Administration of corifollitropin alfa on Day 2 versus Day 4 of the cycle in a GnRH antagonist protocol: A randomized controlled pilot study

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STUDY QUESTION: Does the initiation of corifollitropin alfa administration on cycle day 4 instead of cycle day 2 result in a reduced total rFSH consumption in a GnRH antagonist protocol?

SUMMARY ANSWER: Initiation of corifollitropin alfa on cycle day 4 compared with day 2 results in significantly reduced total rFSH consumption at the end of the follicular phase.

WHAT IS KNOWN ALREADY: *In vitro* fertilization treatment is associated with significant physical, psychological and emotional stress in infertile patients. This notion has fuelled the search for simplified treatment approaches that may reduce the treatment burden. The introduction of corifollitropin alfa has provided a more patient-friendly treatment protocol because it obviates the need for daily hormonal injections. In addition, postponing the initiation of hormonal stimulation should also reduce the total gonadotrophin consumption and the number of injections needed.

STUDY DESIGN, SIZE, DURATION: A prospective randomized controlled pilot study was conducted in a university centre in Belgium. Between December 2011 and March 2013, 59 patients were randomized in the study and 52 of these patients received the allocated intervention.

PARTICIPANTS/MATERIALS, SETTING, METHODS: All patients were randomly assigned to the control group (CD2), with initiation of corifollitropin alfa on cycle day 2, or to the study group (CD4) with initiation of stimulation on day 4. The GnRH antagonist was administered from cycle day 7 onwards in both treatment arms. The main outcome measure was the total rFSH consumption at the end of the follicular phase after corifollitropin alfa treatment.

MAIN RESULTS AND THE ROLE OF CHANCE: The total dose of rFSH at the end of the follicular phase was significantly reduced in the CD4 group compared with the CD2 group (324 (276) IU in the CD2 group versus 173 (255) IU in the CD4 group, $P = 0.015$, mean difference −151, 95% confidence interval (CI) −301 to −1). A significant reduction of total duration of rFSH stimulation in the CD4 group was also observed (8.6 (1.4) days in CD2 group versus 7.8 (1.2) days in the CD4 group, $P = 0.008$, mean difference −0.8, 95% CI −1.6 to −0.1). The number of cumulus-oocyte-complexes was comparable in both treatment groups (12.8 (7.3) in CD2 group versus 14.7 (8.8) in the CD4 group, $P = 0.461$, mean difference 1.8, 95% CI −2.7 to 6.4). Ongoing pregnancy rates of 48% in the CD2 group and 41% in the CD4 group were achieved ($P = 0.60$, relative risk (RR) 0.85, 95% CI 0.46−1.56). Final oocyte maturation was triggered with GnRH agonist instead of hCG in two patients in the CD2 group and in eight patients in the CD4 group, because of an increased risk of ovarian hyperstimulation syndrome ($P = 0.078$, RR 3.7 (95% CI 0.88−15.8).

LIMITATIONS, REASONS FOR CAUTION: Before general implementation can be advised, this trial should be validated in a much larger randomized trial.

WIDER IMPLICATIONS OF THE FINDINGS: If the approach of starting ovarian stimulation on Day 4 of the cycle could be implemented in a large population of infertile patients, it would result in a significant reduction of gonadotrophin consumption.

Introduction

In vitro fertilization (IVF) treatment contributes to a significant physical, psychological and emotional burden in infertile patients (Boivin and Takefman, 1996). High drop-out rates have been reported among couples undergoing fertility treatment (Gleicher *et al.*, 1996; Malcolm and Cumming, 2004; Brandes *et al.*, 2009). Studies have shown that psychological distress is one of the main reasons for discontinuation of treatment (Olivius *et al.*, 2004; Rajkhowa *et al.*, 2006; Brandes *et al.*, 2009). These findings have urged researchers to develop a more simplified treatment approach, which could reduce the burden of infertility treatment (Verberg *et al.*, 2008).

The introduction of the gonadotrophin releasing hormone (GnRH) antagonist cotreatment protocol has resulted in a reduced duration of stimulation with lower total recombinant follicle stimulation hormone (rFSH) consumption compared with the GnRH agonist protocol (Hohmann *et al.*, 2003; Tarlatzis *et al.*, 2006). Prospective randomized trials show that, compared with the conventional agonist protocol, the antagonist protocol is associated with fewer days of stimulation, resulting in similar delivery rates (Kolibianakis *et al.*, 2006; Al-Inany *et al.*, 2011).

