Human Reproduction, pp. 1–9, 2018
doi:10.1093/humrep/dey268

human reproduction

ORIGINAL ARTICLE ***Infertility***

Follicle stimulating hormone versus clomiphene citrate in intrauterine insemination for unexplained subfertility: a randomized controlled trial

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Submitted on March 2, 2018; resubmitted on June 15, 2018; accepted on July 24, 2018

STUDY QUESTION: Is FSH or clomiphene citrate (CC) the most effective stimulation regimen in terms of ongoing pregnancies in couples with unexplained subfertility undergoing IUI with adherence to strict cancellation criteria as a measure to reduce the number of multiple pregnancies?

SUMMARY ANSWER: In IUI with adherence to strict cancellation criteria, ovarian stimulation with FSH is not superior to CC in terms of the cumulative ongoing pregnancy rate, and yields a similar, low multiple pregnancy rate.

WHAT IS ALREADY KNOWN: FSH has been shown to result in higher pregnancy rates compared to CC, but at the cost of high multiple pregnancy rates. To reduce the risk of multiple pregnancy, new ovarian stimulation regimens have been suggested, these include strict cancellation criteria to limit the number of dominant follicles per cycle i.e. withholding insemination when more than three dominant follicles develop. With such a strategy, it is unclear whether the ovarian stimulation should be done with FSH or with CC.

STUDY DESIGN, SIZE, DURATION: We performed an open-label multicenter randomized superiority controlled trial in the Netherlands (NTR 4057).

[†]Members of the SUPER study group are listed in the Acknowledgements.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We randomized couples diagnosed with unexplained subfertility and scheduled for a maximum of four cycles of IUI with ovarian stimulation with 75 IU FSH or 100 mg CC. Cycles were cancelled when more then three dominant follicles developed. The primary outcome was cumulative ongoing pregnancy rate. Multiple pregnancy was a secondary outcome. We analysed the data on intention to treat basis. We calculated relative risks and absolute risk difference with 95% CI.

MAIN RESULTS AND THE ROLE OF CHANCE: Between July 2013 and March 2016, we allocated 369 women to ovarian stimulation with FSH and 369 women to ovarian stimulation with CC. A total of 113 women (31%) had an ongoing pregnancy following ovarian stimulation with FSH and 97 women (26%) had an ongoing pregnancy following ovarian stimulation with CC (RR = 1.16, 95% CI: 0.93–1.47, ARD = 0.04, 95% CI: −0.02 to 0.11). Five women (1.4%) had a multiple pregnancy following ovarian stimulation with FSH and eight women (2.2%) had a multiple pregnancy following ovarian stimulation with CC (RR = 0.63, 95% CI: 0.21–1.89, ARD = −0.01, 95% CI: −0.03 to 0.01).

LIMITATIONS, REASONS FOR CAUTION: We were not able to blind this study due to the nature of the interventions. We consider it unlikely that this has introduced performance bias, since pregnancy outcomes are objective outcome measures.

WIDER IMPLICATIONS OF THE FINDINGS: We revealed that adherence to strict cancellation criteria is a successful solution to reduce the number of multiple pregnancies in IUI. To decide whether ovarian stimulation with FSH or with CC should be the regimen of choice, costs and patients' preferences should be taken into account.

STUDY FUNDING/COMPETING INTEREST(S): This trial received funding from the Dutch Organization for Health Research and Development (ZonMw). Prof. Dr B.W.J. Mol is supported by a NHMRC Practitioner Fellowship (GNT1082548). B.W.M. reports consultancy for Merck, ObsEva and Guerbet. The other authors declare that they have no competing interests.

TRIAL REGISTRATION NUMBER: Nederlands Trial Register NTR4057.

TRIAL REGISTRATION DATE: 1 July 2013.

DATE OF FIRST PATIENT'S ENROLMENT: The first patient was randomized at 27 August 2013.

Key words: IUI / ovarian stimulation / FSH / clomiphene citrate / unexplained subfertility / cancellation criteria

Introduction

Annually, more than 70 million couples worldwide fail to conceive within 1 year of regular unprotected intercourse (Boivin *et al.*, 2007). At present, in many countries the first line treatment for couples diagnosed with unexplained subfertility is IUI with ovarian stimulation (Calhaz-Jorge *et al.*, 2017; The Practice Committee of the American Society for Reproductive Medicine., 2006). The downside of ovarian stimulation is the high multiple pregnancy risk with its increased risk of serious neonatal morbidity, neonatal mortality and maternal morbidity (Guzick *et al.*,1999; Ombelet *et al.*, 2006).

