

# Individualized recombinant human follicle-stimulating hormone dosing using the CONSORT calculator in assisted reproductive technology: a large, multicenter, observational study of routine clinical practice

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**Purpose:** This postmarketing surveillance survey was conducted to investigate the utility of the CONSORT calculator for individualizing recombinant human follicle-stimulating hormone (r-hFSH) starting doses for controlled ovarian stimulation (COS) in routine clinical practice.

**Methods:** This was a 3-year, open-label, observational study evaluating data from women undergoing COS for assisted reproductive technology at 31 German fertility centers. Physicians stated their recommended r-hFSH starting dose, then generated a CONSORT-recommended r-hFSH starting dose. Physicians could prescribe any r-hFSH starting dose. The primary objective was to compare the r-hFSH starting dose recommended by the physician with the CONSORT-calculated dose and that prescribed. Statistical analyses were conducted post hoc.

**Results:** Data were collected from 2,579 patients; the mean (standard deviation [SD]) age was 30.5 (2.93) years (range: 19–40 years). The mean (SD) CONSORT-calculated r-hFSH starting dose was significantly lower than the physician-recommended dose (134.5 [38.0] IU versus 164.6 [47.1] IU;  $P < 0.0001$ ); the mean (SD) starting dose prescribed was 162.2 (48.4) IU. CONSORT-calculated doses were prescribed for 27.3% (number [n] = 677) of patients, and non-CONSORT-calculated doses prescribed for 72.7% (n = 1,800). The mean (SD) number of oocytes retrieved per patient was 10.6 (6.15) and 11.4 (6.66) in the CONSORT and non-CONSORT groups, respectively; the mean (SD) number of embryos transferred per patient was 1.98 (0.41) and 2.03 (0.45), respectively. Clinical pregnancy rates per COS cycle were 38.8% (CONSORT) and 34.8% (non-CONSORT) ( $P = 0.142$ ); clinical pregnancy rates per embryos transferred were 45.0% and 39.5%, respectively ( $P = 0.049$ ). Miscarriage occurred in 14.8% of all clinical pregnancies (CONSORT: 12.5%; non-CONSORT: 15.3%). The rate of grade 3 ovarian hyperstimulation syndrome (OHSS) was 0.3% (n = 2) in the CONSORT group and 0.6% (n = 11) in the non-CONSORT group. OHSS led to hospitalization in 0.81% (n = 21) of cases (CONSORT group: 0.74% [n = 5]; non-CONSORT group: 0.83% [n = 15]).

**Conclusion:** Physician-recommended r-hFSH starting doses were generally higher than those calculated by CONSORT; most patients were prescribed a higher starting dose than that recommended by CONSORT.

**Keywords:** controlled ovarian stimulation, dose algorithm, follitropin alfa, postmarketing product surveillance

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## Introduction

In women undergoing controlled ovarian stimulation (COS) during assisted reproductive technology (ART), daily doses of recombinant human follicle-stimulating hormone (r-hFSH) to induce multifollicular development typically range from 100–350 IU.<sup>1</sup> However, women differ greatly in their ovarian response to gonadotrophin stimulation, and there is currently no established consensus for determining the optimal follicle-stimulating hormone (FSH) dose, with starting doses often based on patient characteristics, such as age, combined with a physician's clinical experience and judgment.<sup>1</sup> Various factors have been identified that may be associated with ovarian response to COS, including: patient age,<sup>2–5</sup> body mass index (BMI),<sup>6</sup> estradiol,<sup>7</sup> basal FSH,<sup>7–9</sup> inhibin-B,<sup>7,8</sup> anti-Müllerian hormone,<sup>2,7</sup> ovarian stromal blood flow,<sup>10</sup> and antral follicle count (AFC).<sup>7,8,10,11</sup>