The more patient-friendly protocol of GnRH antagonist cotreatment was then elaborated further resulting in the development of a mild stimulation protocol, with administration of exogenous FSH only in the mid-to-late follicular phase, allowing the endogenous FSH rise to be utilized (Heijnen *et al.*, 2007). A meta-analysis encompassing three studies initiating rFSH stimulation on cycle day 5 reported a reduced number of oocytes retrieved compared with conventional stimulation (Verberg *et al.*, 2009a). However, similar live birth rates over a 1-year treatment period have been observed using this protocol (Heijnen *et al.*, 2007). Delaying the initiation of stimulation until cycle day 5 results in a significant decrease in total rFSH consumption compared with initiation on cycle day 2 (Hohmann *et al.*, 2003; Blockeel *et al.*, 2011). A mild stimulation protocol is a simplified and more patient-friendly approach, with significantly reduced treatment costs and patient discomfort (Macklon *et al.*, 2006; Heijnen *et al.*, 2007; Nargund and Frydman, 2007).

Recently, a new hybrid molecule with sustained follicle stimulation activity was developed (Fares *et al.*, 1992). This recombinant fusion protein, called corifollitropin alfa, is composed of the α-subunit of FSH and the carboxy terminal peptide (CTP) of the human chorionic gonadotrophin (hCG) β-subunit (Fares *et al.*, 1992). The pharmacodynamic properties of corifollitropin alfa and rFSH are similar during ovarian stimulation for IVF/ICSI, but the pharmacokinetic characteristics differ (Fauser *et al.*, 2010). The elimination half-life ($t_{1/2}$) of corifollitropin alfa is ~2-fold longer in comparison with rFSH and the time-interval (t_{max}) to peak serum levels (C_{max}) is almost 4-fold longer (Duijkers *et al.*, 2002). Due to this pharmacokinetic profile, one dose of corifollitropin alfa keeps the FSH level above the physiological threshold for an entire week (Corifollitropin Alfa Dose-finding Study Group, 2008; Fauser *et al.*, 2009, 2010). Thus, a single injection of corifollitropin alfa can replace seven daily injections of rFSH. Stimulation with corifollitropin alfa enables further simplification of the IVF treatment protocol due to fewer injections and reduced drug administration without any impact on clinical outcomes (Devroey *et al.*, 2009; Fauser *et al.*, 2009).

Initiating ovarian stimulation with rFSH later in the follicular phase results in reduction of rFSH consumption (Hohmann *et al.*, 2003; Blockeel *et al.*, 2011). We hypothesized that the delay of corifollitropin alfa administration may also result in a decrease in total rFSH consumption and thereby further simplify the treatment protocol. The purpose of the present randomized controlled trial was to analyse whether corifollitropin alfa administered on cycle day 4 instead of cycle day 2 results in a decrease in total rFSH consumption at the end of the follicular phase in controlled ovarian stimulation with GnRH antagonist cotreatment.

Materials and Methods

Study design

This study was a prospective randomized controlled trial conducted in women with a standard indication for ICSI between December 2011 and March 2013. All patients were recruited from the IVF outpatient clinic of the Centre for Reproductive Medicine at Universitair Ziekenhuis Brussel. Randomization took place at the outpatient clinic when the results of the pre-treatment hormonal analyses were discussed with the patient. A computer-generated list was used for randomization, assigned via numbered sealed envelopes. Each patient was allowed to participate in the study only once. Since no placebo treatment was used, this trial was not double-blind. The study received institutional review board approval by the local Institute's Ethics Committee, and written informed consent was provided by all subjects. The study was registered on the Clinical Trial website (www.clinicaltrials.gov, NCT01633580).

Subjects

All patients included in the study were women who were below 36 years of age on the day of randomization and who underwent a first or second treatment cycle of controlled ovarian stimulation with intracytoplasmic sperm injection (ICSI). Patients needed to have a regular menstrual cycle of 21–35 days and were presumed to be ovulatory, with a baseline serum FSH <12 IU/l (in the early follicular phase), and a normal ultrasound scan, i.e. presence of both ovaries, without evidence of abnormality within 6 months prior to randomization. A BMI of ≤29 was required with a body weight of >60 kg.

Patients with polycystic ovary syndrome or poor responder patients (development of <4 follicles in a previous IVF/ICSI cycle) were excluded from the study. Endometriosis ≥ grade 3 and endocrine or metabolic abnormalities (pituitary, adrenal, pancreas, liver or kidney) were also exclusion criteria.