According to a Cochrane review published in 2007, FSH is the drug of choice (Cantineau and Cohlen, 2007). The meta-analysis showed statistically significant increased pregnancy rates in favour of FSH compared to ovarian stimulation with clomiphene citrate (CC) in women undergoing IUI (seven studies, 556 women, odds ratio [OR] = 1.8, 95% CI: 1.2–2.7), while the—limited—data on multiple pregnancy rates were similar between FSH and CC and not allowing any conclusions (three studies, 338 women, OR = 0.53, 95% CI: 0.15–1.86) (Cantineau and Cohlen, 2007). Since then, a recent large RCT, comparing FSH with CC in IUI also showed a statistically significant increase in live birth rates compared to CC, but at the cost of 25 twins and six triplets among 301 women (10%) undergoing ovarian stimulation with FSH, while there were 8 twins among 300 women (3%) undergoing ovarian stimulation with CC (Diamond *et al.*, 2015). These high multiple pregnancy rates are no longer acceptable in modern infertility treatment.

To reduce the risk on multiple pregnancy, new ovarian stimulation regimens have been suggested, the quintessence of which are strict cancellation criteria to limit the number of dominant follicles per cycle, i.e. withholding insemination when more than three dominant follicles develop (Rumste van *et al.*, 2006; Rumste van *et al.*, 2008). The Cochrane review included one study that compared FSH to CC in a stimulation regimen with adherence to strict cancellation criteria (Dankert *et al.*, 2007). This study found similar pregnancy rates (34% for FSH versus 38% for CC, relative risk [RR] = 0.90, 95% CI: 0.57–1.41) and low multiple pregnancy rates (4% per cycle for FSH versus 7% per cycle for CC, RR = 0.63, 95% CI: 0.06–6.53), but with only 138 included couples this study was underpowered (Dankert *et al.*, 2007).

We therefore aimed to study, in a well powered randomized clinical trial the effectiveness of ovarian stimulation with 75 IU FSH compared to ovarian stimulation with 100 mg CC, in an IUI programme with adherence to strict cancellation criteria, i.e. cancellation of the cycle when more than three dominant follicles develop in women undergoing IUI, within a time horizon of 6 months.

Materials and Methods

Study design

This study was an open-label multicenter, randomized controlled superiority trial positioned in the Dutch Consortium for Healthcare Evaluation in Obstetrics and Gynaecology (https://zorgevaluatienederland.nl/associations/1). We recruited couples between July 2013 and March 2016. The Medical Ethical Committee of the Academic Medical Centre and the Dutch Central Committee on Research involving Human Subjects approved this study (CCMO NL 43131-018-13) and the board of directors of each participating site approved local execution (NTR4057). The protocol (see Supplementary material) was published previously (Danhof *et al.*, 2017).

Study population

Couples diagnosed with unexplained infertility were eligible for the study. Unexplained subfertility was defined as a failure to conceive after one year of regular unprotected intercourse and a prewash total motile sperm count (TMSC) of at least 3 million (NICE clinical guideline). The inclusion criteria were female age between 18 and 43 years, regular menstrual cycle, at least one side tube patency and a TMSC of at least 3 million (NICE clinical guideline). If women were under 38 years of age, their 12 months prognosis on natural conception according to the model of Hunault had to be lower than 30% (Hunault *et al.*, 2004; Steeg van der *et al.*, 2007). Women were also eligible for inclusion after 6 months of failed expectant management. Women undergoing donor sperm treatment were eligible if they were below 35 years of age, had a regular menstrual cycle, with a least one-sided tubal patency, and had had 12 months of failed intracervical or IUI without ovarian stimulation or were above 35 years of age, had a regular menstrual cycle, with a least one-sided tubal patency and had 6 months of failed intracervical or IUI without ovarian stimulation.

Women with double sided tubal pathology, polycystic ovary syndrome, irregular cycles or other endocrine disorders were not eligible.

