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ORIGINAL ARTICLE *Reproductive endocrinology*

Prospective follow-up of 838 fetuses conceived after ovarian stimulation with corifollitropin alfa: comparative and overall neonatal outcome

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STUDY QUESTION: Is treatment with corifollitropin alfa, a new recombinant gonadotrophin with sustained follicle-stimulating activity, safe in terms of perinatal complications and birth defects in infants conceived following corifollitropin alfa treatment for contolled ovarian stimulation (COS)?

SUMMARY ANSWER: In terms of neonatal outcome and risk of malformations, treatment with a single dose of corifollitropin alfa during COS is as safe as treatment with daily recombinant FSH (rFSH).

WHAT IS KNOWN AND WHAT THIS PAPER ADDS: This is the first pooled analysis of individual safety data in terms of neonatal outcome and major and minor congenital malformations collected following intervention trials of corifollitropin alfa.

DESIGN: Pregnancy and follow-up studies were conducted prospectively and data were collected from all Phase II and III trials with corifollitropin alfa intervention, including two comparative randomized controlled trials (RCTs) in which patients received either a single dose of corifollitropin alfa or daily rFSH for the first 7 days of COS. Patients with ongoing pregnancies at 10 weeks after embryo transfer were followed up to labour and the health of the offspring was assessed up to 4–12 weeks after birth.

PARTICIPANTS AND SETTING: Following corifollitropin alfa treatment prior to IVF or ICSI, the health of 677 pregnant women, 838 fetuses and 806 live born infants was evaluated.

MAIN RESULTS AND THE ROLE OF CHANCE: Among 440 fetuses in the corifollitropin alfa arm and 381 fetuses in the rFSH arm of the two RCTs, there were 424 (96.4%) and 370 (98.7%) live births, respectively. Neonatal characteristics, the frequency of premature births and the incidence of infant adverse events were similar in both treatment arms. The overall incidence of any congenital malformations in live born infants was 16.3 and 17.0%, with major malformation rates of 4.0 and 5.4% in the corifollitropin alfa and rFSH groups, respectively [odds ratio (OR) for major malformations, 0.71; 95% confidence interval, 0.36–1.38]. From 838 fetuses assessed in all corifollitropin alfa intervention trials, there were 806 (96.2%) live births with a major malformation rate of 4.5% in live born infants.

BIAS, CONFOUNDING AND OTHER REASONS FOR CAUTION: Both RCTs had a double-blind and active-controlled design and the adjudication of congenital malformations was also performed in a blinded fashion. As the total number of major malformations was limited (37), the confidence interval around the OR was rather wide.

GENERALISABILITY TO OTHER POPULATIONS: The similarity of corifollitropin alfa and rFSH with respect to the incidence of congenital malformations was consistent across the RCTs and pregnancy type (singleton, multiple). This suggests that this similarity could hold in general. Overall incidences, however, may depend on the definitions of malformations and rules to adjudicate these events as major or minor.

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TRIAL REGISTRATION NUMBERS: NCT00703014, NCT00702624, NCT 00702195, NCT 00702195, NCT 00702988, NCT 00702520, NCT 00702338 and NCT 00702234.

Key words: assisted reproduction techniques / controlled ovarian stimulation / congenital malformations / corifollitropin alfa / GnRH antagonist

Introduction

The health of children born following assisted reproduction technology (ART) using any new procedures or compounds is paramount. Any concerns about the safety of these procedures/compounds may be allayed by evaluating the risk of perinatal complications or birth defects. Obviously, ovarian stimulation protocols for IVF/ICSI should not compromise the health of the mother during pregnancy or the infants born to these mothers (Ericson and Källén, 2001; Anthony *et al.*, 2002; Bonduelle *et al.*, 2002; Hansen *et al.*, 2002).

To date, there have been no reports that specific drugs used in ART programmes increase these potential risks. However, it has been documented that IVF/ICSI children have an increased risk (relative risk of 1.3) of major malformations, especially cardiac malformations (Wen *et al.*, 2010; Tararbit *et al.*, 2011), when compared with the general population (Sutcliffe and Ludwig, 2007). The reason for this increased risk is not fully understood but may be related to the underlying cause of the infertility of the parents (Zhu *et al.*, 2006).

Corifollitropin alfa is a novel recombinant gonadotrophin, used to induce multifollicular development prior to IVF or ICSI, with high specific affinity for the FSH receptor (Fauser *et al.*, 2009). Its FSH receptor binding specificity and activation are comparable with that of recombinant FSH (rFSH) and it lacks intrinsic activity for the LH receptor and the thyroid-stimulating hormone receptor (Verbost *et al.*, 2011). Therefore, it may be assumed that the risks associated with corifollitropin alfa treatment for women trying to achieve a pregnancy and their offspring are comparable with those associated with rFSH treatment, but this assumption is unproved.