The CONSistency in r-FSH Starting dOses for individualized tReatment (CONSORT) dosing algorithm was developed to determine the optimal starting dose of r-hFSH (follitropin alfa) in normo-ovulatory women aged 18–34 years undergoing COS in a long gonadotrophin-releasing hormone (GnRH) agonist protocol.<sup>1,12</sup> Four baseline variables were included in the CONSORT calculator,<sup>1</sup> namely age, BMI, early follicular phase serum FSH level, and AFC. In a multinational pilot study to clinically validate the CONSORT calculator, 76.4% (123/161) of patients were allocated a lower dose than the physician would have prescribed in routine practice.<sup>12</sup> Despite achieving good clinical pregnancy rates (34.2% per started cycle), cycle cancellation owing to an inadequate response often occurred in the lowest starting dose group (75 IU).<sup>12</sup> The CONSORT algorithm was subsequently modified so that the lowest starting dose that could be recommended was 112.5 IU. A multinational, randomized study was then conducted to compare the ovarian response in normo-ovulatory women (number [n] =200) aged 18–34 years who received a daily dose of r-hFSH allocated by the CONSORT calculator versus a standard starting dose of 150 IU.<sup>13</sup> Mean daily and total doses of r-hFSH were significantly lower in the CONSORT group than in the standard-dosing group ( $P<0.001$  for both). In the CONSORT group, fewer oocytes were retrieved when compared with the standard-dosing group ( $P=0.037$ ; primary endpoint); however, the number of embryos transferred (ET) in each group ( $P=0.674$ ) and the clinical pregnancy rates (CONSORT 36.0% versus standard dosing 35.5%; estimated difference [95% confidence interval {CI}]: 0.6 [–13.5, 14.6]) were similar.<sup>13</sup>

The postmarketing surveillance study reported here evaluated the starting dose of r-hFSH recommended by the

treating physician, the dose recommended by the CONSORT calculator, and the dose actually received by the patient in routine clinical practice in Germany.

## Methods

### Study design

This 3-year, multicenter, open-label, observational, post-marketing surveillance study ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT01100333) evaluated data from women treated at 31 German ART centers. Standard practice in Germany for ART during the study period was followed; therefore, up to three embryos could be transferred and supernumerary two pronuclei oocytes could be cryopreserved for future use.

### Primary objective

The primary objective of this noninterventional study was to compare the starting dose of r-hFSH recommended by the treating physician for COS with the starting dose selected by the CONSORT calculator and the dose actually prescribed to the patient.

### Patients

The study collected data from women who were scheduled to undergo COS with follitropin alfa (GONAL-f®; Merck Serono SA, Geneva, Switzerland, a subsidiary of Merck KGaA, Darmstadt, Germany) to induce multifollicular development in an ART cycle. Key inclusion criteria included baseline age  $\leq 35$  years, BMI  $\leq 30$  kg/m<sup>2</sup>, and early follicular phase (cycle days 2–4) basal serum FSH levels  $\leq 12$  IU/L. Patients were excluded if they required combination treatment with clomiphene citrate, follitropin beta, urine-derived human FSH, human menopausal gonadotrophin, or luteinizing hormone during COS. One ART cycle per patient was included in this analysis; in 67.3% of patients, this was their first ART cycle and in 13.6%, this was their second ART cycle. For the remaining patients, this cycle number was three or above.

### Treatment

Prior to the initiation of COS, physicians were asked to record their recommended starting dose of r-hFSH for each patient. Each patient's age, BMI, early follicular phase serum FSH level, and AFC were then entered into the online CONSORT calculator, and the CONSORT-recommended starting dose of r-hFSH was recorded. The CONSORT calculator could select one of seven r-hFSH starting doses: 75 IU; 112.5 IU; 150 IU; 187.5 IU; 225 IU; 262.5 IU; or 300 IU. However, the treating physician could prescribe any starting dose of

r-hFSH, and they were asked to recommend this before they were aware of the CONSORT-recommended dose. After this, they were free to follow the CONSORT-recommended dose, their original recommended dose, or a different prescribing dose. Dose reduction was possible if the treating physician considered a patient to be at risk of ovarian hyperstimulation syndrome (OHSS). Also, cycles could be cancelled in cases of inadequate or excessive ovarian response.

