalized.

Cycle cancellations due to an SAE were similar in the two treatment groups, occurring in five subjects (0.7%) in the corifollitropin alfa group and six subjects (0.9%) in the recombinant FSH group. Seven subjects cancelled the cycle due to an LH increase, resulting in premature ovulation (4 subjects in the corifollitropin alfa arm and 3 in the recombinant FSH arm). One subject in the corifollitropin alfa arm was cancelled

due to OHSS grade II. In the recombinant FSH arm, one subject was cancelled due to atrial tachycardia/cardiomyopathy diagnosed at the time of oocyte pickup, one due to thin endometrial lining considered inadequate for ET, and another due to increased serum LH levels. There was a higher cycle cancellation rate due to no or abnormal fertilization in subjects treated with corifollitropin alfa (25 subjects; 3.6%) than in those treated with recombinant FSH (10 subjects; 1.4%). For 22 of these 25 subjects, no pronuclei were observed in any of the oocytes after IVF (n = 8) or ICSI (n = 14), seen in 17 of 25 subjects in the corifollitropin alfa group and 5 of 10 subjects in the recombinant FSH group. Other reasons for cycle cancellation in the corifollitropin alpha and recombinant FSH groups, respectively, were risk of OHSS (n = 0 and 1), insufficient ovarian response (n = 11 and 17), too high ovarian response (n = 4 and 2), no, too few, or bad quality oocytes (n = 7 and 5), no, too few, or bad quality embryos (n = 3 and 3), and other reasons (n = 7 and 5).

No immediate drug-related hypersensitivity reactions were reported after corifollitropin alfa injection. One subject complained of mild swelling, itching on the face, and hives on the neck on stimulation day 1 after recombinant FSH injection. A total of 685 of 692 subjects treated with corifollitropin alfa had blood samples tested for the presence of anti-corifollitropin alfa antibodies; one subject had a positive result. The sample was depletable with the addition of both corifollitropin alfa as well as recombinant FSH, suggesting that this represented FSH-specific binding. However, the titer was too low to allow further isotyping. Furthermore, the serum samples from this subject tested negative for neutralizing activity, indicating that the non-neutralizing binding did not interfere with the FSH (bio) activity of corifollitropin alfa. Despite the presence of the antibodies, she responded to stimulation, had five oocytes recovered, and two good quality embryos transferred, but did not become pregnant.

DISCUSSION

This US-based randomized, double-blind study demonstrates that a single dose of 150 μg of corifollitropin alfa was noninferior to a daily dose of 300 IU of recombinant FSH in terms of the vital PR in women aged 35–42 years who were undergoing COS before IVF/ICSI. After a predefined hierarchical statistical testing procedure, the number of oocytes retrieved and the live birth rate after corifollitropin alfa treatment were also proven noninferior to daily recombinant FSH.

In prior studies of corifollitropin alfa that included women $\leq$36 years of age (3, 4), dose selection was based on body weight alone ($\leq$60 or >60 kg). In contrast, the current study considers the influence of age on gonadotropin dose, which is particularly important in older women. As women age, higher doses of gonadotropins may be required to recruit oocytes. Older women can tolerate higher doses of gonadotropins without an increased risk for OHSS. Based on these considerations, women aged $\geq$35 to $\leq$42 years with a body weight of $\geq$50 kg and a BMI of $\geq$18 and $\leq$32 kg/m^2 were eligible for enrollment.

The major strengths of this study include its large sample size and the multicenter, randomized, controlled, double-blind study design. These factors reduced the possibility of unrecognized selection bias and of a type II error. In this study, all subjects started stimulation on cycle day 2 or 3 of their naturally occurring menstrual cycle. The protocols for ovarian stimulation, the day of ET, the number and quality of transferred embryos, and luteal phase support were standardized for comparative reasons. By doing so, this study design reduced the possible impact of treatment differences on the primary and secondary end points, such as differences resulting from the number or quality of embryos transferred. This improved our ability to determine true drug-related differences in outcome. However, this strict design may have had a negative impact on the overall PR. The observed vital PR in both treatment groups was somewhat lower than the anticipated rate (i.e., 30%) based on the 2006 Society for Assisted Reproductive Technology (SART) Report on the success rates of US fertility clinics in this age group (13). This was likely related to the restriction of transferring only two embryos in women >38 years of age. It is well recognized that PRs show a sharp decline as a woman ages, even when the number of embryos transferred are increased (8). Because of this, the SART guidelines on ET allow for increasing numbers of embryos to be transferred as age increases (14). In 2012, the US Centers for Disease Control and Prevention reported that the national average for the number of embryos transferred by age was 2.4 for women aged 38–40 years and 2.8 for women aged 41–42 years (7). In contrast, the average number of embryos transferred in the present study was 1.9, lower than the 2012 national average. Reducing the number of embryos transferred resulted in lower PRs in the older subgroups ($\leq$38 years: 30.4% vs. 33.2% and >38 years: 15.0% vs. 18.2%, corifollitropin alfa and recombinant FSH, respectively) and, in turn, reduced the average vital PR in the overall study. Additional factors that may have further impacted the PRs in the older subgroup included the fixed timing of the hCG trigger, especially with asynchronous follicle cohorts, and the restriction of day 3 ETs.