Interventions

We treated couples for a maximum of four cycles or until pregnancy occurred within a time horizon of 6 months. In the first treatment cycle, all women were seen for a baseline visit for a transvaginal ultrasound examination on the third, fourth or fifth day of the menstrual cycle. Women were not allowed to start the treatment cycle if one or more ovarian cysts of >20 mm were seen. In the experimental arm women started with daily subcutaneous injections of 75 IU FSH on Day 3, 4 or 5 of the menstrual cycle and continued these injections until the day of ovulation triggering (Dankert *et al.*, 2007). In the standard arm women started with 100 mg CC on Day 3, 4 or 5 of the menstrual cycle. The tablets were administered orally and stopped after 5 days of daily intake.

In both interventions, we monitored follicular development by transvaginal ultrasound. We triggered ovulation with 5000 IU hCG or with 250 µg recHCG if there was at least one dominant follicle with a mean diameter of 16–18 mm a maximum of three follicles of ≥14 mm. At the final ultrasound examination before ovulation triggering, we measured the total number of follicles their diameters and the endometrial thickness. We cancelled the cycle if more than three follicles with a diameter of ≥14 mm or five follicles with a diameter of ≥12 mm was seen at transvaginal ultrasound, regardless of the endometrial thickness. In these cycles, we advised the couples to have protected or no intercourse. We scheduled IUI 36–42 h after ovulation triggering. On the day of insemination, the partner provided a semen sample after a minimum of 2 days of sexual abstinence. The semen was processed according to local protocol. In case of donor sperm treatment, donor semen was thawed and processed according to local protocol.

Women who did not conceive were scheduled for the next insemination cycle. In case of monofollicular growth, the dose of FSH was increased by 37.5 IU per day or the dose of CC was increased by 50 mg per day in the next cycle. If a cycle was cancelled due to the development of more than three dominant follicles, the dose of FSH was decreased by 37.5 IU per day or the dose of CC was decreased by 50 mg per day in the next cycle.

We treated couples for a maximum of four cycles or until pregnancy occurred within a time horizon of 6 months.

Clinical and ongoing pregnancies were confirmed by ultrasound.

Outcome measures

The primary outcome was ongoing pregnancy per woman, defined as a positive heartbeat at or beyond 12 weeks of gestation. Pregnancies that occurred within the first 6 months after randomization counted for assessment of the primary outcome.

Secondary outcomes per started cycle were cancellation rates, number of cycles with a single follicle, total number of follicles ≥14 mm at the time of ovulation triggering, and secondary outcomes per women were multiple pregnancy defined as registered heartbeat of at least two fetuses at 12 weeks of gestation, time to ongoing pregnancy, clinical pregnancy, defined as any registered foetal heartbeat on ultrasound, miscarriage, defined as pregnancy loss at a gestational age of 20 weeks or less, ectopic pregnancy and live birth.

Serious adverse events were reported to the trial coordinator.

Sample size calculation

We designed the study as a superiority trial. In our original sample size, we assumed the ongoing pregnancy rate was 35% after a maximum of 4 months of IUI with ovarian stimulation with CC. To be able to show a difference of 17.5% between ovarian stimulation with FSH and CC, we needed to recruit 182 couples per treatment arm with a two-sided alpha of 5% and a beta of 20%. Accounting for a 10% drop-out rate, we needed to recruit 404 women. In May 2015, we extended the sample size based on new available data. We applied an ongoing pregnancy rate of 25% following CC after four cycles and within 6 months (Bensdorp *et al.*, 2015). To be able to show a minimally clinical relevant difference of 10% between ovarian stimulation with FSH and CC, we needed to recruit 329 couples per treatment arm with a two-sided alpha of 5% and a beta of 20%. Accounting for a 10% drop-out rate, we needed to recruit 732 women.

Randomization and masking

Eligible women were informed about the study by their doctor or by a dedicated research nurse. After written informed consent women were randomized using a central password protected Internet-based randomization programme. The randomization list had been prepared by an independent statistician with a variable block size with randomly selected block sizes that varied between two, four and six. There was no stratification. Neither the recruiters nor the trial project group could access the randomization sequence.