## Data collection

The physician-planned starting dose of r-hFSH, four baseline factors, CONSORT-calculated starting dose, and the starting dose actually prescribed for the patient were recorded and faxed to ANFOMED GmbH (Möhrendorf, Germany). Additional routine clinical and laboratory data were entered prospectively by the physician into a standardized electronic data collection system (RecDate<sup>14</sup>). All data were recorded anonymously.

## Outcome measures

The primary endpoint was a comparison of the starting doses of r-hFSH recommended by the treating physician, selected by the CONSORT calculator, and those actually administered to the patient. Secondary endpoints were dose of r-hFSH on the last day of COS, total dose of r-hFSH, duration of COS, and the number of oocytes retrieved. Clinical pregnancy (ultrasound identification of an intrauterine gestational sac with fetal cardiac activity) rates were also reported.

Safety outcomes included the incidence of serious adverse events (SAEs). OHSS was considered to be an SAE if it resulted in hospitalization. Grade 1 OHSS was considered to be a normal response to COS.

## Statistical analysis

No formal sample size calculation was performed, owing to the exploratory and observational nature of the study. All statistical analyses were unplanned, and therefore conducted post hoc. The differences between the physician-recommended, CONSORT-calculated, and prescribed starting doses of r-hFSH were compared using the two-sided Wilcoxon signed-rank test, with *P*-values of  $\leq 0.05$  considered to be significant. Secondary outcomes were compared between patients who received the CONSORT-calculated starting dose (CONSORT group) and those who did not receive the CONSORT-calculated dose (non-CONSORT group) using descriptive statistics. Clinical pregnancy rates per started cycle and per embryo transfer were also compared between groups using a two-sided chi-square test, with

*P*-values of  $\leq 0.05$  considered to be significant. There was no imputation for missing data; therefore, for each variable, the number of cycles included differed.

## Changes to planned analyses

The planned inclusion criteria restricted enrollment to patients aged  $\leq 35$  years, with a BMI  $\leq 30$  kg/m<sup>2</sup> and who used a long GnRH agonist protocol; however, patients aged  $\geq 35$  years ( $n=87$ ) with a BMI  $>30$  kg/m<sup>2</sup> ( $n=16$ ), or who used a GnRH antagonist protocol ( $n=707$ ), were included in the analyses, as data on the use of the CONSORT algorithm in these patient groups were considered to be of scientific value.

## Subgroup analysis

Additional comparisons of pregnancy rates in each group were performed for patients aged  $<35$  years and  $\geq 35$  years. A two-sided chi-square test was used to compare the clinical pregnancy rates of patients aged  $<35$  years, while a two-sided Fisher's exact test was used to compare clinical pregnancy rates in patients aged  $\geq 35$  years owing to the small sample size.

## Results

### Baseline characteristics

Evaluable data on 2,579 patients were matched with cycle data saved on the RecDate database for 2,579 cycles of ART between April 2008 and July 2011. Baseline patient characteristics are shown in Table 1.

A long GnRH agonist protocol was used in 70.0% (1,649/2,356) of cycles, while the remaining 30.0% (707/2,356) of cycles used a GnRH antagonist, or a short or ultralong GnRH agonist protocol. Details of the GnRH protocol used for downregulation were missing for 208 patients; 15 patients did not undergo downregulation.

### Starting dose of r-hFSH

In patients with both the CONSORT-calculated and the prescribed starting doses available ( $n=2,477$ ), 27.3% (677/2,477) received the CONSORT-calculated starting dose and 72.7% (1,800/2,477) received a non-CONSORT-calculated starting dose.

The proportion of cycles during which patients in the non-CONSORT group were prescribed r-hFSH starting doses that were higher or lower than their CONSORT-recommended dose are shown in Figure 1.