The median total duration of stimulation was 9 days in both treatment groups. One-third of these subjects treated with corifollitropin alfa reached the criterion for recombinant hCG administration on day 8 after a single corifollitropin alfa injection and did not require open-label recombinant FSH. The duration of stimulation and the percentage of subjects who reached hCG criterion by stimulation day 8 were identical to results from the ENGAGE study, which compared corifollitropin alfa to recombinant FSH in a GnRH antagonist protocol in 1,506 IVF patients aged $\leq$36 years (4). This suggests that the growth rate of developing follicles is comparable across all age cohorts examined and irrespective of the type of stimulation used (corifollitropin alfa or daily recombinant FSH) (5).

In the present study, an average of 10.7 oocytes was obtained after stimulation with corifollitropin alfa, an ovarian response that is close to the maximum of the dose-response curve, regardless of age (6). The treatment difference in oocytes retrieved of 0.5 oocytes (corifollitropin alfa and recombinant FSH) suggests that 300 IU was an appropriate starting dose in the reference group and resulted in very few cancellations because of too low or too high ovarian response.

The total number of growing follicles, serum E_2 levels, mean number of oocytes recovered, and mean implantation rates were considerably lower in both treatment groups in this study than those observed in the ENGAGE study in the corifollitropin alfa and recombinant FSH treatment groups (4). The lack of any meaningful difference between treatment arms in the present study suggests that these reductions were related to age. Also, when compared with ENGAGE, the miscarriage rate per clinical pregnancy (i.e., the presence of an intrauterine gestational sac, regardless of the presence of a heartbeat) in this study was relatively high in both treatment groups (16.8% vs. 20.9%, corifollitropin alfa and recombinant FSH, respectively), as was the miscarriage rate per positive pregnancy test (27.3% vs. 30.4%, corifollitropin alfa and recombinant FSH, respectively). However, these rates are consistent with the previously reported incidences of pregnancy losses in the older IVF population (15, 16). Therefore, especially for this older subgroup, the final treatment outcome is best judged from the ongoing PR (i.e., pregnancy 10 weeks after ET) or live birth rates rather than vital PRs.

A previous pooled analysis of data from three randomized clinical trials showed a low incidence (1%–2%) of premature LH increases ($\geq$ 10 IU/L) during treatment with 0.25 mg/d ganirelix in women aged 18–39 years (N = 2,096) (17). Nevertheless, spontaneous ovulations are seldom reported. In the present study, seven women were cancelled due to premature ovulation, which occurred at a similar incidence in both treatment groups. Thus, this finding is unlikely related to the stimulation protocol, but may be specific to the study population of older women with a higher mean body weight (18) than was previously studied.

Corifollitropin alfa treatment was generally well tolerated. Although one woman developed antibodies during the trial, they did not interfere with her ability to respond to the medication. Therefore, the presence of these antibodies was judged to be of no clinically meaningful significance. The overall incidence of OHSS was equal between the two treatment groups and very low overall (1.7%) compared with the OHSS incidences (6%–7%) reported in young patients after corifollitropin alfa or recombinant FSH treatment (4, 19). The low incidence of OHSS in the current study reflects the lower underlying risk of OHSS in older women.

This study has several limitations. The strict treatment protocol may have had a negative impact on PRs in the oldest subgroups of women, which may have been reflected in the lower than expected overall PRs in this study. The efficacy and safety findings of this trial are restricted to older IVF patients with regular menstrual cycles, as anovulatory women, women with PCOS, or women with known ovarian insufficiency were excluded, making it difficult to generalize these results to those populations. The stimulation protocol for this study did not include the use of gonadotropins containing LH activity or test other treatment alterations that may be used in clinical practice based on physician recommendation (e.g., cycle programming with oral contraceptives [OC]). Therefore, the efficacy and safety of corifollitropin alfa in a combined (mixed) treatment protocol has not been established.

In conclusion, a single injection of 150 μg of corifollitropin alfa can effectively replace the first seven daily injections of 300 IU of recombinant FSH for the development of multiple follicles during COS in older patients undergoing IVF. Treatment with a single dose of 150 μg of corifollitropin alfa was proven to be noninferior to treatment with daily 300 IU of recombinant FSH with respect to vital PRs, the number of cumulus-oocyte complexes and live birth rates. A single injection of 150 μg of corifollitropin alfa had a safety profile comparable to a daily dose of 300 IU of recombinant FSH, with no evidence of clinically meaningful immunogenicity.

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