



# Corifollitropin alfa vs recombinant FSH for controlled ovarian stimulation in women aged 35–42 years with a body weight $\geq 50$ kg: a randomized controlled trial

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**STUDY QUESTION:** Is corifollitropin alfa 150  $\mu$ g equivalent to follitropin beta 300 IU/day for controlled ovarian hyperstimulation (COS) in older women weighing  $\geq 50$  kg undergoing IVF and/or ICSI in Vietnam?

**SUMMARY ANSWER:** Corifollitropin alfa 150  $\mu$ g was equivalent to follitropin beta 300 IU/day with respect to the number of oocytes retrieved, the ongoing, cumulative and live birth rates and obstetric outcomes.

**WHAT IS KNOWN ALREADY:** Corifollitropin alfa is a recombinant FSH (rFSH) preparation with slow absorption and a long half-life allowing administration of a single dose for COS lasting 7 days. Several randomized, controlled clinical trials have reported that COS with corifollitropin alfa is associated with similar outcomes compared with COS using daily rFSH. However, limited data are available in Asian patients.

**STUDY DESIGN, SIZE, DURATION:** This randomized controlled trial was conducted at a single large IVF centre in Vietnam from June 2015 to August 2016. A total of 400 patients were included, 200 in each treatment group. The primary outcome measure was the number of oocytes retrieved. Patients were followed for 1 year after randomization.

**PARTICIPANTS / MATERIALS, SETTING, METHODS:** Participants aged 35–42 years with a body weight  $\geq 50$  kg who were undergoing an IVF cycle were randomized to undergo COS with a single dose of corifollitropin alfa 150  $\mu$ g on Day 2 or 3 of the menstrual cycle, or follitropin beta 300 IU/day for 7 days starting on Day 2 or 3 of the menstrual cycle. All underwent ICSI according to standard institutional protocols. A beta hCG test was performed 17 days after ovum pick-up, and positive tests were confirmed on vaginal and/or abdominal ultrasound at 5–6 weeks after embryo transfer (clinical pregnancy) and at  $\geq 10$  weeks (ongoing pregnancy). Rates of ovarian hyperstimulation syndrome, and maternal and foetal outcomes after one cycle of ICSI were monitored over 12 months.

**MAIN RESULTS AND THE ROLE OF CHANCE:** Patients in the corifollitropin alfa and follitropin beta groups were well matched at baseline (mean age  $37.5 \pm 1.9$  vs  $37.7 \pm 2.0$  years, mean body weight  $53.7 \pm 5.4$  vs  $52.5 \pm 4.8$  kg). There was no significant difference between the corifollitropin alfa and follitropin beta groups in the number of oocytes retrieved ( $11.4 \pm 5.9$  vs  $10.8 \pm 5.8$ ;  $P = 0.338$ ). The ongoing pregnancy rate ( $31.5$  vs  $32.0\%$ ;  $P = 0.99$ ) and live birth rate ( $30.5$  vs  $32.0\%$ ;  $P = 0.83$ ) (both per initiated cycle at 12 months after randomization) were also similar in the two treatment groups. Complication rates were low and similar in the corifollitropin alfa and follitropin beta groups, and there were no significant between-group differences in obstetric outcomes.

**LIMITATIONS, REASONS FOR CAUTION:** This study had an open-label design, and therefore, the potential for bias cannot be excluded. The findings are only applicable to patient populations with similar characteristics to those enrolled in the study.

**WIDER IMPLICATIONS OF THE FINDINGS:** This study adds to the body of evidence supporting the equivalence of corifollitropin alfa and follitropin beta for COS in a variety of patients undergoing IVF and/or ICSI. The ability to provide COS with corifollitropin alfa has the potential to reduce the burden of treatment for patients.

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**TRIAL REGISTRATION NUMBER:** The trial was registered with clinicaltrials.gov (NCT02466204).

**TRIAL REGISTRATION DATE:** 2 June 2015.

**DATE OF FIRST PATIENT'S ENROLMENT:** 19 June 2015.

**Key words:** controlled ovarian stimulation / IVF / corifollitropin alfa / follitropin beta / recombinant FSH / ICSI / pregnancy / live birth

## WHAT DOES THIS MEANS FOR PATIENTS?

Ovarian stimulation is a key part of IVF treatment and this study investigates whether the use of a longer-lasting drug to stimulate the ovaries works as well as the standard daily injections used to do this.

The new drug is absorbed more slowly so one dose lasts seven days which would make the process easier for patients. Some trials have suggested that it works as well as standard drugs, but these studies have focused on Western women. In contrast, this trial was carried out in Vietnam where the researchers wanted to know if the previous results would be replicated in Asian women. The women in this trial had a lower body weight and a similar age to, or were slightly older than, those in the previous studies.

Women who were having IVF were randomized to have controlled ovarian stimulation with either standard treatment or the longer-lasting drug. The study found that there were no significant differences between the two groups in the number of eggs the women produced or in pregnancy or live birth rates.

## Introduction

Controlled ovarian stimulation (COS) with gonadotropins is the first step in each cycle of in IVF/ICSI. The effectiveness of this approach is dependent on maintenance of adequate daily levels of FSH during COS. This can be challenging due to the short elimination half-life and rapid metabolic clearance of the traditional agents used in this setting, including hMG and recombinant FSH (rFSH). As a result, these agents need to be administered daily for the duration of stimulation (Fauser and Van Heusden, 1997).

A novel recombinant hormone has been developed to overcome the issues associated with short product half-life. The pharmacokinetic profile of the new agent, corifollitropin alfa, differs from that of rFSH. It shows slower absorption to peak serum levels and has a half-life of up to 68 hours (Fares et al., 1992; Duijkers et al., 2002; Devroey et al., 2004; Fauser et al., 2009). As a result, a single dose of corifollitropin alfa has prolonged activity over a full week, compared with the requirement for daily injections of rFSH (Fares et al., 1992; Bouloux et al., 2001; Duijkers et al., 2002). The ability to provide COS for 1 week with a single dose rather than daily injections reduces the burden of IVF treatment for patients, which in turn could contribute to reduced patient drop-out and improved effectiveness of assisted reproductive technologies (Verberg et al., 2008).

A single dose of corifollitropin alfa administered early in the follicular phase of the cycle can stimulate and sustain the development of multiple follicles over a 1-week period (Corifollitropin Alfa Dose-finding

Study Group, 2008; Fauser et al., 2009). Corifollitropin alfa has been shown to be associated with similar outcomes to rFSH in several randomized, controlled clinical trials (Corifollitropin Alfa Dose-finding Study Group, 2008; Devroey et al., 2009; Corifollitropin Alfa Ensure Study Group, 2010; Boostanfar et al., 2015), and this equivalence has been highlighted in a meta-analysis (Griesinger et al., 2016a,b). In addition, corifollitropin alfa is well tolerated, with no immunogenicity issues (Norman et al., 2011).