Two large-scale, prospective, multinational, double-blind, randomized Phase III trials have confirmed the effectiveness of one injection of corifollitropin alfa for the first 7 days of controlled ovarian stimulation (COS) compared with daily rFSH injections in achieving good ongoing pregnancy rates in a GnRH antagonist protocol (Devroey *et al.*, 2009; Corifollitropin Alfa Ensure Study Group, 2010).

Analyses of these two comparative randomized controlled trials (RCTs) may be considered most valid when comparing corifollitropin alfa with daily FSH because the same double-blind protocol design was followed and the same inclusion/exclusion criteria used with the exception of body weight. In the two recommended body weight categories, the two dosages were also shown to provide equal exposure and the same ovarian response (Ledger *et al.*, 2011).

In addition, the current investigation is a follow-up of all fetuses and infants from two comparative RCTs with corifollitropin alfa versus rFSH, and all Phase II and III trials with corifollitropin alfa intervention.

Materials and Methods

Follow-up of Phase III RCTs

Two follow-up protocols (NCT00703014 and NCT00702624) collected the safety follow-up data of neonatal outcomes from two Phase III, double-blind, RCTs (see Table I), Engage (NCT00696800) and Ensure (NCT00702845) trials have been described previously (Devroey *et al.*, 2009; Corifollitropin Alfa Ensure Study Group, 2010).

Table I Phase II and III trials included in the pregnancy and infant follow-up after corifollitropin alfa intervention.

Phase	Trial with follow-up	Pregnant women in follow-up (n = 677)	Fetuses in follow-up (n = 838)	Live born infants in follow-up (n = 806)
II	NCT 00702585, Balen *et al.* (2004)	2	2	2
	NCT 00702806, Devroey *et al.* (2004)	16	20	19
	NCT 00598208, The Corifollitropin Alfa Dose-finding Study Group (2008)	33	40	36
	NCT 00702351, Fatemi *et al.* (2010)	15	19	19
	NCT 00697255, Sterrenburg *et al.* (2009)	1	2	2
III	NCT 00696800, Engage trial, Devroey *et al.* (2009)	274	352	344
	NCT 00702845, Ensure trial, Corifollitropin alfa Ensure study group (2010)	68	88	80
	NCT 00696878, Trust trial, Norman *et al.* (2011)	268	315	304

Patients received a single injection of corifollitropin alfa (Elonva,® N.V. Organon, The Netherlands) in a dose of 100 or 150 μg during the first 7 days of COS. Patients were recruited using identical inclusion and exclusion criteria with the exception of body weight: patients in the Engage trial weighed ≥60 kg ($N = 1506$) and patients in the Ensure trial weighed ≤60 kg ($N = 396$). All patients were treated from stimulation Day 5 onward with a GnRH antagonist, and ovarian stimulation was initiated in the Engage trial with either 150 μg corifollitropin alfa or daily 200 IU rFSH (treatment ratio: 1:1) and in the Ensure trial with 100 μg corifollitropin alfa or 150 IU rFSH (treatment ratio: 2:1). Apart from these differences in dosages according to body weight, the treatment regimens were identical. All subjects with an ultrasonically confirmed ongoing pregnancy of at least 10 weeks after embryo transfer were eligible for enrolment in the pregnancy and neonatal follow-up study. The studies were approved by the local health authorities and the independent medical ethics committee of each study centre, and all patients had to provide informed consent to participate in this follow-up study. Pregnant patients only completed the trial if the examination of the newborns at 4–12 weeks' post-partum was completed.

Follow-up on other Phase II and III trials

Data on fetal and neonatal outcomes were also collected from eight international trials, five Phase II and three Phase III trials with corifollitropin alfa intervention (see Table I). Patients received corifollitropin alfa in doses ranging from 7.5 to 240 μg during the first 7 days of COS. The following other trials included were:

(i) NCT 00702585 (pregnancy and infant follow-up trial NCT 00702195) was a randomized, double-blind, placebo-controlled, comparative trial to investigate the optimal dose of a single administration of corifollitropin alfa (7.5, 15 and 30 μg) to induce monofollicular ovulation in women with World Health Organization (WHO) Group II anovulatory infertility (Balen *et al.*, 2004).