Statistical analysis

We analysed all outcomes on an intention to treat basis. We also performed a per protocol analysis for the primary outcome and time to ongoing pregnancy, which was not pre-planned. We expressed all outcomes per couple randomized unless otherwise stated. We estimated differences in the primary and secondary outcomes as relative risks and absolute risk difference with 95% CI and used a Chi square test for formal analysis. We assessed the association between multiple pregnancy and follicle count using logistic regression models. We constructed Kaplan–Meier curves for the time to ongoing pregnancy. Pregnancies were timed at conception and a few women had undetected spontaneous pregnancies at randomization. These were included in the intention to treat analysis and appear as pregnancies at zero time (Lachin, 2000). We considered *P* values below 0.05 to indicate statistical significance.

Study oversight and role of the funding source

This trial was funded by the Netherlands Organization for Health Research and Development (ZonMw) (Health Care Efficiency Research; project number 80-83600-98-10192). The sponsor of the study had no role in study design, data collection, data analysis, data interpretation or writing the report. The corresponding author confirms to have had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 2013 and March 2016, we recruited 738 couples in 24 fertility clinics participating in the Dutch Consortium for Healthcare Evaluation in Obstetrics and Gynaecology (https://zorgevaluatienederland.nl/associations/1). A total of 369 couples were allocated to ovarian stimulation with FSH and 369 couples to ovarian stimulation with CC. The baseline characteristics were well balanced between couples that were randomized to FSH and those to CC (Table I). In the FSH treatment arm 338 couples received the allocated intervention and in the CC-treatment arm 346 couples (Fig. 1).

Pregnancy outcomes are presented in Table II. Within the 6 months treatment horizon, there were 113 ongoing pregnancies (31%) in the FSH treatment arm and 97 ongoing pregnancies (26%) in the CC-treatment arm (RR = 1.16, 95% CI: 0.93–1.47). The absolute risk difference for FSH compared to CC was 0.04 with a 95% CI of −0.02 to 0.11. In the per protocol analysis, there were 82 (25%) ongoing pregnancies in the FSH treatment arm and 70 ongoing pregnancies (21%) in the CC-treatment arm (RR = 1.19, 95% CI: 0.90–1.57). In the FSH treatment arm, 17 women conceived naturally before they could start with IUI and nine women in between treatment cycles. In the CC-treatment arm, 15 women conceived naturally before they could start with IUI and seven women in between treatment cycles.

The number of twin pregnancies was 5 (1.4%) in the FSH treatment arm and 8 (2.2%) in the CC-treatment arm (RR = 0.63, 95% CI: 0.21–1.89, absolute rate difference [ARD] = −0.01, 95% CI: −0.03 to 0.01). There were no higher order multiple pregnancies. The number of live births was 105 (28%) in the FSH treatment arm and 92 (25%) in the CC-treatment arm (RR = 1.14, 95% CI: 0.90–1.45).

Ovarian stimulation outcomes are shown in Table III. There was no difference in the cancellation rate due to the development of more than three dominant follicles between ovarian stimulation with FSH and ovarian stimulation with CC (FSH n = 115, CC n = 101, RR = 1.06, 95% CI: 0.91–1.23). Other reasons for cycle cancellation were impaired folliculogenesis (FSH n = 32, CC n = 39), personal circumstances (FSH n = 9, CC n = 11) and other medical reasons (FSH n = 9, CC n = 2). There were slightly more cycles with monofollicular growth in ovarian stimulation with FSH compared to ovarian stimulation with CC (RR = 1.12, 95% CI: 0.99–1.27).

Table I Baseline characteristics of the participating couples.*

Characteristics	FSH (n = 369)	Clomiphene citrate (n = 369)
Mean female age (years)	33.1 ± 5.6	33.1 ± 4.6
Primary subfertility	273 (74)	268 (73)
Diagnosis of subfertility		
One-sided tubal pathology	28 (8)	38 (10)
Mild male subfertility	16 (4)	14 (4)
Median duration of subfertility (months)	24.0 (19.0–33.0)	24.0 (19.0–32.0)
Current smokers	61 (17)	55 (15)
Mean BMI (kg/m^2)	24.2 ± 4.5	23.8 ± 3.9
Median total motile sperm count (×10^6)	48.0 (22.0–96.8)	58.4 (25.9–118.0)

*Data are n (%), mean (SD) or median (quartiles). There were no significant differences (P < 0.05) between the two groups in any of the baseline characteristics.