Our centre currently performs ~7000 IVF/ICSI cycles a year, and about one-quarter of treated women are aged  $\geq 35$  years and weigh  $\leq 60$  kg. These patients usually receive a GnRH antagonist protocol and undergo COS with rFSH 200–300 IU/day. The Pursue study found no significant difference in number of oocytes retrieved, implantation rate and vital pregnancy rate between patients who received COS with corifollitropin alfa compared with follitropin beta in Western patients aged  $\geq 35$ –42 years and weighing  $\geq 50$  kg (Boostanfar et al., 2015). However, Asian patients differ from predominantly Caucasian populations in a number of important ways, including a lower BMI (WHO Expert Consultation, 2004), higher body fat percentage at the same BMI (Deurenberg et al., 2002), and diminished ovarian reserve (Lan et al., 2013; Bleil et al., 2014; Iglesias et al., 2014).

Therefore, we replicated the Pursue study in a local population to compare the efficacy and safety of corifollitropin alfa 150  $\mu$ g and rFSH (follitropin beta) 300 IU/day for COS in patients from Vietnam aged 35–42 years with a body weight of  $\geq 50$  kg undergoing IVF and/or

ICSI. The aim was to generate data to better inform clinical management of this group of patients.

## Materials and Methods

This randomized controlled trial with an equivalence design (NCT02466204) was conducted from 19 June 2015 to 10 August 2016 at IVFMD, My Duc Hospital, Ho Chi Minh City, Vietnam.

### Ethical approval

The Institutional Review Board (IRB) approved the study protocol on 18 May 2015 (IRB reference number: 06/QĐ-CGRH-NCKH&ĐT). Ethical Committee approval was obtained on 26 May 2015 (reference number: 03/15/ĐĐ-BVMD). All patients provided written informed consent to participate in the study, which was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization guidelines for Good Clinical Practice, and local regulatory requirements.

### Study population

Patients were undergoing a routine ART cycle. Those who provided written informed consent and satisfied all the inclusion and none of the exclusion criteria (Table 1) were enrolled in the trial.

### Randomization and sample size

Eligible subjects were randomized in blocks of four via computer-generated lists to ovarian stimulation with either corifollitropin alfa (Elonva®) 150 µg or follitropin beta (Puregon®) 300 IU/day for 7 days. After a patient agreed to participate to the study, the investigator contacted an administrator not involved in the study who opened a sealed envelope and informed the investigator of the randomization group (corifollitropin alfa or follitropin beta). The sample size was calculated based on a between-group difference in the number of oocytes retrieved from -3 to +5 being clinically equivalent. For comparing mean values between groups with  $\alpha = 0.05$ , power of 90% and assuming a standard deviation of almost 8 for the number of oocytes retrieved, the required sample size was calculated as 150 patients per group. Assuming a dropout rate of 20%, the sample size was set at 200 per group (400 subjects overall).

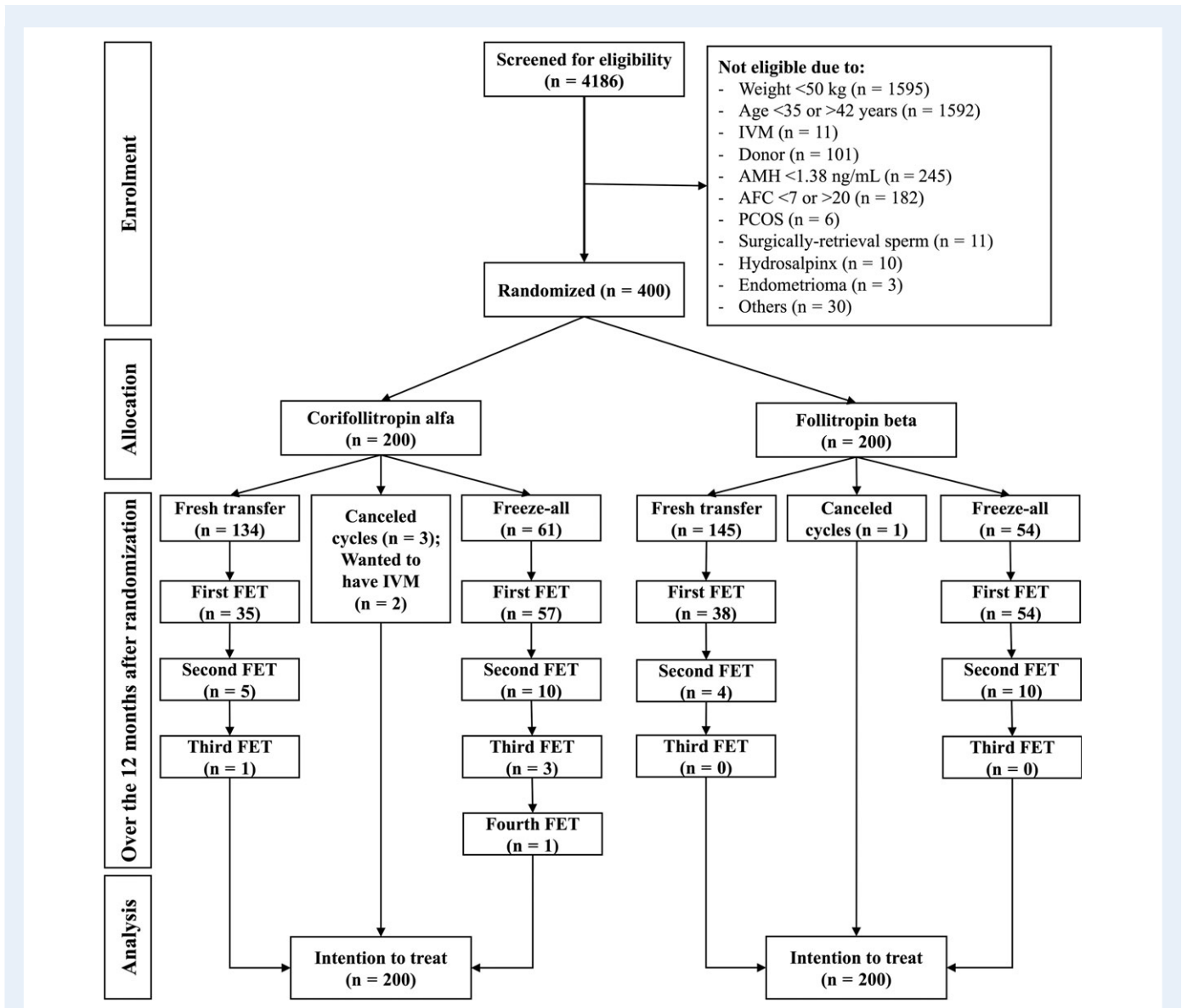
### Study treatments

Participants in the corifollitropin alfa group received a single subcutaneous (SC) injection of corifollitropin alfa 150 mg in 0.5 mL on Day 2 or 3 of the menstrual cycle. Those in the follitropin beta group received daily SC injections of follitropin beta 300 IU/day starting on Day 2 or 3 of the menstrual cycle (stimulation Day 1) continuing up to and including stimulation Day 7.