The mean doses recommended by the physician and CONSORT-calculated doses are shown in Table 2. The CONSORT-calculated mean dose was significantly lower

**Table 1** Baseline patient demographic and disease characteristics

Characteristic	All patients (N=2,579)	CONSORT group (n=677)	Non-CONSORT group (n=1,800)
Age (years), mean (SD) <sup>a</sup>	30.5 (2.93)	30.2 (3.10)	30.6 (2.86)
BMI (kg/m <sup>2</sup> ), mean (SD) <sup>b</sup>	22.7 (3.02)	22.6 (3.01)	22.7 (2.99)
Baseline FSH level (IU/L), mean (SD) <sup>c</sup>	5.8 (3.93)	6.1 (5.44)	5.7 (3.19)
AFC, mean (SD) <sup>d</sup>	7.4 (4.89)	7.3 (5.03)	7.6 (4.79)
Main indication, % (n/N) <sup>e</sup>			
Male infertility	54.4 (1,300/2,388)	56.5 (336/595)	52.8 (893/1,691)
Female infertility <sup>f</sup>	14.5 (347/2,388)	14.0 (83/595)	14.9 (252/1,691)
Male and female infertility	26.8 (641/2,388)	25.9 (154/595)	28.2 (477/1,691)
Idiopathic infertility	4.2 (100/2,388)	3.7 (22/595)	4.1 (69/1,691)

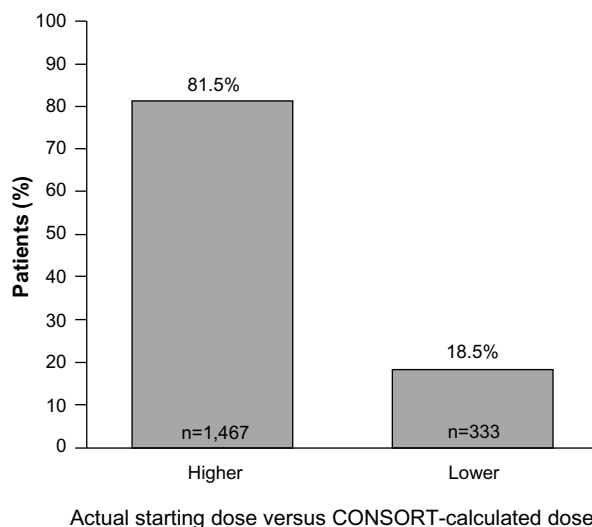
**Notes:** Data were available for different numbers of patients for each parameter. <sup>a</sup>Range: 19–40 years,  $P=0.0018$  (Wilcoxon two-sample test); all patients: data missing for one patient; CONSORT group: no missing data; non-CONSORT group: data missing for one patient; <sup>b</sup>range 16.0–40 kg/m<sup>2</sup>,  $P=0.4283$  (Wilcoxon two-sample test); all patients: data missing for four patients; CONSORT group: no missing data; non-CONSORT group: data missing for two patients; <sup>c</sup> $P=0.0534$  (Wilcoxon two-sample test); all patients: data missing for 104 patients; CONSORT group: data missing for six patients; non-CONSORT group: data missing for seven patients; <sup>d</sup> $P=0.1209$  (Wilcoxon two-sample test); all patients: data missing for 52 patients; CONSORT group: data missing for eleven patients; non-CONSORT group: data missing for 12 patients; <sup>e</sup> $P=0.4946$  (chi-square test); all patients: data missing for 191 patients; CONSORT group: data missing for 82 patients; non-CONSORT group: data missing for 109 patients; the most common causes of female infertility were tubal pathology (19.0%; 328/1,724) and endometriosis (17.6%; 304/1,724).

**Abbreviations:** N, total number; CONSORT, CONSistency in r-FSH Starting doses for individualized tReatment; n, sample number; SD, standard deviation; BMI, body mass index; FSH, follicle-stimulating hormone; AFC, antral follicle count.

than the physician-recommended mean dose ( $P<0.0001$ ); however, no significant difference was found between the mean starting doses of r-hFSH recommended by the physician and the actual dose received (Table 2).