(ii) NCT 00702806 (pregnancy and infant follow-up trial NCT 00702195) was an open-label, prospective, randomized, comparative clinical trial to investigate the appropriate dose of a single injection of corifollitropin alfa (100, 180 and 240 μg) versus daily 150 IU of rFSH to initiate multiple follicular growth in a COS protocol for IVF or IVF/ICSI (Devroey *et al.*, 2004).

(iii) NCT 00598208 (pregnancy and infant follow-up trial NCT 00702988) was an open-label, randomized trial to investigate the dose–response relationship of a single injection of corifollitropin alfa (60, 120 and 180 μg) versus daily 150 IU of rFSH to initiate multiple follicular growth in a COS protocol for IVF or ICSI (the Corifollitropin Alfa Dose-finding Study Group, 2008).

(iv) NCT 00702351 (pregnancy and infant follow-up trial NCT 00702520) was an uncontrolled pilot trial to evaluate whether a single dose of 100 or 150 μg corifollitropin alfa (for patients weighing ≤60 and >60 kg, respectively) is able to induce multiple follicular growth during the first week of COS for IVF or ICSI using a long GnRH agonist protocol (Fatemi *et al.*, 2010).

(v) NCT 00697255 (pregnancy and infant follow-up trial NCT 00702338) was a pilot study to evaluate if a single or repeated dose (maximum three) of 15 μg of corifollitropin alfa followed by a low daily dose of either hCG or rFSH can induce monofollicular growth in women with WHO Group II anovulatory infertility (Sterrenburg *et al.*, 2009).

(vi) NCT 00696878 (pregnancy and infant follow-up trial NCT 00702234) was an open-label, uncontrolled trial, which evaluated the safety and tolerability of repeated cycles (up to three per patient) with a single injection of 150 μg corifollitropin alfa for the first 7 days of COS ($N = 682$) in a GnRH antagonist protocol (Norman *et al.*, 2011).

Data collection

Information was collected prospectively on pregnancy outcome, mode of delivery and neonatal characteristics (gestational age, gender, weight, length, head circumference and Apgar score). All adverse events (AEs) and serious AEs (SAEs) in the infants were recorded after assessment by the infant's physician at birth and at follow-up 4–12 weeks post-partum. All SAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 12.0) to enable analysis by organ system.

Any congenital abnormality was recorded as a SAE. All AEs and SAEs were adjudicated by an independent medical expert as being either major or minor congenital malformations according to the broad classification. Major malformations were defined as any congenital malformation that causes functional impairment or requires surgical correction (broad definition; Bonduelle *et al.*, 2002). In this follow-up project, the definition of major malformation also included inguinal hernia for children born after 36 weeks of gestation, patent ductus arteriosus (if the ductus was still patent after 3 months for children born at term or after 6 months for children born before 36 weeks of gestation), atrium septum defect type I (type ostium primum), hypospadias if the meatus was not glandular, pyloric stenosis, inherited diseases and chromosomal anomalies. Minor malformations were defined as any congenital malformation not classified as major.

Statistical analysis

Characteristics of live born infants were summarized by treatment group using means and SDs for continuous variables and frequencies and percentages for categorical variables.

All statistical analyses were performed for the two RCTs unless stated otherwise. Continuous characteristics were compared between treatment groups using an analysis of variance correcting for protocol and pregnancy type (singleton versus multiple). Categorical characteristics were compared using the Cochran–Mantel–Haenszel test stratified for protocol and pregnancy type. *P*-values were reported only if <0.05.

AEs classified as major congenital malformation were coded using MedDRA. More specifically, these AEs were 'mapped' to preferred terms (PTs), which, in turn, were mapped to high-level group terms (HLGTs) to enable further analysis by organ class. The incidence of AEs classified as major congenital malformation was summarized by HLGT, PT and treatment group.

Corifollitropin alfa to rFSH odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for major (respectively, any) congenital malformation were obtained using the Cochran–Mantel–Haenszel method stratified for protocol and pregnancy type. With 440 and 381 fetuses in the corifollitropin alfa and rFSH group, respectively, there was close to 80% power to detect a doubling of the incidence of major malformations (i.e. from 5 to 10%), using a 0.05 two-sided significance level.

Results

Comparative follow-up data from RCTs

Evolution of pregnancies

From the RCTs, 342 women with ongoing pregnancies at 10 weeks who had received corifollitropin alfa during the first 7 days of COS and 312 women in the comparator arm who had received rFSH were enrolled in the follow-up study. The evolution of ongoing pregnancies and number of live born infants in the corifollitropin alfa and rFSH arms of the RCTs are presented in Table II. In total, 302 (88.3%) mothers with 383 (87.0%) infants in the corifollitropin alfa

Table II Ongoing pregnancies, fetuses and infants born following the Phase III RCTs (pooled) and after intervention in all corifollitropin alfa intervention trials (pooled).