**Table 1 Patient inclusion and exclusion criteria.**

Inclusion criteria	Exclusion criteria
Female aged $\geq 35$ to $\leq 42$ years when informed consent form signed	Endocrine abnormality within the previous 3 years
Indication for COS and IVF or ICSI	History of PCOS, recurrent miscarriage ( $\geq 3$ ), $< 2$ ovaries, endometrioma $> 10$ mm, unilateral or bilateral hydrosalpinx, any uterine fibroids $> 5$ cm or other pathology that could impair implantation and ongoing pregnancy, previous low ovarian response to FSH/hMG, $\geq 3$ previous unsuccessful COS cycles for IVF/ICSI, FSH $> 15.0$ IU/L or LH $> 12.0$ IU/L during the early follicle phase (menstrual cycle Days 2–5)
Body weight $\geq 50$ kg and BMI $\geq 18$ to $\leq 32$ kg/m <sup>2</sup>	History of ovarian hyper-response (previous COS cycle with $> 30$ follicles $\geq 11$ mm on ultrasound or OHSS)
Regular spontaneous menstrual cycle (intra-individual variation of 24–35 days)	$> 20$ basal antral follicles $< 11$ mm on USS in the early follicle phase (menstrual cycle Days 2–5)
Ejaculatory sperm available	Sperm obtained via surgical retrieval
Clinical laboratory test and physical examination results within normal ranges or clinically acceptable to the investigator	History of alcohol abuse, current or recent smoking (within previous 3 months), positivity for HIV or hepatitis B
AMH $\geq 1.38$ ng/mL (AMH Gen II, Beckman Coulter, USA) or AFC 7–20, measured within 2 months of ovarian stimulation (Lan <i>et al.</i> (2013))	Contraindications to the use of gonadotropins
Ability to adhere to dose and visit schedules and willingness to report medical events to the investigator	Concomitant use of either LH or hMG/uFSH preparations in study cycle
	History of or current epilepsy, thrombophilia, diabetes, cardiovascular, gastrointestinal, hepatic, renal, pulmonary or auto-immune disease requiring regular treatment
	Subject or sperm donor has known gene defects, genetic abnormalities, or abnormal karyotyping, relevant for the current indications or for the health of the offspring
	Use of any investigational drugs in the previous 3 months or participation in another clinical trial
	Known allergy/sensitivity to the investigational drugs or their excipients

AFC, antral follicle count; AMH, anti-Müllerian hormone; COS, controlled ovarian hyperstimulation; PCOS, polycystic ovary syndrome; uFSH, urinary follicle-stimulating hormone; USS, ultrasound scan.



**Figure 1** CONSORT diagram showing flow of patients through the study. AFC, antral follicle count; AMH, anti-Müllerian hormone; FET, frozen embryo transfer; IVM, *in vitro* maturation; PCOS, polycystic ovary syndrome.

## IVF protocol

From stimulation Day 8 onwards, subjects in both treatment groups continued with a daily SC dose of follitropin beta up to the day before administration of hCG or the day of GnRH agonist administration. Lower follitropin beta doses could be used if deemed appropriate, but the maximum dose daily dose was 300 IU. A GnRH antagonist (ganirelix acetate 0.25 mg in 0.5 mL SC) was started on Day 5 of stimulation in both groups to prevent premature LH surges.

As soon as  $\geq 3$  follicles of 17 mm in diameter were observed on ultrasound scan (USS), recombinant hCG was given for final oocyte maturation; a GnRH agonist (triptorelin) was used when there were  $>19$  follicles of  $\geq 11$  mm on the day of trigger to avoid ovarian hyperstimulation syndrome (OHSS) (Griesinger et al., 2016a,b). Ovum pick-up (OPU) followed by ICSI was performed ~34–36 h later. Two or three embryos were transferred 3 days after OPU. The centre operates 7 days a week, and OPU as possible on each and every day of the week.

Patients given recombinant hCG for final oocyte maturation received luteal phase support with intra-vaginal progesterone gel (90 mg twice daily), started on the day of OPU. When a GnRH agonist was used to trigger final oocyte maturation, luteal support was given as above with the addition of progesterone 50 mg intramuscular injection daily and estradiol (2 mg/day orally, four times daily), or all embryos could be frozen for later transfer.

## Outcome measures

The primary endpoint was the number of oocytes retrieved. Secondary endpoints were the number of MII oocytes, the number of two pronuclear (2PN) fertilized oocytes, the number of follicles  $>11$  mm in diameter on the day of hCG administration, estradiol level on the day of hCG administration, the FSH dose (daily dose, days and total dose), the rate of cycle cancellation prior to hCG due to poor response or hyper-response, the rate of moderate and severe OHSS, the implantation rate (defined as the

**Table II Patient demographic characteristics at baseline.**

	Corifollitropin alfa (n = 200)	Follitropin beta (n = 200)	P-value
Age, years	37.51 ± 1.88	37.70 ± 2.03	0.319
Weight, kg	53.72 ± 5.36	52.51 ± 4.75	0.675
BMI, kg/m <sup>2</sup>	22.09 ± 2.20	21.90 ± 1.97	0.367
Anti-Müllerian hormone, ng/mL	4.07 ± 2.59	3.98 ± 2.36	0.712
Antral follicle count, n	10.59 ± 4.05	10.77 ± 4.43	0.669
Duration of infertility, years	5.78 ± 4.11	5.30 ± 4.07	0.243
Type of infertility, n (%)			0.838
Primary	80 (40.0)	77 (38.5)	
Secondary	120 (60.0)	123 (61.5)	
Number of IVF attempts, n (%)			0.267
1	128 (64.0)	143 (71.5)	
2	52 (26.0)	40 (20.0)	
3	20 (10.0)	17 (8.5)	
IVF indication, n (%)			0.108
Male factor	62 (31.0)	60 (30.0)	
Tubal factor	58 (29.0)	50 (25.0)	
Advanced age	40 (20.0)	58 (29.0)	
Unexplained	32 (16.0)	30 (15.0)	
Ovulation disorder	8 (4.0)	2 (1.0)	

Values are mean ± standard deviation, or number of patients (%).

number of sacs with heart beat per total number of embryos transferred), rates of clinical pregnancy, ongoing pregnancy, cumulative ongoing pregnancy, multiple pregnancy, live birth, cumulative live birth and obstetric outcomes (hypertension, diabetes mellitus, delivery rate at <24, <32, <37 and ≥37 weeks, reasons for delivery and birthweight). Clinical safety was assessed by recording the occurrence of serious adverse events (including moderate and severe OHSS), and local injection site tolerance.