## COS characteristics

The mean dose of r-hFSH on the last day of COS and the mean total dose of r-hFSH were both lower in the CONSORT group when compared with the non-CONSORT group;



**Figure 1** Starting doses of r-hFSH received by patients in the non-CONSORT group (n=1,800) compared with their CONSORT-calculated dose<sup>a</sup>.

**Note:** <sup>a</sup>Only patients with data on both the starting dose of r-hFSH selected by the CONSORT calculator and the actual dose prescribed are shown.

**Abbreviations:** n, sample number; CONSORT, CONSistency in r-FSH Starting doses for individualized tReatment; r-hFSH, recombinant human follicle-stimulating hormone.

however, the need for dose adjustment and duration of COS were similar in both groups (Table 3).

For patients who received an r-hFSH starting dose that was higher or lower than the CONSORT-calculated dose, the mean (standard deviation [SD]) doses of r-hFSH on the last day of COS and of total r-hFSH were higher than those in the “CONSORT-calculated dose” group (Table 4).

## Treatment outcomes

Treatment outcomes for the CONSORT and non-CONSORT starting dose groups are shown in Table 5. Similar numbers of oocytes were retrieved and similar numbers of embryos per patient were transferred in the two groups.

The clinical pregnancy rate per ET was higher in the CONSORT group than in the non-CONSORT group ( $P=0.049$ ), but there was no difference in the clinical pregnancy rates per COS cycle started between the two groups ( $P=0.142$ ).

**Table 2** Starting doses of r-hFSH

	Starting dose of r-hFSH (IU)	
	Mean (SD)	Range
Physician-recommended doses <sup>a</sup>	164.6 (47.1)*	75.0–450.0
CONSORT-calculated doses <sup>b</sup>	134.5 (38.0) <sup>†</sup>	75.0–300.0
Actual doses received by patients <sup>c</sup>	162.2 (48.4)	37.5–450.0

**Notes:** <sup>a</sup>Data missing for 153 patients; <sup>b</sup>data missing for 99 patients; <sup>c</sup>data missing for seven patients; \*no significant difference versus actual dose received; <sup>†</sup> $P<0.0001$  versus physician-recommended dose.

**Abbreviations:** r-hFSH, recombinant human follicle-stimulating hormone; SD, standard deviation; CONSORT, CONSistency in r-FSH Starting doses for individualized tReatment.

**Table 3** COS characteristics in the CONSORT and non-CONSORT starting dose groups<sup>a</sup>

Characteristic	CONSORT group (n=677)	Non-CONSORT group (n=1,800)	P-value
Need for dose adjustment during COS, % (n)	45.4 (264) <sup>b</sup>	42.9 (703) <sup>c</sup>	0.3021 <sup>d</sup>
r-hFSH dose on the last day of COS (IU), mean (SD)	145.2 (50.7)	177.5 (60.9)	<0.0001 <sup>e</sup>
Total r-hFSH dose requirement (IU), mean (SD)	1,575.9 (641.9)	1,916.1 (837.8)	<0.0001 <sup>e</sup>
Duration of COS (days), mean (SD)	10.9 (2.44)	11.0 (2.54)	0.1559 <sup>e</sup>

**Notes:** <sup>a</sup>CONSORT-calculated r-hFSH starting doses were available for 2,480 patients; a starting dose of 75 IU was recommended for three patients, 112.5 IU for 1,642 patients, 150 IU for 466 patients, 187.5 IU for 191 patients, 225 IU for 123 patients, 262.5 IU for 35 patients, and 300 IU for 20 patients. Data on both the CONSORT-calculated dose and the actual starting doses were available for 2,477 cycles; <sup>b</sup>percentage calculated from 582 patients, as data were missing for 95 patients; <sup>c</sup>percentage calculated from 1,639 patients, as data were missing for 161 patients; <sup>d</sup>chi-square test; <sup>e</sup>Wilcoxon two-sample test.