	Follow-up Phase III RCTs: Engage and Ensure		Follow-up of all Phase II and III trials
	Corifollitropin alfa [*n* (%)]	rFSH [*n* (%)]	Corifollitropin alfa [*n* (%)]
Pregnancies[a]			
Ongoing pregnancies ≥10 weeks	342	312	677
Singleton pregnancies ≥10 weeks	247 (72.2)	243 (77.9)	522 (77.1)
Multiple pregnancies ≥10 weeks	95 (27.8)	69 (22.1)	155 (22.9)
Ongoing pregnancies ≥20 weeks	336 (98.2)	306 (98.1)	662 (7.8)
Singleton pregnancies at 20 weeks	243 (71.1)	239 (76.6)	512 (75.6)
Multiple pregnancies at 20 weeks	93 (27.2)	67 (21.5)	150 (22.2)
Pregnancies resulting in ≥1 live born	332 (97.1)	304 (97.4)	655 (96.8)
Fetuses and live born infants[a]			
Fetuses at 10 weeks after embryo transfer	440	381	838
Fetuses with known outcome	438 (99.5)	376 (98.7)	833 (99.4)
Fetuses lost between 10 and 20 weeks	6 (1.4)	4 (1.0)	15 (1.8)
Fetuses lost ≥20 weeks	8 (1.9)	2 (0.5)	12 (1.4)
Live born infants	424 (96.4)	370 (97.1)	806 (96.2)
From singleton pregnancy	241 (54.8)	237 (62.2)	507 (60.5)
From multiple pregnancy	183 (41.6)	133 (34.9)	299 (35.7)
Infants with follow-up completed	383 (87.0)	339 (89.0)	735 (87.7)

rFSH, recombinant FSH. All percentages were based on the number of ongoing pregnancies at 10 weeks.
[a]Enrolled in the follow-up trial.

group and 280 (89.7%) mothers with 339 (89.0%) infants in the rFSH group completed the follow-up including the examination of their newborns at 4–12 weeks after birth.

At week 10 of gestation, there were 247 (72.2%) and 243 (77.9%) singletons in the corifollitropin alfa and rFSH group, respectively, whereas the incidence of multiple pregnancies was 95 (27.8%) and 69 (22.1%), respectively, and this difference was not statistically significant. There were three triplet pregnancies in the corifollitropin group which all resulted from the transfer of excellent (Grade 1) embryos; in one case only one embryo was replaced on Day 5 which resulted in one gestational sac, in one case two excellent embryos were replaced on Day 5 resulting in three gestational sacs and in the last case two embryos were replaced at Day 3 and resulted in two gestational sacs.

In total, 6 (1.4%) and 4 (1.0%) ongoing pregnancies terminated at 10–20 weeks in the corifollitropin alfa and rFSH groups, respectively. The incidence of intrauterine death/stillbirth (≥20 weeks of gestation) was 1.9% ($n = 8$) in corifollitropin alfa-treated patients and 0.5% ($n = 2$) in rFSH-treated patients. The incidence was 0.8% in singleton pregnancies and 3.2% in multiple pregnancies after treatment with corifollitropin alfa and, respectively, 0.8 and 0.0% after treatment with rFSH. This resulted in 332/342 (97.1%) pregnancies with a live born infant in the corifollitropin alfa group and 304/312 (97.4%) in the rFSH group. From the 440 fetuses at 10 weeks after embryo transfer in the corifollitropin alfa group, there were 424 (96.4%) live born infants and from 381 fetuses in the rFSH arm there were 370 (97.1%) live born infants.

Neonatal outcome of live born infants

In both treatment groups, most infants were delivered by elective or emergency Caesarean section (54 and 50% in the corifollitropin alfa and rFSH groups, respectively). The percentage of infants delivered vaginally and requiring obstetric assistance via induction, forceps delivery and vacuum extraction was similar in both treatment groups. Gestational age, gender, birthweight, length, head circumference and Apgar scores of live born infants at birth are summarized in Table III. Data are also given separately for singleton and multiple births (see also Supplementary data, Table S1 and Figure S1 for data by trial and treatment group differences and OR). There were no notable differences in these characteristics between the corifollitropin alfa and rFSH groups and none of the differences were statistically significant.