## Assessments

USS and blood sampling were performed on stimulation Day 5 in the follitropin beta group, on Day 8 in the corifollitropin group, and on the day of hCG or GnRH agonist administration. Measures of injection site tolerance were assessed by clinic staff at 30 min after injection of study medication.

A serum beta hCG test was performed at least 17 days after OPU. In patients with a positive test, vaginal and/or abdominal USS was performed at 5–6 weeks after embryo transfer to confirm a clinical pregnancy and at ≥10 weeks to confirm an ongoing pregnancy.

The severity of OHSS was determined based on a classification adapted from Mathur (Royal College of Obstetrics and Gynaecology, 2006) (Mathur, 2006).

## Statistical analysis

The study was designed as an equivalence trial. The null hypothesis was that there is no difference between the corifollitropin alfa and follitropin beta groups with respect to the number of oocytes retrieved. Values were compared using the Student's *t*-test, with a *P*-value of 0.05 as the threshold for statistical significance. All efficacy analyses were performed on an intention-to-treat basis, including all randomized patients who received

corifollitropin alfa or at least one dose of rFSH. Rates were compared by calculating relative risks and 95% CI. Between-group differences in non-continuous and continuous variables were assessed using the Fisher's exact test and Student's *t*-test, respectively. Safety analyses included all treated subjects who received corifollitropin alfa or follitropin beta. The percentage of patients with moderate or severe OHSS in each treatment group was compared using Fisher's exact test. Kaplan–Meier curves were constructed to estimate cumulative ongoing pregnancy rate at 12 months after randomization. The two groups were compared using a log-rank test and Cox regression model. All analyses were performed using the R statistical package (R version 3.3.1). *P*-values were calculated two-sided, and *P* < 0.05 was considered statistically significant.

## Results

Of 4186 eligible patients, a total of 400 patients were enrolled in the study, 200 in each treatment group. A CONSORT flow diagram is shown in Fig. 1. Patient demographic data at baseline did not differ significantly between the corifollitropin alfa and follitropin beta treatment groups (Table II). Clinical and cycle characteristics are shown in Table III. The duration of stimulation was one day longer in the corifollitropin alfa vs follitropin beta group (10 vs 9 days; *P* < 0.001), and the number of follicles ≥11 or ≥14 mm was significantly greater (both *P* < 0.001) (Table III). In terms of hormone levels, estradiol on the day of trigger and the number of cycles with a premature progesterone rise were significantly higher in the corifollitropin alfa group (*P* = 0.022 and *P* = 0.048, respectively, vs follitropin beta) (Table III). Four cycles were cancelled at the patients' request (3 in the corifollitropin alfa group and one in the follitropin beta group).

**Table III Clinical and cycle characteristics.**

	Corifollitropin alfa (n = 200)	Follitropin beta (n = 200)	Between-group difference (95% CI)	Rate ratio for corifollitropin alfa vs follitropin beta (95% CI)	P-value
Duration of stimulation, days	9.89 ± 1.66	8.99 ± 1.22	0.90 (0.61, 1.16)		<0.001
Type of trigger, n (%)					0.401
Agonist trigger	15 (7.6)	10 (5.0)			
hCG trigger	183 (92.4)	189 (95.0)			
Follicles ≥ 11 mm, n	12.22 ± 5.15	10.47 ± 4.74	1.75 (0.78, 2.73)		<0.001
Follicles ≥ 14 mm, n	10.54 ± 5.13	8.76 ± 4.65	1.78 (0.82, 2.75)		<0.001
Estradiol level on day of trigger, pg/mL	5742.64 ± 4597.39	4760.26 ± 3872.91	982.4 (143.31, 1821.46)		0.022
Progesterone level on day of trigger, ng/mL	1.71 ± 4.55	1.63 ± 3.90	0.08 (−0.78, 0.91)		0.854
Cycles with premature progesterone rise (>1.5 ng/mL), n (%)	58 (29.0)	40 (20.0)	9.0 (0.3, 18.1)	1.46 (1.03, 2.07)	0.048
Patients reaching trigger criteria before Day 8, n (%)	17 (8.5)	9 (4.5)	4.0 (−4.6, 12.3)	1.37 (0.73, 2.59)	0.363
Endometrial thickness, mm	12.03 ± 2.10	11.83 ± 2.00	0.20 (−0.21, 0.60)		0.343
Embryos, n	5.92 ± 3.61	5.63 ± 3.30	0.29 (−0.56, 0.92)		0.403
Good embryos, n	1.48 ± 1.77	1.34 ± 1.38	0.14 (−0.19, 0.43)		0.403
Oocytes retrieved, n	11.39 ± 5.93	10.82 ± 5.84			0.338
MII oocytes, n	9.38 ± 5.20	8.65 ± 4.68			0.144
Fertilized oocytes, n	6.81 ± 4.41	6.39 ± 3.90			0.31
Frozen embryos, n	2.63 ± 2.84	2.29 ± 2.51	0.34 (−0.21, 0.84)		0.203
Cycles with extra embryos for freezing, n (%)	67 (33.5)	70 (35.0)	−1.5 (−11.3, 8.3)	0.96 (0.73, 1.26)	0.833
Embryos transfer, n (%)					0.507
Fresh transfer	134 (67.0)	145 (72.5)			
Freeze-all	61 (30.5)	54 (27.0)			
Freeze-all indications, n (%)					0.101
Patients' preference	21 (34.4)	27 (50.0)			
Premature progesterone rise	23 (37.7)	9 (16.7)			
Agonist trigger	5 (8.2)	3 (5.6)			
Endometrial polyp	3 (4.9)	6 (11.1)			
Unfavourable endometrium	6 (9.8)	6 (11.1)			
Fluid in cavity	2 (3.3)	0 (0.0)			
Risk of OHSS	1 (1.6)	1 (1.9)			
Others	0 (0.0)	2 (3.7)			

Values are mean ± standard deviation, or number of patients (%).

OHSS, ovarian hyperstimulation syndrome.

## Number of oocytes retrieved

There was no significant difference between the corifollitropin alfa and follitropin beta groups in the numbers of oocytes retrieved, MII oocytes and fertilized oocytes (Table III).