**Abbreviations:** COS, controlled ovarian stimulation; CONSORT, CONSistency in r-FSH Starting doses for individualized treatment; n, sample number; SD, standard deviation; r-hFSH, recombinant human follicle-stimulating hormone.

In women aged <35 years (96.6%; n=2,491), clinical pregnancy rates per ET were higher in the CONSORT than in the non-CONSORT group ( $P=0.044$ ), but clinical pregnancy rates per started cycle were similar in the two groups ( $P=0.144$ ; Table 6). For women aged  $\geq 35$  years (3.4%; n=87), clinical pregnancy rates per ET ( $P=0.273$ ) and per COS cycle ( $P=0.296$ ) were slightly lower in the CONSORT group versus the non-CONSORT group, but these differences were not significant (Table 6).

## Safety

Symptoms of OHSS were reported in 11.3% (291/2,579) of cycles (OHSS data were missing for 34.6% [892/2,579] of

**Table 4** COS characteristics in the higher than, actual, and lower than CONSORT-calculated dose groups

Characteristic	Higher than CONSORT-calculated dose group	CONSORT-calculated dose group	Lower than CONSORT-calculated dose group
r-hFSH dose on the last day of COS (IU), mean (SD)	182.9 (60.03)	145.2 (50.71)	154.5 (59.42)
Total r-hFSH dose requirement (IU), mean (SD)	1,980.3 (858.25)	1,575.9 (641.94)	1,639.2 (677.56)

**Abbreviations:** COS, controlled ovarian stimulation; CONSORT, CONSistency in r-FSH Starting doses for individualized treatment; r-hFSH, recombinant human follicle-stimulating hormone; SD, standard deviation.

**Table 5** Treatment outcomes in the CONSORT and non-CONSORT starting dose groups

Outcome <sup>a</sup>	CONSORT group (n=677)	Non-CONSORT group (n=1,800)
hCG administered, % (n) <sup>b</sup>	92.5 (626)	92.9 (1,673)
Oocyte retrieval attempted, % (n) <sup>c</sup>	95.6 (647)	96.7 (1,741)
Number of oocytes retrieved, mean (SD) <sup>d</sup>	10.6 (6.15)	11.4 (6.66)
Number of embryos transferred per patient, mean (SD) <sup>e</sup>	1.98 (0.41)	2.03 (0.45)
Clinical pregnancy rate per started COS cycle, % (n) <sup>f</sup>	38.8 (263)	34.8 (626)
Clinical pregnancy rate per ET, % (n) <sup>g</sup>	45.0 (263)	39.5 (626)

**Notes:** <sup>a</sup>Oocyte retrieval was attempted in 96.5% (2,490/2,579) of cycles, with 2,405/2,490 cycles resulting in the retrieval of at least one oocyte. Fertilization was attempted using ICSI in 78.8% (1,894/2,405) of cycles, IVF in 17.8% (428/2,405) of cycles, and both ICSI and IVF (for different oocytes in the same cohort) in 2.8% (68/2,405) of cycles. Neither IVF nor ICSI was reported in 0.58% (14/2,405) of cycles, and fertilization technique was unspecified in one cycle. Pregnancy rates were calculated as a proportion of all patients starting COS cycles (CONSORT n=677; non-CONSORT n=1,800), and as a proportion of all patients who completed ET (CONSORT n=585; non-CONSORT n=1,587); <sup>b</sup> $P=0.5749$  (chi-square test); <sup>c</sup> $P=0.1692$  (chi-square test); <sup>d</sup>Per cycles with attempted oocyte retrieval;  $P=0.0341$  (Wilcoxon two-sample test); <sup>e</sup> $P=0.0043$  (Wilcoxon two-sample test); <sup>f</sup>CONSORT versus non-CONSORT;  $P=0.142$  (chi-square test), data were missing for 102 patients (95 patients <35 years; seven patients  $\geq 35$  years); <sup>g</sup>CONSORT versus non-CONSORT;  $P=0.049$  (chi-square test), data missing for 90 patients (85 patients <35 years; five patients  $\geq 35$  years).