Ovarian stimulation protocol

This trial was designed to compare two protocols using corifollitropin alfa with GnRH antagonist cotreatment for ovarian stimulation. One group

received the standard corifollitropin alfa protocol with administration of a single injection of 150 μg corifollitropin alfa (Elonva®; MSD; New Jersey, USA) on cycle day 2 (group CD2, control group). Patients enrolled into the study group were administered 150 μg corifollitropin alfa on cycle day 4 (group CD4). An outline of both treatment groups is presented in Fig. 1. From stimulation day 8 onwards, ovarian stimulation in both groups was continued with daily recombinant FSH injections of 200 IU (recFSH; Puregon®; MSD; New Jersey, USA), up until the day before hCG administration. Administration of the GnRH antagonist ganirelix (Orgalutran®; MSD; New Jersey, USA) was initiated on cycle day 7 in both treatment arms, at a daily dose of 0.25 mg, to prevent a premature LH surge. Suppression with GnRH antagonist was continued until the day of final oocyte maturation.

Human chorionic gonadotrophin (10 000 IU) (hCG; Pregnyl®; MSD; New Jersey, USA) was administered to induce final oocyte maturation as soon as three follicles with a diameter of ≥17 mm were visualized on ultrasonography. In case of an increased risk of ovarian hyperstimulation syndrome (OHSS), defined as at least 14 follicles of ≥ 11 mm as observed on ultrasound scan (Papanikolaou et al., 2006), 0.2 mg the GnRH agonist, triptorelin (Decapeptyl®; Ferring Pharmaceuticals Ltd; Copenhagen, Denmark), was administered instead of hCG to trigger ovulation. Oocyte retrieval was performed 36 h after hCG administration. In all patients, ICSI was performed to avoid any confounding factors, as well as to enable an assessment of the oocyte maturation rate. A single embryo was transferred 5 days after oocyte retrieval. For luteal phase support, 200 mg intravaginal micronized progesterone (Utrogestan®; Besins International, Paris, France) was given three times daily, starting on the day after oocyte retrieval, until 7 weeks of pregnancy. Patients who had been administered with a triptorelin ovulation trigger instead of hCG received a single injection of hCG 1500 IU, 1 h after oocyte retrieval and received modified luteal phase support, including progesterone as described above as well as 4 mg of estradiol valerate (Progynova®, BayerScheringPharma, Antwerp, Belgium) per day (Humaidan et al., 2006, 2010).

Assessments and hormone assays

Blood samples for hormonal analysis were collected every 2 days from cycle day 7 onwards, to investigate the impact of both protocols on the endocrine profile in the follicular phase. Automated immune analysis was performed to measure serum levels of FSH, LH, estradiol (E_2) and progesterone (P). This analysis was performed by the laboratory for hormonal analysis at the Universitair Ziekenhuis Brussel (Brussels, Belgium) by validated laboratory immunoassay methods (Electrochemiluminescence on Cobas 6000, Roche, Indianapolis, IN, USA). In addition, transvaginal ovarian ultrasound scans were performed every other day from cycle day 6 onwards, in order to assess follicular growth. In case of a positive pregnancy test (hCG > 20 IU/l), an ultrasound scan was done to determine the viability of the pregnancy. Fetal cardiac activity on ultrasound scan at 7 weeks of gestation was considered as a clinical ongoing pregnancy.

End-points

The primary end-point of the study was the total consumption of rFSH at the end of the follicular phase. Secondary end-points were mean number of COC, duration of stimulation and ongoing pregnancy rate. The implantation rate equals pregnancy rate, since only one embryo was transferred. Data about demographic and clinical characteristics, such as age, weight and height, were also collected.

Power calculation

Power calculation was performed based on a previous study, according to which, when the start of ovarian stimulation in the follicular phase was delayed by 3 days, a significant decrease of 187 IU in the total consumption of rFSH was observed, without affecting pregnancy outcomes (Blockeel et al., 2011). We assumed that such a difference would also be present when the administration of corifollitropin alfa was delayed. Consequently, we calculated that group sample sizes of 25 in each arm could achieve 80% power to detect a difference of 187 IU in the additional FSH dose needed following stimulation day 8, between the null hypothesis that in both groups the mean additional FSH dose needed is 400 and the alternative hypothesis that the mean FSH dose needed in the group commencing their treatment on cycle day 4 is 213 with estimated group standard deviations of 295 and 213 (for CD4 and CD2 groups) and a significance level (alpha) of 0.05.