The overall incidence of AEs in live born infants was similar between treatments, 47.4% in the corifollitropin alfa group and 50.8% in the rFSH group ($P = 0.35$). The frequency of infant premature birth (gestational age ≤37 weeks) was similar in both maternal treatment groups (27.8 and 25.7% of live born infants in the corifollitropin alfa and rFSH maternal groups, respectively) and the proportions of infants with low birthweights and very low birthweights or with low Apgar scores were comparable, as shown in Table IV, where none of the differences were statistically significant (see also Supplementary data, Table S2 and Figure S2 for data by trial and treatment group OR). Data are also given separately for singleton and multiple births. Neonatal deaths were reported for 8/424 (1.9%) and 6/370 (1.6%) of live born infants in the corifollitropin alfa and rFSH groups, respectively.

Table III Characteristics of live born infants born after intervention in the Phase III RCTs (pooled) and after intervention in all corifollitropin alfa intervention trials (pooled).

	Follow-up data of Phase III RCTs: Engage and Ensure		Follow-up of all Phase II and III trials
	Corifollitropin alfa (n = 424)	rFSH (n = 370)	Corifollitropin alfa (n = 806)
Female sex [n (%)]	210 (49.5), 424	190 (51.4), 370	397 (49.3), 806
Gestational age (weeks)[a]	37.8 (3.2), 424	38.2 (2.8), 370	38.0 (3.2), 806
Singletons	39.4 (1.9), 242	39.4 (2.1), 237	39.3 (2.2), 507
Multiples	35.6 (3.2), 183	36.2 (2.7), 132	35.7 (3.3), 299
Birthweight, all (g)	2860 (755), 424	2928 (716), 370	2929 (776), 806
Singletons	3297 (534), 241	3247 (586), 237	3303 (594), 507
Multiples	2284 (603), 183	2364 (552), 132	2295 (623), 299
Length at birth, all (cm)	48.2 (4.1), 370	48.6 (4.1), 333	48.4 (4.1), 712
Singletons	50.1 (3.0), 220	50.0 (3.5), 217	49.9 (3.3), 464
Multiples	45.4 (3.8), 150	46.0 (3.9), 116	45.5 (3.9), 248
Head circumference, all (cm)	33.6 (2.2), 303	33.5 (2.6), 272	33.7 (2.2), 576
Singletons	34.4 (1.7), 184	34.2 (2.2), 184	34.3 (1.9), 381
Multiples	32.4 (2.4), 119	32.1 (2.9), 88	32.5 (2.2), 195

Data as mean (SD), n unless otherwise stated.
[a]Enrolled in the follow-up trial.

Congenital malformations

The incidence of any or major congenital malformation (according to the broad definition) detected among live born infants is presented in Table V (see also Supplementary data, Table S3 and Figure S3 for data by trial and treatment group OR and Supplementary data, Table S4). The incidence of any malformation was 16.3% in the corifollitropin alfa maternal treatment group and 17.0% in the rFSH treatment group and statistical analysis showed no significant difference between the treatment groups (OR, 0.94; 95% CI, 0.65–1.37). The incidence of major malformations was 4.0 and 5.4% in the corifollitropin alfa and rFSH groups, respectively. Statistical analysis showed no significant difference in major malformations between the treatment groups (OR,

Table IV Premature live births, infants with low birthweight and low Apgar scores at birth in the Phase III RCTs (pooled) and all corifollitropin alfa intervention trials (pooled).

	Follow-up Phase III RCTs: Engage and Ensure		Follow-up of all Phase II and III trials
	Corifollitropin alfa [n (%), N]	rFSH [n (%), N]	Corifollitropin alfa [n (%), N]
Premature births[a], all	118 (27.8), 424	95 (25.7), 370	208 (25.8), 806
Singletons	20 (8.3), 241	22 (9.3), 237	52 (10.3), 507
Multiples	98 (53.6), 183	72 (54.5), 132	156 (52.2), 299
Birthweight ≤1500 g, all	22 (5.2), 424	14 (3.8), 370	38 (4.7), 806
Singletons	2 (0.8), 241	6 (2.5), 237	6 (1.2), 507
Multiples	20 (10.9), 183	8 (6.1), 132	32 (10.7), 299
Birthweight ≤2500 g, all	129 (30.4), 424	91 (24.6), 370	216 (26.8), 806
Singletons	16 (6.6), 241	16 (6.8), 237	39 (7.7), 507
Multiples	113 (61.7), 183	74 (56.1), 132	177 (59.2), 299
Birthweight <10th percentile, all	60 (14.2), 424	52 (14.1), 370	93 (11.5), 806
Singletons	15 (6.2), 241	21 (8.9, 237	31 (6.1), 507
Multiples	45 (24.6), 183	30 (22.7), 132	62 (20.7), 299
Apgar score (5 min) <7, all	8 (2.1), 377	5 (1.5), 340	17 (2.3), 749
Singletons	3 (1.4), 219	3 (1.4), 221	6 (1.3), 477
Multiples	5 (3.2), 158	2 (1.7), 119	11 (4.0), 272

[a]Gestational age <37 weeks.
n, number of live born infants.