**Abbreviations:** CONSORT, CONSistency in r-FSH Starting doses for individualized treatment; n, sample number; hCG, human chorionic gonadotrophin; SD, standard deviation; COS, controlled ovarian stimulation; ET, embryos transferred; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization.

cycles); 3.0% (78/2,579) were grade 2 (CONSORT: 2.8% [19/677]; non-CONSORT: 2.9% [53/1,800]) and 0.5% (14/2,579) were grade 3 (CONSORT: 0.3% [2/677]; non-CONSORT: 0.6% [11/1,800]). OHSS was considered an SAE (ie, required hospitalization) in 0.81% (21/2,579) of cases (CONSORT group: 0.74% [5/677]; non-CONSORT group: 0.83% [15/1,800]).

Miscarriage occurred in 14.8% (132/889) of clinical pregnancies (CONSORT: 12.5% [33/263]; non-CONSORT: 15.3% [96/626]). Singleton births occurred in 55.2% (363/658) of patients, twins in 24.3% (160/658), and triplets in 0.46% (3/658). No births were reported in 20.1% (132/658) of cycles. Data were missing for 265 cycles.

## Discussion

This postmarketing surveillance study compared the starting dose of r-hFSH recommended by the CONSORT calculator with that planned by the treating physician and the starting dose actually received by the patient. Overall, approximately one-third of patients were prescribed the CONSORT-calculated starting dose of r-hFSH. Most of the patients in the non-CONSORT group (81.5%) received a starting dose

**Table 6** Clinical pregnancy rates in the CONSORT and non-CONSORT starting dose groups for patients aged <35 years and ≥35 years

Outcome	CONSORT group (n=677)	Non-CONSORT group (n=1,800)	P-value
Clinical pregnancy rate per started COS cycle, % (n/N) <sup>a</sup>			
Patients aged <35 years	39.1 (259/662)	34.9 (605/1,734)	0.144
Patients aged ≥35 years	26.7 (4/15)	32.3 (21/65)	0.296
Clinical pregnancy rate per ET, % (n/N) <sup>b</sup>			
Patients aged <35 years	45.4 (259/571)	39.5 (605/1,531)	0.044
Patients aged ≥35 years	28.6 (4/14)	38.2 (21/55)	0.273

**Notes:** Owing to the small sample size, a two-sided Fisher's exact test was used to compare clinical pregnancy rates of patients aged ≥35 years. A chi-square test was used to compare clinical pregnancy rates of patients aged <35 years. <sup>a</sup>Data missing for 95 patients aged <35 years and seven patients aged ≥35 years; <sup>b</sup>data missing for 85 patients aged <35 years and five patients aged ≥35 years.

**Abbreviations:** CONSORT, CONSistency in r-FSH Starting dOses for individualized tReatment; n, sample number; N, total number; COS, controlled ovarian stimulation; ET, embryos transferred.

of r-hFSH that was higher than the CONSORT-calculated dose. Indeed, the mean CONSORT-calculated starting dose (134.5 IU) was lower than both the starting dose recommended by the physician (164.6 IU) and the actual starting dose (162.2 IU). Although similar proportions of patients in the CONSORT and non-CONSORT groups required dose adjustments during COS, the mean r-hFSH dose on the last day of COS and mean total r-hFSH dose were higher in the non-CONSORT group.