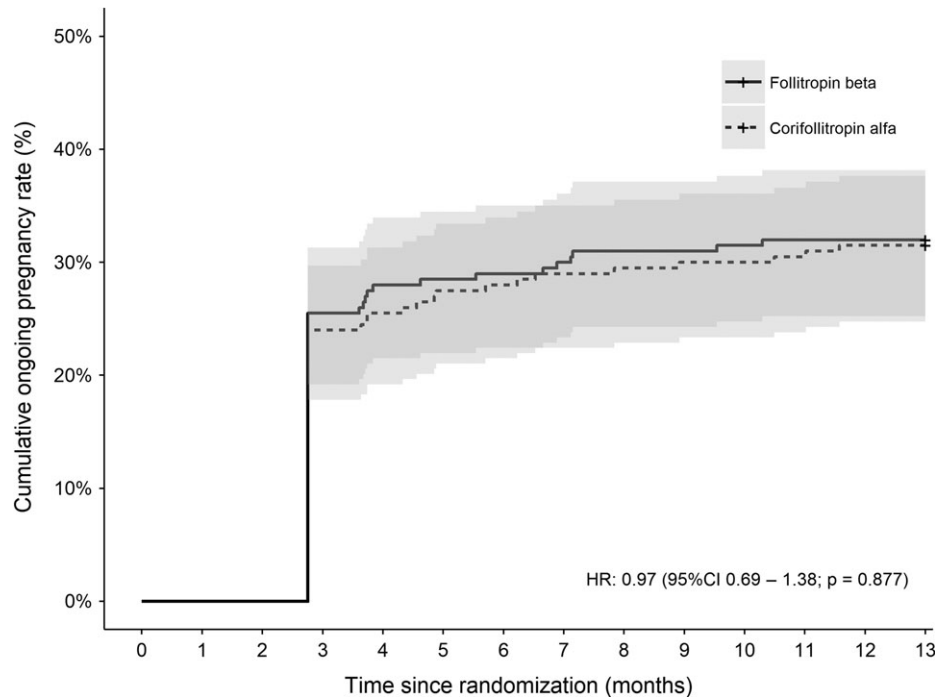
## Fertility and pregnancy outcomes

Corifollitropin alfa was non-inferior to follitropin beta with respect to the cumulative ongoing pregnancy rate (hazard ratio 0.97, 95% CI: 0.69–1.38;  $P = 0.83$ ) (Fig. 2), and live birth rate per initiated cycle at 12 months after randomization (30.5 vs 32.0%;  $P = 0.88$ ). Outcomes in the two groups

were similar when analyzed per embryo transfer, per initiated cycle and per initiated cycle at 12 months after randomization (Table IV).

## Safety

OHSS was documented in 2 patients (1%) in the corifollitropin alfa group and 1 patient (0.5%) in the follitropin beta group. Rates of other complications and obstetric outcomes were similar in the two treatment groups when analyzed per embryo transfer, per initiated cycle and per initiated cycle at 12 months after randomization (Table V). No injection site reactions were observed during the study.



**Figure 2** Cumulative ongoing pregnancy rate.

## Discussion

This randomized, controlled clinical trial demonstrates that corifollitropin alfa 150 µg was equivalent to treatment with follitropin beta 300 IU/day with respect to the number of oocytes retrieved, the ongoing, cumulative ongoing and live birth rates, and obstetric outcomes in older, low body weight women from Vietnam. Patients in the corifollitropin alfa group had a significantly higher number of follicles  $\geq 11$  and  $\geq 14$  mm in diameter than those in the follitropin beta group, and also significantly higher levels of progesterone and estradiol. This is consistent with data showing that an increased number of follicles is associated with higher hormone levels (Kyrou *et al.*, 2012).

Our results showing no significant differences in outcomes between corifollitropin alfa and follitropin beta in women undergoing IVF are consistent with those of previous randomized, controlled studies (Corifollitropin Alfa Dose-finding Study Group, 2008; Devroey *et al.*, 2009; Corifollitropin Alfa Ensure Study Group, 2010; Boostanfar *et al.*, 2015). Of these, the trial most similar to ours was the Pursue study (Boostanfar *et al.*, 2015), which used the same age and body weight inclusion criteria to define eligible patients, and the same drugs and dosages. Despite the similar inclusion criteria, mean body weight in our study (53 kg) was lower than that in the Pursue study (66–68 kg), possibly reflecting the different ethnicities of the two populations. In addition, our patients had a higher baseline anti-Müllerian hormone (AMH) levels than the Pursue population (3.9 vs 1.8 ng/mL, respectively), although the antral follicle count (AFC) was similar (10–11 in both trials). Despite the differences in patient baseline characteristics, the findings of the two trials were almost identical in terms of the number of oocytes retrieved (11.4 and 10.8 with corifollitropin alfa and follitropin beta in our study vs 10.7 and 10.3 in the Pursue trial), ongoing pregnancy rate (25 and 23% vs 22 and 24%) and implantation rate (20 and 18% vs 19 and 21%) (Boostanfar *et al.*, 2015). We also reported the cumulative ongoing pregnancy rate based on the potential for higher numbers of

oocytes after COS with corifollitropin alfa, which could lead to an increase in the cumulative pregnancy rate. Our data showed an increase of one oocyte in the corifollitropin alfa vs follitropin beta group, but the cumulative pregnancy rate in the two treatment arms was similar. Another difference compared with the Pursue trial was the comparative duration of stimulation in the two treatment groups. This was similar in both the Pursue (Boostanfar *et al.*, 2015) and Engage (Devroey *et al.*, 2009) studies (in the latter about one-third of patients in the corifollitropin alfa group did not need any FSH top-up doses), but one day longer in the corifollitropin alfa vs follitropin beta group in our study. The reason for this is not yet known.

Patients in the Ensure trial (Corifollitropin Alfa Ensure Study Group, 2010) had a similar bodyweight to those included in our study (i.e. usually below 60 kg) and the results of that study also showed the equivalent oocyte numbers for corifollitropin alfa and rFSH. In the Ensure trial, patients were younger than in our trial (mean 31 vs 38 years) and lower dosages of both corifollitropin alfa (100 µg) and follitropin beta (150 IU/day) were used. The lower corifollitropin alfa dosage was based on modelling data showing that the 100 µg dose in patients weighing  $\leq 60$  kg provided drug exposure equivalent to that achieved after a 150 µg dose in those weighing  $>60$  kg (De Greef *et al.*, 2007). An analysis of data from the Pursue trial in older women (age 35–42 years) (Boostanfar *et al.*, 2015) and the Engage trial in younger women (age 18–36 years) (Devroey *et al.*, 2009), both of which used corifollitropin alfa and follitropin beta doses of 150 µg and 200 IU/day in Ensure and  $\leq 300$  IU/day in Pursue, respectively, showed no significant differences in the fertilization rate, number of embryos obtained, and number of good quality embryos obtained between patient subgroups based on BMI ( $\leq 25$  vs  $> 25$  kg/m<sup>2</sup>) (Schieber *et al.*, 2013).