The multiple pregnancy rate was 0.2% after one dominant follicle and 0.7% after two dominant follicles (OR = 3.3, 95% CI: 0.7–16.5), while it increased to 1.8% following three dominant follicles (OR = 8.0 compared to one dominant follicle, 95% CI: 1.5–41.6)

In the intention to treat analysis, there was no difference in time to ongoing pregnancy between ovarian stimulation in the FSH treatment arm (P = 0.30) (Fig. 2). Likewise there was no difference in time to ongoing pregnancy between ovarian stimulation with FSH in the per protocol analysis (P = 0.30) (Fig. 3).

Discussion

In this multicenter, non-blinded, randomized controlled superiority trial, we found no statistically significant difference between FSH and CC in couples with unexplained subfertility undergoing IUI with ovarian stimulation in a regimen of strict cancellation criteria, in terms of ongoing pregnancies, and a low multiple pregnancy rate. Our cumulative ongoing pregnancy rate of around 30% after four cycles of IUI within 6 months is comparable to the rates reported in a previous study, but we were able to reduce the high multiple pregnancy rate of 32% described in that study to 4% per cycle, which can be translated to a reduction of 11% to1% per woman (Diamond et al., 2015).

We feel that our findings are of importance, since IUI with ovarian stimulation is -as a first line treatment for couples with unexplained subfertility, applied worldwide on a large scale, as it is considered to be effective, but less invasive, less burdensome and less costly compared to IVF (Bensdorp et al., 2015). The new stimulation regimen described here can reduce the number of multiple pregnancies to such low levels that IUI with ovarian stimulation can now be regarded as a safe treatment if strict cancellation criteria are met.

The strength of this study is that, in our opinion, we had adequate power to show that there is no statistically significant difference between FSH and CC in IUI in terms of cumulative ongoing pregnancy rates ([ARD] = 0.04, 95% CI: −0.02 to 0.11), with both strategies leading to very low multiple pregnancy rates when adhering to strict cancellation criteria. This confirms the previous findings of the smaller study also aiming to reduce multiple pregnancy rate by means of adherence to strict cancellation criteria (Dankert et al., 2007) Our per protocol analysis showed the same results as the intention to treat analysis, suggesting that a switch in treatment did not affect the cumulative ongoing pregnancy rates, thereby underpinning the robustness of the data. We provided cumulative pregnancy outcomes because they give insight in the actual way of conceiving and represent true life. We were thus able to detect that as many as 48 (23%) ongoing pregnancies were conceived without medical assistance; 32 couples conceived before the start of IUI and 16 couples conceived in between treatment cycles. This again emphasizes that some of these couples, even though their prognosis of a natural conception was low and even though they were undergoing treatment, still manage to become pregnant in cycles without or in between treatment. This is important data to share with the couples in counselling.

Although our study is replication research, replication studies are fundamental in establishing progress, as they provide a more