The mean number of oocytes retrieved (11.4 oocytes versus 10.6 oocytes, respectively) and clinical pregnancy rates per started cycle (34.8% versus 38.8%, respectively [ $P=0.142$ ]) were similar in the non-CONSORT and CONSORT groups. However, clinical pregnancy rates per ET were lower in the non-CONSORT group (39.5%) than in the CONSORT group (45.0% [ $P=0.049$ ]). This may have been due to differences in procedures across the 31 centers. Furthermore, this study was not powered to analyze secondary endpoints. Nevertheless, the clinical pregnancy rates per ET in our study compare favorably with those reported from the German IVF Registry, which includes women aged >35 years using in vitro fertilization (29.5%–30.0%) and 28.4% using intracytoplasmic sperm injection.<sup>15,16</sup>

Severe OHSS (grade 3) was reported in 0.5% of cycles, with a lower frequency in the CONSORT group than in the non-CONSORT group (0.3% versus 0.6%, respectively). Miscarriage occurred in 14.8% of clinical pregnancies, with a numerically lower rate in the CONSORT group than in the

non-CONSORT group (12.5% versus 15.3%, respectively). The rates of miscarriage per clinical pregnancy observed in this study were lower than those calculated using data (fresh cycles) from the 2008 and 2010 reports of the German IVF Registry (18.9% and 18.8% per clinical pregnancy, respectively).<sup>15,16</sup>

We acknowledge the limitations associated with the observational nature of this postmarketing surveillance study, which include a lack of randomization, potential patient selection bias, and the reliance on the accurate reporting of events. One of the main criticisms of observational data is the selection bias that may arise during assignment of a treatment by the physician and the lack of matched patient populations in treatment groups.<sup>17</sup> In this study, the treating physicians may have based their choice of r-hFSH starting dose on nonstudied covariates, or they may have been influenced by the CONSORT calculator, altering their opinion of an appropriate recommended dose for consecutive patients treated. In addition, patients at greater risk of poor or excessive ovarian response were more likely to have cycles cancelled; the withdrawal of these patients could bias the results, for example, when calculating clinical pregnancy rates per ET. Also, owing to reliance on the accurate reporting of events, the numbers of cycles for which evaluable data were available for outcomes differed and, therefore, these results may not be generalizable to all populations of women undergoing ART. Furthermore, since the primary population in this study comprised women aged ≤35 years with a BMI of ≤30 kg/m<sup>2</sup> – a population of women less commonly seen in United States clinical practice, for example – these data may not be applicable to all populations of women. Although SAEs have been described here, the reporting of adverse events is not required in German postmarketing surveillance studies. Finally, it should also be noted that all statistical analyses were carried out post hoc, so any conclusions from these data should be made with caution.

In the present study, the CONSORT calculator only selected 75 IU as the starting dose in three patients. Interestingly, the CONSORT calculator pilot study found an inadequate response using starting doses of 75 IU, and this dose was subsequently excluded from the CONSORT randomized controlled study.<sup>13</sup>

Despite the original CONSORT algorithm being developed for women aged <35 years (undergoing COS using a long GnRH agonist protocol),<sup>1,12</sup> no significant difference was found in clinical pregnancy rates (per ET or per started cycle) for the CONSORT and non-CONSORT groups for the subset of older (≥35 years) women in this study. However, owing to the small

patient number, these findings should be treated with caution. Also, short or ultralong GnRH agonist or antagonist protocols were used for some patients, again representing scenarios that the CONSORT calculator was not developed for.

## Conclusion

Dosing models for use in COS represent an important step toward individualization of ART protocols. In this large observational study, the starting doses of r-hFSH for COS recommended by physicians in routine clinical practice were generally higher than the CONSORT-calculated doses. In addition, most patients received an actual starting dose of r-hFSH that was higher than the CONSORT-calculated dose, suggesting a lack of trust by the physician in the CONSORT-calculated dose. Further research to evaluate the full clinical impact of dosing algorithms on safety and efficacy during COS is warranted.

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## Author contributions

Olaf GJ Naether contributed to the study design, data analysis, manuscript drafting, and critical discussion. Andreas Tandler-Schneider contributed to the study design, data analysis, manuscript drafting, and critical discussion. Wilma Bilger contributed to the study design, study administration, data analysis, manuscript drafting, and critical discussion.

## Disclosure

Olaf GJ Naether and Andreas Tandler-Schneider have nothing to disclose. Wilma Bilger is an employee of Merck Serono GmbH, Germany.

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