Ours is the first study to investigate the equivalence of corifollitropin alfa and follitropin beta in a group of Asian patients with both low body weight and older age. Additional strengths of the study are the reporting of

**Table IV** Fertility and pregnancy outcomes.

	Corifollitropin alfa	Follitropin beta	Between-group difference (95% CI)	Rate ratio for corifollitropin alfa vs follitropin beta (95% CI)	P-value
<b>Per first fresh embryo transfer</b>	(n = 134)	(n = 145)			
Embryos transferred, <i>n</i>	2.31 ± 0.69	2.27 ± 0.74			0.604
Good embryos transferred, <i>n</i>	0.93 ± 0.89	1.03 ± 0.86			0.329
Positive pregnancy test	50 (37.3)	56 (38.6)	-1.3 (-13.4, 10.8)	0.97 (0.72, 1.3)	0.902
Clinical pregnancy	47 (35.1)	50 (34.5)	0.6 (-11.2, 12.4)	1.02 (0.74, 1.4)	0.99
Multiple pregnancy	19 (14.2)	15 (10.3)	3.9 (-4.6, 12.3)	1.37 (0.73, 2.59)	0.363
Implantation rate, (%)	19.6 ± 32.2	18.1 ± 30.0	1.5 (-5.9, 8.8)		0.691
Miscarriage, <i>n</i> (%)	12 (9.0)	14 (9.7)	-0.7 (-8.2, 6.8)	0.93 (0.45, 1.93)	0.99
Ectopic pregnancy, <i>n</i> (%)	2 (1.5)	2 (1.4)	0.1 (-2.8, 3)	1.08 (0.15, 7.57)	0.99
Ongoing pregnancy	33 (24.6)	34 (23.4)	1.2 (-9.6, 11.9)	1.05 (0.69, 1.59)	0.889
Singleton	21 (15.7)	26 (17.9)	-2.3 (-11.7, 7.2)	0.87 (0.52, 1.48)	0.635
Twins	12 (9.0)	8 (5.5)	3.4 (-3.4, 10.3)	1.62 (0.68, 3.85)	0.354
Live birth, <i>n</i> (%)	32 (23.9)	34 (23.4)	0.5 (-10.0, 10.8)	1.02 (0.67, 1.55)	0.99
Singleton	22 (16.4)	28 (19.3)	-2.9 (-12.6, 6.8)	0.85 (0.51, 1.41)	0.537
Twins	10 (7.4)	6 (4.1)	3.3 (-2.9, 9.5)	1.80 (0.67, 4.83)	0.305
<b>Per initiated cycle</b>	(n = 200)	(n = 200)			
Embryos transferred, <i>n</i>	2.31 ± 0.69	2.27 ± 0.74			0.604
Good embryos transferred, <i>n</i>	0.93 ± 0.89	1.03 ± 0.86			0.329
Positive pregnancy test	50 (25.0)	56 (28.0)	-3 (-12.1, 6.1)	0.89 (0.64, 1.24)	0.571
Clinical pregnancy	47 (23.5)	50 (25.0)	-1.5 (-10.4, 7.4)	0.94 (0.66, 1.33)	0.816
Multiple pregnancy	19 (9.5)	15 (7.5)	2.0 (-4.0, 8.0)	1.27 (0.66, 2.42)	0.591
Implantation rate, <i>n</i> (%)	19.6 ± 32.2	18.1 ± 30.0	1.5 (-5.9, 8.8)		0.691
Miscarriage, <i>n</i> (%)	12 (6.0)	14 (7.0)	-1.0 (-6.3, 4.3)	0.86 (0.41, 1.81)	0.84
Ectopic pregnancy, <i>n</i> (%)	2 (1.0)	2 (1.0)			
Ongoing pregnancy	33 (16.5)	34 (17.0)	-0.5 (-8.3, 7.3)	0.97 (0.63, 1.5)	0.99
Singleton	21 (10.5)	26 (13.0)	-2.5 (-9.3, 4.3)	0.81 (0.47, 1.39)	0.535
Twins	12 (6.0)	8 (4.0)	2 (-2.8, 6.8)	1.5 (0.63, 3.59)	0.492
Live birth, <i>n</i> (%)	32 (16.0)	34 (17.0)	-1 (-8.8, 6.8)	0.94 (0.61, 1.46)	0.893
Singleton	22 (11.0)	28 (14.0)	-3.0 (-10.0, 4.0)	0.79 (0.47, 1.33)	0.45
Twins	10 (5.0)	6 (3.0)	2 (-2.3, 6.3)	1.67 (0.62, 4.5)	0.445
<b>Per initiated cycle at 12 months after randomization</b>	(n = 200)	(n = 200)			
Total embryo transfer cycles, <i>n</i>	246	251			
Embryos transferred, <i>n</i>	2.23 ± 0.68	2.25 ± 0.65			0.764
Good embryos transferred, <i>n</i>	0.88 ± 0.88	0.90 ± 0.85			0.980
Fertility outcomes, <i>n</i> (%)					
Positive pregnancy test	98 (49.0)	107 (53.5)	-4.5 (-14.8, 5.8)	0.92 (0.76, 1.11)	0.424
Clinical pregnancy	90 (45.0)	95 (47.5)	-2.5 (-12.8, 7.8)	0.95 (0.77, 1.17)	0.688
Implantation rate	19.4 ± 30.3	18.7 ± 30.1	0.7 (-5.3, 18.7)		0.798
Ectopic pregnancy	3 (1.5)	2 (1.0)	0.5 (-2.2, 3.2)	1.5 (0.25, 8.88)	0.99
Miscarriage	24 (12)	29 (14.5)	-2.5 (-9.6, 4.6)	0.83 (0.5, 1.37)	0.556
Ongoing pregnancy, <i>n</i> (%)	63 (31.5)	64 (32.0)	-0.5 (-10.1, 9.1)	0.98 (0.74, 1.31)	0.99
Singleton	46 (23.0)	50 (25.0)	-2 (-10.9, 6.9)	0.92 (0.65, 1.3)	0.726
Twins	17 (8.5)	14 (7.0)	1.5 (-4.2, 7.2)	1.21 (0.62, 2.4)	0.709
Live birth, <i>n</i> (%)	61 (30.5)	64 (32.0)	-1.5 (-11.1, 8.1)	0.95 (0.71, 1.27)	0.829
Singleton	45 (22.5)	54 (27.0)	-4.5 (-13.4, 4.4)	0.83 (0.59, 1.18)	0.354
Twins	16 (8.0)	10 (5.0)	3 (-2.3, 8.3)	1.6 (0.74, 3.44)	0.311

Values are mean ± standard deviation, or number of patients (%).