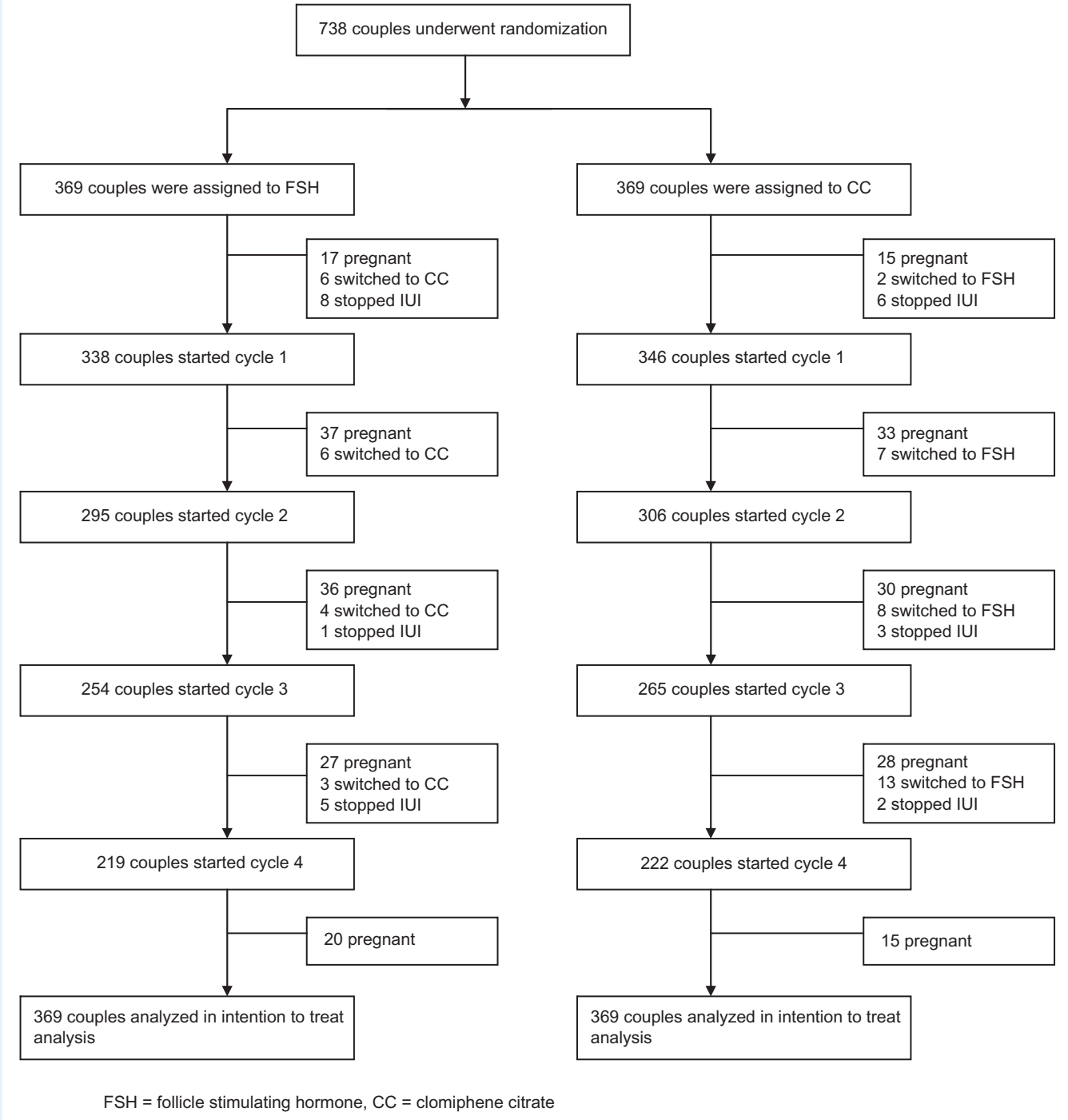


Figure 1 Study flowchart.

respectable basis of knowledge (Ioannidis, 2013). Pooling the data of our study and those of the smaller similar study, we find an ongoing pregnancy rate of 30% for FSH and of 27% for CC in IUI (RR = 1.13, 95% CI: 0.91–1.40) and a multiple pregnancy rate of 1% for FSH and of 2% for CC in IUI (RR = 1.65, 95% CI: 0.60–4.50) (Dankert *et al.*, 2007).

Several limitations also need mentioning. According to ESHRE guidelines, live birth rate should be the primary outcome and we chose ongoing pregnancy as such. This is because ongoing pregnancy is seen as a valid and cost effective outcome measure of effectiveness (Clarke *et al.*, 2010; Braakhekke *et al.*, 2014). Nevertheless, we also do report on live birth rate. We were not able to blind this study due to the type of interventions. We consider it unlikely that this has introduced performance bias, since pregnancy outcomes are objective outcome measures. Another potential limitation of this study is that we based our sample size calculation on a 10% difference in ongoing pregnancy rate