Data analysis

Data are presented as percentages for count data and as means with standard deviation (SD) for continuous data. Differences between treatment arms are presented as P-values for between-group difference. These statistical comparisons for continuous data were assessed with t-test or Mann–Whitney U-test, dependent on the normality of the distribution. The x^2 test was performed to compare count data. Two-sided $P < 0.05$ was considered statistically significant.

Results

Subjects and characteristics

A total of 67 patients were assessed for eligibility to participate in this trial (Fig. 2). Of these patients, eight were excluded from the trial because they did not meet the inclusion criteria ($n = 4$) or declined to participate ($n = 4$). Eventually, 59 patients were randomized to one of the two treatment groups and 52 patients received the allocated intervention. For the remaining seven patients, the reasons for cancelling are listed in Fig. 2. In the CD2 group, one patient did not undergo embryo transfer due to absence of blastocyst development. In the CD4 group, one patient did not receive oocyte retrieval due to cyst formation, and three patients did not undergo embryo transfer because of total fertilization failure or absence of blastocyst development.

There were no significant differences between the groups with regard to demographic characteristics, as shown in Table I.
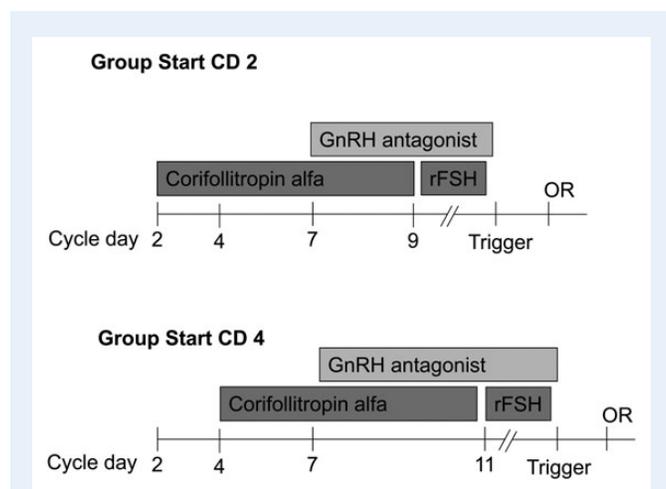

Figure 1 Schematic overview of treatment protocols in both groups. OR, oocyte retrieval; Trigger, trigger for final oocyte maturation.
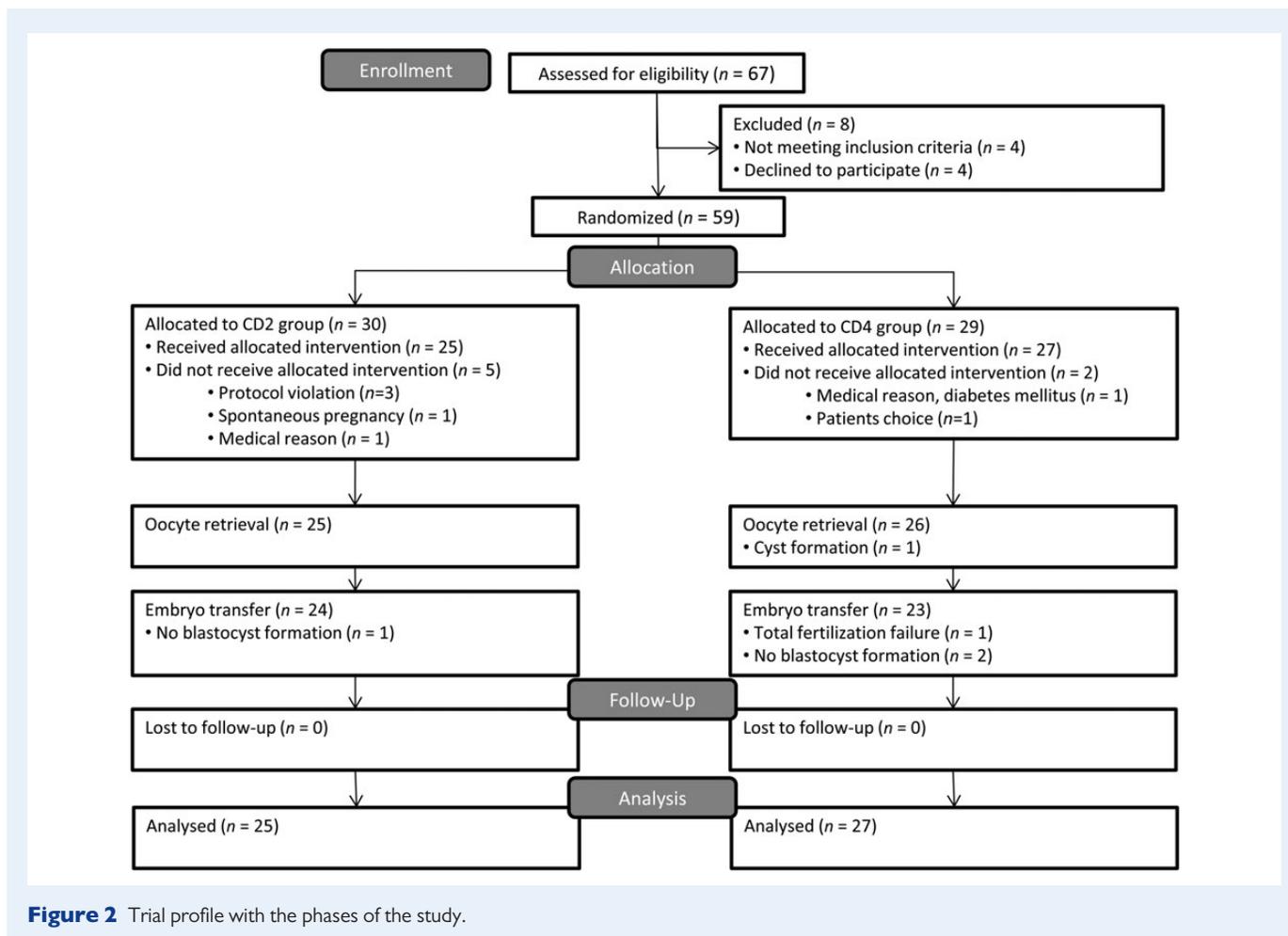
Figure 2 Trial profile with the phases of the study.