Table V Incidence of minor and major congenital malformations in live born infants in the Phase III RCTs (pooled).

	Corifollitropin alfa ($n = 424$)[a]	rFSH ($n = 370$)[b]
Major malformations	4.0% ($n = 17$)	5.4% ($n = 20$)
Singletons	2.9% ($n = 7$)	5.1% ($n = 12$)
Multiples	5.5% ($n = 10$)	6.1% ($n = 8$)
Minor malformations only	12.3% ($n = 52$)	11.6% ($n = 43$)
Singletons	12.4% ($n = 30$)	9.3% ($n = 22$)
Multiples	12.0% ($n = 22$)	15.9% ($n = 21$)
Any malformation	16.3% ($n = 69$)	17.0% ($n = 63$)
Singletons	15.4% ($n = 37$)	14.3% ($n = 34$)
Multiples	17.5% ($n = 32$)	21.8% ($n = 29$)
OR (95% confidence interval), major malformations[c]	0.71 (0.36–1.38)	
OR ratio (95% confidence interval), any malformation[c]	0.94 (0.65–1.37)	

[a]241 infants from singleton pregnancies and 183 from multiple pregnancies.
[b]237 infants from singleton pregnancies and 133 from multiple pregnancies.
[c]Stratified by protocol and pregnancy type.

0.71; 95% CI, 0.36–1.38). In singleton births, the rates of major malformations were 2.9 and 5.1% in the corifollitropin alfa and rFSH groups, respectively, and in multiple births these rates were 5.5 and 6.1%, respectively. The incidence of congenital malformations in all fetuses with cardiac activity at 10 weeks after embryo transfer (including fetuses of pregnancies that were spontaneously or medically terminated) was similar to that of live born infants (any malformation, 16.1% in the corifollitropin alfa maternal treatment group and 17.6% in the rFSH treatment group; major malformations, 4.3 and 6.3% in the corifollitropin alfa and rFSH groups, respectively). Hydrops fetalis and congenital hydrocephalus were reported for spontaneously or medically terminated fetuses in the corifollitropin alfa group. In the rFSH group, anencephaly and ventricular septal defect were reported in one fetus and hydrops fetalis, trisomy 21 and renal aplasia were reported in three subsequent cases.

All major malformations in live born infants in the RCTs are listed in Table VI showing data for the corifollitropin alfa group and rFSH group separately (see also Supplementary data, Table S5 for major malformations by MedDRA high-level group and PT). In both maternal treatment groups, the reported major malformations were most frequently cardiac and vascular congenital disorders (2.4% for the corifollitropin alfa group and 2.7% for the rFSH group) and gastrointestinal tract congenital disorders (0.9% as major for the corifollitropin alfa group and 1.1% for the rFSH group). Antral septal defects were the only specific major malformations occurring in >1% of infants in either maternal treatment group (0.7% in the corifollitropin alfa group and 1.6% in the rFSH group).

In the corifollitropin alfa and rFSH groups, respectively, the most commonly reported congenital minor malformations were cardiac and vascular disorders (3.1 and 4.9%), musculoskeletal and connective tissue disorders (2.6 and 2.2%), gastrointestinal tract disorders (2.1 and 1.1%), eye disorders (1.2 and 1.4%), skin and subcutaneous tissue disorders (1.2 and 1.1%) and renal and urinary tract disorders (0 and 1.1%).

Combined follow-up data after corifollitropin alfa treatment including all Phase II and III trials

Evolution of pregnancies

Pooling all Phase II and III trials (including Engage and Ensure), 677 pregnant women with 838 fetuses with cardiac activity at 10 weeks after embryo transfer and 806 live births were followed up for safety evaluation, as shown in Tables I and II. In total, 602 (88.9%) mothers with 735 (87.7%) infants completed the follow-up, including the examination of their newborns at 4–12 weeks after birth.

Ongoing pregnancies ≥10 weeks included 522 (77.1%) singleton and 155 (22.9%) multiple pregnancies. In total, 15 (1.8%) ongoing pregnancies terminated at 10–20 weeks and the incidence of intrauterine death/stillbirth (≥20 weeks of gestation) was 1.4% ($n = 12$). This resulted in 655 (96.8%) pregnancies with at least one live born infant. From 838 fetuses at 10 weeks after embryo transfer following corifollitropin alfa treatment, there were 806 (96.2%) live born infants.