**Table V** Complication rates and obstetric outcomes.

	Corifollitropin alfa	Follitropin beta	Between-group difference (95% CI)	Rate ratio for corifollitropin alfa vs follitropin beta (95% CI)	P-value
<b>Per embryo transfer</b>	<b>(n = 134)</b>	<b>(n = 145)</b>			
Obstetric complications, n (%)					
Hypertension	1 (0.7)	1 (0.7)	0.1 (-2, 2.1)	1.08 (0.07, 17.13)	0.99
Diabetes	2 (1.5)	0 (0.0)	1.5 (-1.3, 4.3)		0.23
Delivery, n (%)					
< 24 weeks	1 (0.7)	0 (0.0)	0.7 (-1.4, 2.9)		0.48
24 to < 32 weeks	0 (0.0)	1 (0.7)	-0.7 (-2.7, 1.3)		0.99
32 to < 37 weeks	5 (3.7)	4 (2.8)	1 (-3.9, 5.9)	1.35 (0.37, 4.93)	0.742
≥37 weeks	27 (20.1)	29 (20.0)	0.1 (-9.4, 9.7)	1.01 (0.63, 1.61)	0.99
Reasons for delivery, n (%)					
Iatrogenic	4 (3.0)	1 (0.7)	2.3 (-1.6, 6.2)	4.33 (0.49, 38.24)	0.198
Spontaneous	13 (9.7)	11 (7.6)	2.1 (-5.2, 9.4)	1.28 (0.59, 2.76)	0.67
Elective	15 (11.2)	22 (15.2)	-4 (-12.6, 4.7)	0.74 (0.4, 1.36)	0.379
Birth weight, g					
Singleton	3033.3 ± 543.4	2969.2 ± 600.5	64.1 (-272.7, 400.9)		0.703
Twins	2466.7 ± 460.2	2512.5 ± 394.4	-45.8 (-421.0, 329.3)		0.799
<b>Per initiated cycle</b>	<b>(n = 200)</b>	<b>(n = 200)</b>			
Obstetric complications, n (%)					
Hypertension	1 (0.5)	1 (0.5)			
Diabetes	2 (1.0)	0 (0)	1 (-0.9, 2.9)		0.499
Delivery, n (%)					
< 24 weeks	1 (0.5)	0 (0)	0.5 (-1, 2)		0.99
24 to < 32 weeks	0 (0)	1 (0.5)	-0.5 (-2, 1)		0.99
32 to < 37 weeks	5 (2.5)	4 (2.0)	0.5 (-2.9, 3.9)	1.25 (0.34, 4.59)	0.99
≥37 weeks	27 (13.5)	29 (14.5)	-1 (-8.3, 6.3)	0.93 (0.57, 1.51)	0.886
Reasons for delivery, n (%)					
Iatrogenic	4 (2.0)	1 (0.5)	1.5 (-1.2, 4.2)	4 (0.45, 35.47)	0.372
Spontaneous	13 (6.5)	11 (5.5)	1 (-4.2, 6.2)	1.18 (0.54, 2.57)	0.834
Elective	15 (7.5)	22 (11.0)	-3.5 (-9.7, 2.7)	0.68 (0.36, 1.28)	0.3
Birth weight, g					
Singleton	3033.3 ± 543.4	2969.2 ± 600.5	64.1 (-272.7, 400.9)		0.703
Twins	2466.7 ± 460.2	2512.5 ± 394.4	-45.8 (-421.0, 329.3)		0.799
<b>Per initiated cycle at 12 months after randomization</b>	<b>(n = 200)</b>	<b>(n = 200)</b>			
Obstetric complications, n (%)					
Hypertension	3 (1.5)	3 (1.5)	0 (-2.4, 2.4)	1 (0.2, 4.9)	0.99
Diabetes	4 (2)	3 (1.5)	0.5 (-2.6, 3.6)	1.33 (0.3, 5.88)	0.99
Delivery, n (%)					
< 24 weeks	2 (1)	0 (0)	1 (-0.9, 2.9)		0.499
24 to < 32 weeks	0 (0)	1 (0.5)	-0.5 (-2, 1)		0.99
32 to < 37 weeks	6 (3)	7 (3.5)	-0.5 (-4.5, 3.5)	0.86 (0.29, 2.51)	0.99
≥37 weeks	55 (27.5)	56 (28)	-0.5 (-9.8, 8.8)	0.98 (0.72, 1.35)	0.99
Reasons for delivery, n (%)					
Iatrogenic	7 (3.5)	5 (2.5)	1 (-2.8, 4.8)	1.4 (0.45, 4.34)	0.771
Spontaneous	19 (9.5)	16 (8)	1.5 (-4.5, 7.5)	1.19 (0.63, 2.24)	0.724
Elective	35 (17.5)	43 (21.5)	-4 (-12.3, 4.3)	0.81 (0.55, 1.22)	0.377

Continued

**Table V** Continued

	Corifollitropin alfa	Follitropin beta	Between-group difference (95% CI)	Rate ratio for corifollitropin alfa vs follitropin beta (95% CI)	P-value
Birth weight, g					
Singleton	3085.0 ± 490.7	3014.4 ± 535.4	70.6 (−150.8, 292.0)		0.528
Twins	2490.9 ± 437.4	2320.0 ± 535.0	170.9 (−241.5, 583.4)		0.391

Values are mean ± standard deviation, or number of patients (%).

obstetric outcomes after up to four embryo transfers over a follow-up period of 1 year. However, there are a number of limitations that need to be taken into account when interpreting the results. The findings are only applicable to patients and populations similar to those enrolled in the trial, i.e. Asian women aged 35–42 years weighing ≥50 kg. However, similar results showing the equivalence of corifollitropin alfa and rFSH have been obtained in younger and heavier patients of different ethnicities (Devroey et al., 2009, Corifollitropin Alfa Ensure Study Group, 2010, Boostanfar et al., 2015), suggesting that a single dose of corifollitropin alfa may be an appropriate option for COS in patient with a range of characteristics. Also, all patients in the current study underwent ICSI, as is common practice in Asia, so the results only apply when this technique is used. Finally, the study had an open-label design and therefore the potential for bias cannot be excluded.

In conclusion, this study shows that a single injection of corifollitropin alfa 150 µg is an effective and equivalent alternative to follitropin beta 300 IU/day for COS in older women with lower body weight from Vietnam, and adds to the body of evidence for the equivalence of the two treatments in a range of patients. Corifollitropin alfa is an attractive option for women because it reduces the burden of COS therapy, and is better for healthcare professionals because it requires fewer staff resources for drug administration and monitoring while providing equivalent outcomes.