Stimulation and embryological characteristics

Details regarding the stimulation and embryological characteristics are presented in Table II. The total consumption of rFSH after corifollitropin alfa stimulation was significantly lower in the CD4 group compared with the CD2 group, 173 (255) IU versus 324 (276) IU ($P = 0.015$, mean difference -151 with CI -301 to -1). The duration of stimulation was significantly shorter in the CD4 group, namely 7.8 (1.2) days compared with 8.6 (1.4) days in the CD2 group ($P = 0.008$, mean difference -0.8 with 95% CI -1.6 to -0.1). The criteria for final oocyte maturation were reached in 20% (5/25) of the patients in the CD2 group compared with 56% (15/27) of the patients in the CD4 group after one single injection of corifollitropin alfa, obviating the need for additional rFSH injections. The number of cumulus-oocyte-complexes obtained was similar in both groups, as well as the number of MII oocytes and 2PN oocytes (Table II).

Final oocyte maturation was induced with GnRH agonist (Decapeptyl® 0.2 mg) instead of hCG (Pregnyl®) in two patients in the CD2 group and eight patients in the CD4 group, because of the risk for OHSS ($P = 0.078$; RR 3.7 with 95% CI 0.88–15.8). Nevertheless, a fresh embryo transfer was subsequently performed in these patients and they received modified luteal phase support as described above (Humaidan *et al.*, 2006, 2010).

Clinical outcome

The clinical outcomes of this trial are also shown in Table II. Ongoing pregnancy rates per started cycle of 48.0% in CD2 group and 40.7% in CD4 group were obtained, with no significant difference ($P = 0.60$, RR of 0.85 with 95% CI 0.46–1.56). Among the patients, who had been administered a GnRH agonist ovulation trigger instead of hCG, one patient in the CD2 group and four patients in the CD4 group became pregnant. The rates of positive hCG, biochemical pregnancy and miscarriage were similar between the two treatment groups. A biochemical pregnancy was defined as a positive hCG test without a clinical pregnancy. A miscarriage was defined as a pregnancy loss prior to 12 weeks of gestation.

Endocrinology

Figure 3 represents the serum levels of FSH, LH, E$_2$ and progesterone throughout the follicular phase. The serum hormone levels on the different days of the cycle were similar between the treatment groups, except for FSH levels on Day 7 and Day 9 and estradiol as well as LH levels on the day of trigger.

Table I Baseline characteristics.