Neonatal outcome of live born infants

Gestational age, gender, birthweight, length, head circumference and Apgar scores of all live born infants are also summarized in Table III. The overall incidence of AEs was 43.2% (35.7% in singleton pregnancies and 55.9% in multiple pregnancies). The incidence of neonatal deaths was 2.0%.

Congenital malformations

The incidence of any congenital malformation (according to the broad definition) detected among all live born infants was 14.5% (13.0% in singletons and 17.1% in multiples, see Table VII) and 15.0% in all fetuses with heart beat activity at 10 weeks.

For the nine fetuses that were spontaneously or medically terminated, the following congenital malformations were reported: kidney malformation, Ebstein's anomaly, hydrops fetalis and congenital hydrocephalus, trisomy 21, trisomy 18, cystic lymphangioma, talipes. For one fetus multiple congenital malformations were reported: solitary kidney, cleft palate, renal dysplasia, skull malformation, congenital pulmonary artery anomaly and pulmonary malformation.

Major malformations (according to the broad definition) were reported in 4.5% of live born infants, 2.8 and 7.4% in singletons and multiple births, respectively. From all fetuses with cardiac activity at 10 weeks after embryo transfer, there were 5.4% major malformations. The major malformations in live born infants from all corifollitropin alfa intervention trials are listed in Table VI; the most frequently recorded major malformations did occur in the organ system classes of cardiac and vascular disorders, and gastrointestinal tract disorders (see also Supplementary data, Table S5 for expansion of categories).

Discussion

In this study, the infant follow-up data from two large RCTs showed that the health of 424 live born infants conceived after treatment

Table VI Major congenital malformations in live born infants according to the broad definition (by Medical Dictionary for Regulatory Activities HLGT) observed in the RCTs (pooled) and all corifollitropin alfa intervention trials (pooled).

Category	Follow-up of Phase III RCTs: Engage and Ensure		Follow-up of all Phase II and III trials
	Corifollitropin alfa (n = 424), n (%)	rFSH (n = 370), n (%)	Corifollitropin alfa (n = 806), n (%)
Blood and lymphatic system disorders congenital	0	0	3 (0.4)
Cardiac and vascular disorders congenital	10 (2.4)	10 (2.7)	15 (1.9)
Chromosomal abnormalities and abnormal gene carriers	0	2 (0.5)	2 (0.2)
Congenital and hereditary disorders	0	1 (0.3)	1 (0.1)
Eye disorders congenital	1 (0.2)	0	1 (0.1)
Gastrointestinal tract disorders congenital	4 (0.9)	4 (1.1)	8 (1.0)
Immune system disorders congenital	0	1 (0.3)	0
Infections and infestations congenital	0	0	1 (0.1)
Musculoskeletal/connective tissue disorders congenital	1 (0.2)	1 (0.3)	3 (0.4)
Neurologic disorders congenital	2 (0.5)	0	3 (0.4)
Renal and urinary tract disorders congenital	1 (0.2)	0	1 (0.1)
Reproductive tract and breast disorders congenital	2 (0.5)	2 (0.5)	3 (0.4)
Respiratory disorders congenital	1 (0.2)	0	3 (0.4)
Soft tissue neoplasms benign	0	1 (0.3)	0
Hypothalamus and pituitary gland disorders	1 (0.2)	0	2 (0.2)
Lipid metabolism disorders	0	1 (0.3)	0
Hearing disorders	1 (0.2)	0	2 (0.2)
Cardiac valve disorders	0	1 (0.3)	0
Cardiac arrhythmias	1 (0.2)	0	1 (0.1)
Myocardial disorders	0	1 (0.3)	0
Coronary artery disorders	1 (0.2)	0	1 (0.1)
Penile and scrotal disorders (not infections or inflammations)	0	1 (0.3)	0
Fatal outcomes	1 (0.2)	2 (0.5)	1 (0.1)
Haematology investigations (including blood groups)	0	1 (0.3)	0
Abdominal hernias and other abdominal wall conditions	0	0	1 (0.1)
Reproduction tract disorders NEC	0	0	1 (0.1)

NEC, not elsewhere classified.

with a single dose of corifollitropin alfa during the first 7 days of COS was no different from that of 370 live born infants conceived after COS with daily rFSH. There were no treatment-related differences in neonatal characteristics or in the incidence of major or minor malformations. The live birth rates, mode of delivery, number of premature births and premature births with low birthweights, congenital malformations and stillbirths or neonatal deaths were similar between the treatment groups. The safety data from the two large RCTs are supported and strengthened by the infant follow-up data, from 806 infants, following all trials to date with maternal corifollitropin alfa treatment. The incidence of major malformations in live born infants in the RCTs (4.0% in the corifollitropin alfa group and 5.4% in the rFSH group) was comparable with the incidence when all trials with corifollitropin alfa intervention were included (4.5%).