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## Authors' roles

N.L.V. was involved in study design, execution, analysis, manuscript drafting, critical discussion and final approval of the article. M.T.H. was involved in study design, execution, critical discussion and final approval of the article. D.T.P. was involved in analysis, critical discussion and final approval of the article. H.T.P., H.N.G., G.B.H. and T.T.L.N. were involved in execution, critical discussion and final approval of the article.

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## Conflict of interest

The authors state that they have no financial or commercial conflicts of interest to report.

## References

- Bleil ME, Gregorich SE, Adler NE, Sternfeld B, Rosen MP, Cedars MI. Race/ethnic disparities in reproductive age: an examination of ovarian reserve estimates across four race/ethnic groups of healthy, regularly cycling women. *Fertil Steril* 2014;**101**:199–207.
- Boostanfar R, Shapiro B, Levy M, Rosenwaks Z, Witjes H, Stegmann BJ, Elbers J, Gordon K, Mannaerts B, Pursue i.. 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. *Fertil Steril* 2015;**104**:94–103.e101.
- Bouloux PM, Handelsman DJ, Jockenhovel F, Nieschlag E, Rabinovici J, Frasa WL, de Bie JJ, Voortman G, Itskovitz-Eldor J, group F-Cs. First human exposure to FSH-CTP in hypogonadotrophic hypogonadal males. *Hum Reprod* 2001;**16**:1592–1597.
- Corifollitropin Alfa Dose-finding Study Group. A randomized dose-response trial of a single injection of corifollitropin alfa to sustain multifollicular growth during controlled ovarian stimulation. *Hum Reprod* 2008;**23**:2484–2492.
- Corifollitropin Alfa Ensure Study Group. Corifollitropin alfa for ovarian stimulation in IVF: a randomized trial in lower-body-weight women. *Reprod Biomed Online* 2010;**21**:66–76.
- De Greef R, Struijs MJ, de Haan A, Marintcheva-Petrova M, Mannaerts BMJL. Dose selection of Org 36286 (corifollitropin alfa) using pharmacokinetic and dynamic modeling and simulation. *Hum Reprod* 2007;**22**:i39 (abstract O-099).
- Deurenberg P, Deurenberg-Yap M, Guricci S. Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. *Obes Rev* 2002;**3**:141–146.
- Devroey P, Boostanfar R, Koper NP, Mannaerts BM, Ijzerman-Boon PC, Fauser BC, Investigators E. A double-blind, non-inferiority RCT comparing corifollitropin alfa and recombinant FSH during the first seven days of ovarian stimulation using a GnRH antagonist protocol. *Hum Reprod* 2009;**24**:3063–3072.
- Devroey P, Fauser BC, Platteau P, Beckers NG, Dhont M, Mannaerts BM. Induction of multiple follicular development by a single dose of long-acting recombinant follicle-stimulating hormone (FSH-CTP, corifollitropin alfa) for controlled ovarian stimulation before in vitro fertilization. *J Clin Endocrinol Metab* 2004;**89**:2062–2070.
- Duijkers IJ, Klipping C, Boerrigter PJ, Machielsen CS, De Bie JJ, Voortman G. Single dose pharmacokinetics and effects on follicular growth and serum hormones of a long-acting recombinant FSH preparation (FSH-CTP) in healthy pituitary-suppressed females. *Hum Reprod* 2002;**17**:1987–1993.
- Fares FA, Suganuma N, Nishimori K, LaPolt PS, Hsueh AJ, Boime I. Design of a long-acting follitropin agonist by fusing the C-terminal sequence of the chorionic gonadotropin beta subunit to the follitropin beta subunit. *Proc Natl Acad Sci USA* 1992;**89**:4304–4308.

- Fauser BC, Mannaerts BM, Devroey P, Leader A, Boime I, Baird DT. Advances in recombinant DNA technology: corifollitropin alfa, a hybrid molecule with sustained follicle-stimulating activity and reduced injection frequency. *Hum Reprod Update* 2009;**15**:309–321.
- Fauser BC, Van Heusden AM. Manipulation of human ovarian function: physiological concepts and clinical consequences. *Endocr Rev* 1997;**18**:71–106.
- Griesinger G, Boostanfar R, Gordon K, Gates D, McCrary Sisk C, Stegmann BJ. Corifollitropin alfa versus recombinant follicle-stimulating hormone: an individual patient data meta-analysis. *Reprod Biomed Online* 2016a;**33**:56–60.
- Griesinger G, Verweij PJ, Gates D, Devroey P, Gordon K, Stegmann BJ, Tarlatzis BC. Prediction of ovarian hyperstimulation syndrome in patients treated with corifollitropin alfa or rFSH in a GnRH antagonist protocol. *PLoS One* 2016b;**11**:e0149615.
- Iglesias C, Banker M, Mahajan N, Herrero L, Meseguer M, Garcia-Velasco JA. Ethnicity as a determinant of ovarian reserve: differences in ovarian aging between Spanish and Indian women. *Fertil Steril* 2014;**102**:244–249.
- Kyrou D, Al-Azemi M, Papanikolaou EG, Donoso P, Tziomalos K, Devroey P, Fatemi HM. The relationship of premature progesterone rise with serum estradiol levels and number of follicles in GnRH antagonist/recombinant FSH-stimulated cycles. *Eur J Obstet Gynecol Reprod Biol* 2012;**162**:165–168.
- Lan VT, Linh NK, Tuong HM, Wong PC, Howles CM. Anti-Mullerian hormone versus antral follicle count for defining the starting dose of FSH. *Reprod Biomed Online* 2013;**27**:390–399.
- Mathur R. The management of ovarian hyperstimulation syndrome (Royal College of Obstetricians and Gynaecologists). 2006.
- Norman RJ, Zegers-Hochschild F, Salle BS, Elbers J, Heijnen E, Marintcheva-Petrova M, Mannaerts B, Trust I. Repeated ovarian stimulation with corifollitropin alfa in patients in a GnRH antagonist protocol: no concern for immunogenicity. *Hum Reprod* 2011;**26**:2200–2208.
- Schieber M, Stegmann B, Gordon K, Verweij P. Impact of body mass index on the number and quality of embryos obtained following ovarian stimulation with corifollitropin alfa or recombinant FSH in IVF centers in North America. *Fertil Steril* 2013;**100**:S18.
- Verberg MF, Eijkemans MJ, Heijnen EM, Broekmans FJ, de Klerk C, Fauser BC, Macklon NS. Why do couples drop-out from IVF treatment? A prospective cohort study. *Hum Reprod* 2008;**23**:2050–2055.
- WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004;**363**:157–163.