Table II Pregnancy outcomes per woman randomized.*

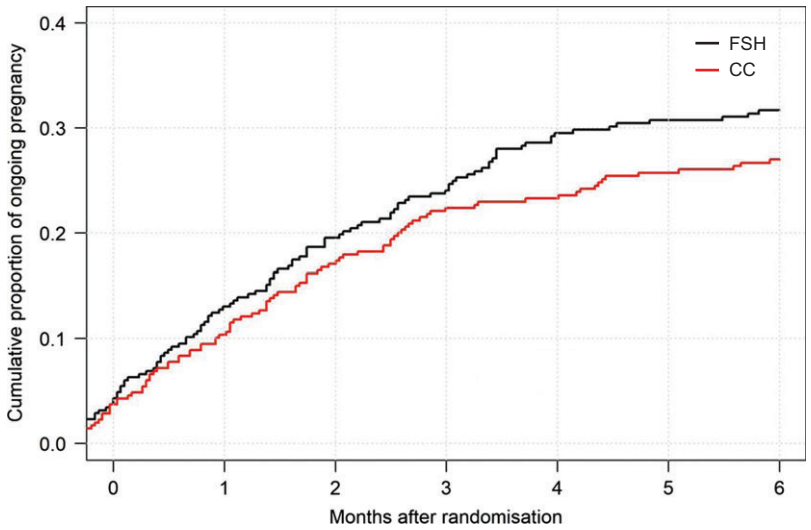
	FSH ($n = 369$)	Comiphene citrate ($n = 369$)	Relative risk (95% CI)
Ongoing pregnancy	113 (31)	97 (26)	1.16 (0.93–1.47)
Multiple pregnancy	5 (1)	8 (2)	0.63 (0.21–1.89)
Live birth	105 (28)	92 (25)	1.14 (0.90–1.45)
Clinical pregnancy	115 (32)	101 (27)	1.14 (0.91–1.43)
Miscarriage	32 (9)	31 (8)	1.03 (0.64–1.66)
Ectopic pregnancy	2 (1)	3 (1)	0.80 (0.38–1.64)

*n (%).

Table III Ovarian stimulation outcomes on a cycle level.*

	FSH ($n = 1162$)	Clomiphene citrate ($n = 1212$)	Relative Risk (95% CI)	*P*
Mean total dosage ovarian stimulation per cycle†	586 IU (328.9)	406 mg (423.1)	–	–
Mean duration of stimulation (days)†	8.1 (3.18)	4.9 (3.74)	–	–
Mean number of follicles ≥14 mm at day of ovulation triggering	1.8 (1.43)	1.9 (1.11)	–	0.52
Cycles with monofollicular growth	352 (30)	328 (27)	1.12 (0.99–1.27)	–
Cancellation rate	165 (14)	153 (13)	1.12 (0.92–1.38)	–
Due to multifollicular growth	115 (70)	101 (66)	1.06 (0.91–1.23)	–

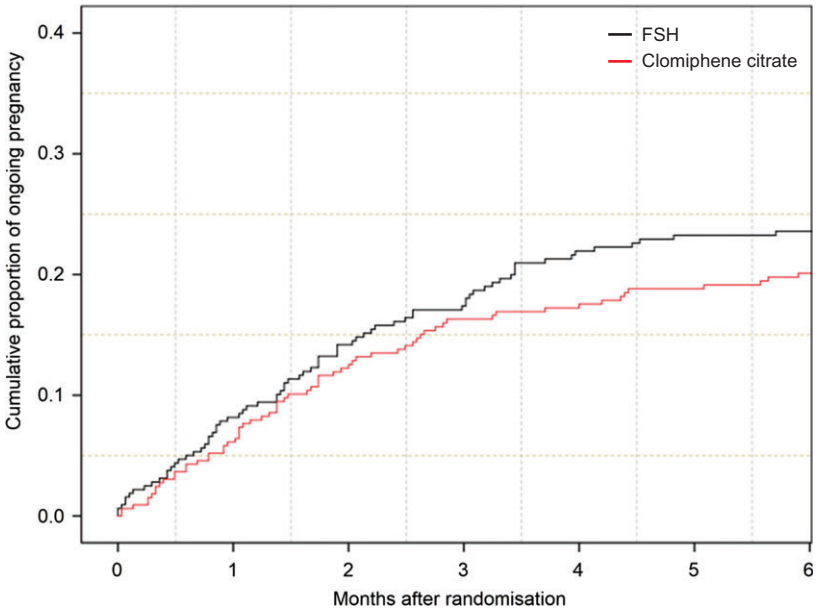
*Data are *n* (%), mean (SD).
†No *P* value was calculated since these outcomes are related to the type of ovarian stimulation.



FSH = follicle stimulating hormone, CC = clomiphene citrate

Numbers at risk							
	0	1	2	3	4	5	6
FSH	369	338	291	274	254	247	244
CC	369	346	301	284	272	264	262

Figure 2 Time to ongoing pregnancy.



Numbers at risk							
	0	1	2	3	4	5	6
FSH	333	333	280	262	242	236	233
CC	344	344	293	276	264	256	254

Figure 3 Time to ongoing pregnancy—per protocol analysis.

between the two stimulation agents. We can thus not rule out smaller differences. Future studies should thus be designed with a larger sample size to prove or reject any smaller difference.