The incidence and type of major malformations with the corifollitropin alfa therapy in the current study was comparable with the 5% incidence reported in a large study including 1000 fetuses following maternal COS with rFSH in a GnRH antagonist (ganirelix) protocol using the same methodology and definitions (Bonduelle *et al.*, 2010).

The definition of a major malformation, which may vary between studies, influences its absolute incidence which then may vary between 1 and 10% (Rimm *et al.*, 2004). In addition to the definition,

Table VII Incidence of minor and major congenital malformations in all Phase II and III trials with corifollitropin alfa intervention.

	All pregnancies	Singleton pregnancy	Multiple pregnancy
Live born infants	$n = 806$	$n = 507$	$n = 299$
Major malformations	4.5% ($n = 36$)	2.8% ($n = 14$)	7.4% ($n = 22$)
Minor malformations only	10.0% ($n = 81$)	10.3% ($n = 52$)	9.7% ($n = 29$)
Any malformation	14.5% ($n = 117$)	13.0% ($n = 66$)	17.1% ($n = 51$)

the number of observations, the duration of follow-up after birth, the incidence of multiple pregnancies and the thoroughness of the examination are other determining factors. Care should be taken when comparing the incidence of major malformations between different prospective studies or even population surveillance data, as the latter is often hampered by underreporting (Simpson, 1996).

Taking into account any malformation, thus both major and minor malformations, the overall incidence was 16–17% and similar in both treatment groups. This incidence may be considered relatively high but is known to be related to the thoroughness of paediatric examination as well as the awareness of physicians participating in a prospective trial to collect malformations after exposure to a new fertility drug (Leppig *et al.*, 1987).

In the current RCTs, the incidence of multiple pregnancies tended to be higher in patients treated with corifollitropin alfa (43.2%) than in patients treated with rFSH (35.9%), whereas the average number (maximal two) of embryos replaced was similar in both arms of the trials. This difference included three triplets in the corifollitropin alfa arm versus none in the rFSH arm. The occurrence of a monozygotic triplet after replacement of a single embryo is rare, and in general, the occurrence of monozygotic multiples is thought to be related to prolonged culture (Chang *et al.*, 2009; Knopman *et al.*, 2010).

The incidence of intrauterine death/stillbirths at $\geq$20 weeks and neonatal deaths in women treated with corifollitropin alfa for COS (1.5 and 2.0%, respectively, in the current analysis of all trials) was comparable with previously reported data in a large cohort of women undergoing COS for ICSI or IVF (stillbirths of 1.5% and neonatal deaths of 1.1%; Bonduelle *et al.*, 2002) and in the GnRH antagonist arm of the 2010 Bonduelle study (stillbirths of 1.5% and neonatal deaths of 1.2%; Bonduelle *et al.*, 2010).

The data from the current prospective RCTs are reassuring. Despite previous reassuring reports on obstetric and neonatal complications and congenital abnormalities after ART (Ericson and Källén, 2001; Boerrigter *et al.*, 2002; Anthony *et al.*, 2002; Bonduelle *et al.*, 2002; Nygren *et al.*, 2007), the debate continues about the safety of ART for children, and the ways in which safety is evaluated. Concerns about the limitations of commonly used methods of assessment (including lack of appropriate comparison (control) groups, failure to take into account potential confounding variables and differences in the criteria used to evaluate anomalies in the ART population versus the general population) have prompted calls for more rigorous evaluation, including prospective surveillance of congenital abnormalities (Simpson, 1996) and a hesitancy to dismiss observed increases in the risk of adverse outcomes found in literature reviews (Kurinczuk, 2003; Hansen *et al.*, 2005; Reefhuis *et al.*, 2009).

In conclusion, the current neonatal follow-up data, including comparative data of 440 fetuses and overall data of 838 fetuses conceived after maternal treatment with corifollitropin alfa, further support the safety of this new treatment option in IVF.

Authors' roles

M.B., B.M., A.L., C.B., D.P. and P.D. took part in the analysis and interpretation of data, writing the manuscript and in the final approval of the version to be published.

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Conflict of interest

M.B. has received funding from Merck International, MSD Belgium, IBSA and Ferring International. A.L. has been a speaker for Merck, Inc. and was an investigator in the Phase III trials. B.M. and D.P. are employees of MSD.

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