	CD2 group (n = 25)	CD4 group (n = 27)
Demographics[a]		
Age (years)	30.5 (2.1)	30.7 (3.3)
Body weight (kg)	66.9 (6.8)	69.2 (7.9)
Height (m)	1.7 (0.1)	1.7 (0.1)
BMI (kg/m^2)	23.2 (2.1)	24.4 (3.3)
Parity, n (%)[b]		
One or more	2/25 (8.0)	4/27 (14.8)
Zero	23/25 (92.0)	23/27 (85.2)
Hormone levels[a]		
FSH (IU/l)	7.1 (2.1)	6.7 (1.8)
LH (IU/l)	5.9 (2.1)	5.7 (1.7)
Progesterone (μg/l)	0.6 (0.2)	0.7 (0.3)
Estradiol (ng/l)	37.3 (15.3)	40.4 (15.5)
AMH (ng/ml)	3.2 (2.2)	3.7 (2.2)
Indication, n (%)[b]		
Male factor	12/25 (48.0)	13/27 (48.1)
Tubal factor	2/25 (8.0)	2/27 (7.4)
Idiopathic	11/25 (44.0)	12/27 (44.4)

Baseline characteristics were similar in both treatment groups.
BMI, body mass index; FSH, follicle stimulating hormone; LH, lutenising hormone; AMH, anti-Mullerian hormone.
[a]Data are presented as mean (SD).
[b]Data are presented as number of cases including nominator and denominator values (percentage).

Discussion

The current study is the first randomized controlled trial in which ovarian stimulation with corifollitropin alfa is initiated on different days of the menstrual cycle. The findings of a previous study testing different days for the start of daily injections of recFSH have urged us to test the feasibility of a more flexible start in corifollitropin alfa antagonist cycles. The major finding of that trial was the presence of only subtle differences in the endocrine profile and follicular development between the two groups (Blockeel *et al.*, 2011).

The major conclusion of the current trial is that the administration of corifollitropin alfa on Day 4 instead of Day 2 results in a significant reduction of total recombinant FSH consumption (173 [255] IU versus 324 [276] IU; $P = 0.015$; mean difference −151 with CI −301 to −1).

To some degree, this reduction of total rFSH consumption could have been anticipated, since the protocol is based on the FSH window concept. Initially, this window is opened by the rise in endogenous FSH, followed by exogenous gonadotrophin administration during the late follicular phase (Fauser and Van Heusden, 1997; Verberg *et al.*, 2009b). This enables the endogenous FSH rise in the early follicular phase to be utilized, without medical intervention (Verberg *et al.*, 2009b). Moreover, it implies a more patient-friendly approach, with a significant reduction of treatment cost and patient discomfort (Macklon *et al.*, 2006; Heijnen *et al.*, 2007; Nargund and Frydman, 2007).

In our trial, after a single injection of corifollitropin alfa, the criteria for final oocyte maturation were reached in 20% (5/25) of the patients in the CD2 group compared with 56% (15/27) of the patients in the CD4 group, obviating the need for additional rFSH injections. This finding is important in terms of patient friendliness, since over half of the patients report that their everyday life is impacted by daily injections (Huisman

Table II Stimulation and embryological characteristics; Reproductive outcome.

	CD2 group (n = 25)	CD4 group (n = 27)	Mean difference[a] (95% CI)	P-value[b]
Stimulation characteristics				
Total dose of rFSH (IU)[c]	324 (276)	173 (255)	−151 (−301, −1)	**0.015**
Total duration of stimulation (days)[c]	8.6 (1.4)	7.8 (1.2)	−0.8 (−1.5, −0.1)	**0.008**
Days of GnRH antagonist administration[c]	4.7 (1.4)	5.4 (1.6)	0.7 (−0.1, 1.6)	**0.009**
Total length of the follicular phase[c]	9.4 (1.5)	10.6 (1.5)	1.1 (0.3, 2.0)	**0.009**
GnRH agonist trigger, n (%)	2 (8%)	8 (30%)	3.7 (0.88–15.8)[d]	0.078
Embryological characteristics[c]				
Number of COCs	12.8 (7.3)	14.7 (8.8)	1.8 (−2.7, 6.4)	0.461
Number of MII oocytes	10.2 (6.0)	11.6 (7.3)	1.4 (−2.4, 5.1)	0.533
Number of 2-PN oocytes	7.8 (5.4)	8.7 (6.3)	0.9 (−2.5, 4.2)	0.828
Number of vitrified blastocysts	1.8 (2.6)	2.8 (3.2)	1.0 (−0.7, 2.7)	0.303
Reproductive outcome[e]				
Positive hCG per cycle, n (%)	13/25 (52.0)	12/27 (44.4)	0.86 (0.49–1.50)[d]	0.59
Ongoing pregnancy rate per cycle, n (%)	12/25 (48.0)	11/27 (40.7)	0.85 (0.46–1.56)[d]	0.60

P-values in bold are statistically significant.
GnRH, gonadotrophin releasing hormone; rFSH, recombinant follicle stimulation hormone; COC, cumulus-oocyte complex; MII, metaphase II; 2-PN, 2 pronuclei.
[a]Mean difference and 95% CI for CD4 versus CD2.
[b]*P*-value for between-group difference from Mann–Whitney *U*-test.
[c]Data are presented as mean (SD).
[d]Relative risk and 95% CI for CD4 versus CD2.
[e]Data are presented as number of cases including nominator and denominator values (percentage).
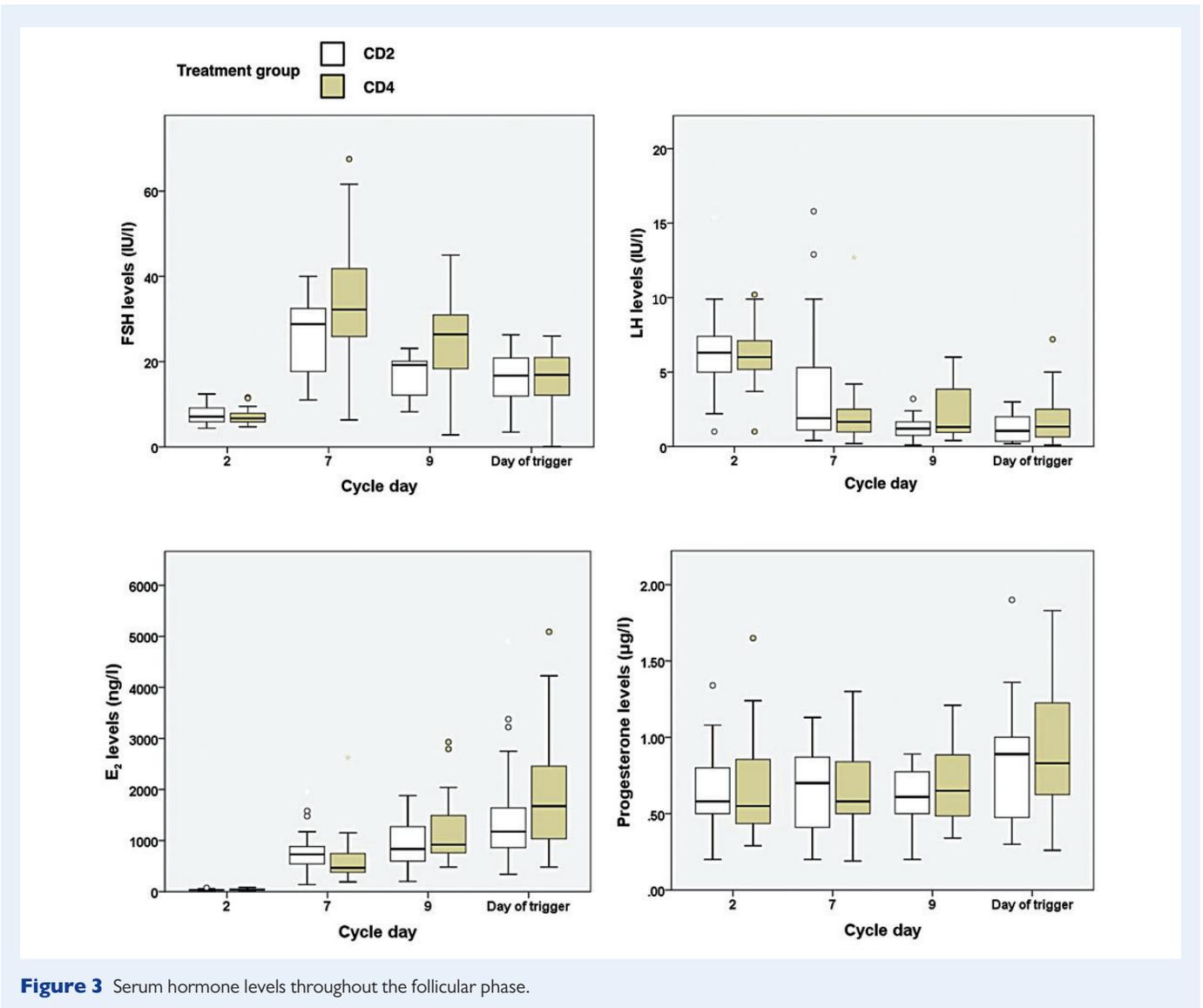
Figure 3 Serum hormone levels throughout the follicular phase.

et al., 2009). The reduction of the treatment burden may also have a positive impact on the overall treatment success since patients are more willing to continue the treatment following failed attempts (Verberg et al., 2008).

Additionally, in terms of cost reduction, the 150 IU decrease in total gonadotrophin consumption reported in this study results in a small decrease in the stimulation cost. In contrast, the consumption of GnRH antagonist was increased in the CD4 group due to a fixed timepoint of antagonist initiation and a longer follicular phase. The total reduction of treatment cost is therefore debatable.

An overall decrease in the duration of stimulation by almost 1 day was observed in the CD4 group, which was significant (mean difference −0.8, CI −1.5, −0.1). However, in this group, stimulation was initiated 2 days later compared with the CD2 group, resulting in a longer follicular phase. It has been demonstrated that a prolonged follicular phase is associated with higher progesterone levels, which may have a negative impact on the implantation potential due to endometrial advancement (Develioglu et al., 1999; Kolibianakis et al., 2005; Bosch et al, 2010). In the

current trial, similar serum levels of progesterone on the day of trigger (0.8 ± 0.4 μg/l in CD2 group versus 0.9 ± 0.4 μg/l in CD4 group, $P = 0.692$) were observed in both groups, despite a longer follicular phase in the CD4 group. Consequently, the increased mean length of the follicular phase of 10.8 days, which was observed in the CD4 group, did probably not result in endometrial advancement.

With regard to the safety of the used protocols, although no case of OHSS was observed, the sample size of the study was too small to detect any significant differences. Furthermore, the number of patients with more than 20 follicles >11 mm on the day of ovulation trigger and the number of patients triggered with a GnRH agonist due to a high risk of OHSS were higher in the CD4 group. These findings may imply that administration of corifollitropin alfa treatment on cycle day 4 instead of day 2 might result in an increased risk of OHSS. Nonetheless, this deserves further scrutiny in a much larger trial. Finally, we need to highlight that clinicians have now universally embraced the strategy of GnRH agonist triggering as a tool to prevent OHSS. Thus, by using GnRH agonist triggering and a bolus of 1500 IU hCG on the day of

oocyte retrieval to rescue the luteal phase, as we did in the current trial, the risk of OHSS can be significantly minimized (Humaidan et al., 2006, 2010).

The serum hormone levels of FSH were significantly higher on cycle days 7 and 9 in the CD4 group compared with the CD2 group. A possible explanation is that the peak FSH concentration is reached ~2 days after administration of corifollitropin alfa (Fauser et al., 2010). Accordingly, the peak FSH concentration in the CD4 group will be reached on cycle day 6 when compared with cycle day 4 in the CD2 group. By combining the rise in endogenous FSH and the administration of exogenous FSH only 2 days later in the follicular phase, FSH levels will remain above the threshold, keeping the FSH window open and will rescue a supplementary cohort of follicles from atresia (Fauser and Van Heusden, 1997).

A limitation of this trial is its low sample size. In this regard, the results show a significant decrease in total rFSH consumption. In addition, our results demonstrate similar pregnancy rates in the two treatment groups. However, this trial was not sufficiently powered to detect a significant difference in pregnancy rates. A much larger sample size would be needed to show any significant difference in terms of implantation rates, pregnancy rates and live birth rates. In addition, as a consequence of the small sample size, the range of the 95% confidence intervals of the outcome measures is wide. Moreover, patients included in this study were young (mean age of 30.5 years old), and were expected normal responders with a regular menstrual cycle; therefore, before application to all IVF patients could be considered, more experience needs to be gathered for more general conclusions to be made.

In conclusion, the results of this study show a significant reduction in total rFSH consumption when corifollitropin alfa is administered on cycle day 4 instead of cycle day 2, without affecting clinical outcome. However, based on the potentially increased risk of OHSS with corifollitropin alfa administration on Day 4, we cannot recommend this protocol yet for routine clinical practice.

Authors' roles

C.B. designed the concept and wrote the manuscript; N.P.P. analysed the data and revised the paper; L.D. drafted the manuscript and was responsible for acquisition of the data; M.D.B., V.V., A.v.d.V. and M.D.V. recruited the patients and revised the paper; and H.T. revised the paper and gave final approval of the version to be published.

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Conflict of interest

C.B. and N.P.P. have received honoraria from MSD. Otherwise the authors declare no conflict of interest regarding this study.

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