Our results are widely generalizable, since the baseline characteristics of our patient population were similar to those reported in other international studies on IUI for unexplained subfertility (Cantineau and Cohlen, 2007; Bensdorp *et al.*, 2015; Peeraer *et al.*, 2015). As far as BMI is concerned, the mean BMI in studies from Europe are lower than those in the USA (Diamond *et al.*, 2015).

With our regimen, the core of which is adherence to strict cancellation criteria, we were able to yield an average of two dominant follicles in both treatment arms. The strong association between an increase in the number of dominant follicles and multiple pregnancy, provide the rationale for this type of ovarian stimulation practice and explains its good safety profile (Rumste van *et al.*, 2008). The question then rises whether ovarian stimulation with FSH or with CC should be the regimen of choice. A formal cost-effectiveness analysis will answer this question. Another strategy suggested to avoid multiple pregnancies in IUI for unexplained subfertility, has been selective ultrasound guided follicle aspiration prior to IUI when more than three dominant follicles develop (Stoop *et al.*,2010; Peeraer *et al.*,2015). Although this strategy has indeed been proven to be effective in reducing multiple pregnancies, it has never been compared to a strategy with adherence to strict cancellation criteria with respect to preference, burden and costs. Since patient care involves more domains than effectiveness, data are currently insufficient to advise this aspiration approach (Dancet *et al.*,2014).

Diamond *et al.* compared Letrozole to FSH and CC with multiple pregnancy as the primary outcome. The administration of Letrozole resulted in a similar low multiple pregnancy rate when compared to CC, but at the cost of live birth rates when compared to FSH. The live birth rates were 32% after FSH, 23% after CC and 19% after Letrozole (Diamond *et al.*, 2015). At present, we cannot draw any firm conclusions on the effectiveness of Letrozole as a stimulation regimen in IUI for unexplained subfertility. Further studies are needed to investigate whether Letrozole can be considered in IUI for unexplained subfertility.

The discussion on single embryo transfer in IVF to reduce multiple pregnancies with its inherent risks for the mother and the offspring has taken years, when finally, single embryo transfer was successfully implemented and even today embryo transfer of more than one embryo is still common practice (Land and Evers, 2003, 2004; van Montfoort *et al.* 2005). Our study provides the protocol to also reduce multiple pregnancies in IUI with ovarian stimulation. Hopefully, this protocol will soon be implemented in clinical practice, regardless of the setting in which reproductive services are provided. In conclusion, we have shown that there is no statistically significant difference between an ovarian stimulation regimen with FSH compared to CC and adherence

to strict cancellation criteria in couples with unexplained subfertility undergoing IUI in terms of ongoing pregnancies, live births and time to pregnancy, while yielding similar and low multiple pregnancy rates.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Acknowledgements

We thank all couples that participated in the trial, the hospitals and their staff, the research nurses and the staff of the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology for logistic support and the staff of the Clinical Research Unit of the Academic Medical Center, Amsterdam for their help with the randomization programme and the online database. The SUPER study group consist of: N.A. Danhof, MD. Centre for Reproductive Medicine, Academic Medical Centre, Amsterdam Madelon van Wely, PhD. Centre for Reproductive Medicine, Academic Medical Centre Amsterdam. S. Repping, Prof. Centre for Reproductive Medicine, Academic Medical Centre, Amsterdam Carolien Koks, MD PhD. Department of Obstetrics and Gynaecology, Máxima Medical Centre, Veldhoven. J.G., MD PhD. Department of Obstetrics and Gynaecology, Kennemer hospital, Haarlem. Jan Peter de Bruin, MD PhD. Jeroen Bosch Hospital, Department of Obstetrics and Gynecology, Den Bosch. B.J. Cohlen, MD PhD. Isala Hospital. Department of Obstetrics and Gynecology, Zwolle. D.P. van der Ham, MD PhD. Department of Obstetrics and Gynaecology, Martini Hospital, Groningen N. Klijn, MD. Department of Obstetrics and Gynaecology, Leiden University Medical Centre, Leiden. M.H.A. van Hooff, MD PhD. Department of Obstetrics and Gynaecology Sint Franciscus Gasthuis, Rotterdam. F.J.M. Broekmans, Prof. Centre for Reproductive Medicine, University Medical Centre Utrecht, Utrecht. K. Fleischer, MD PhD, Centre for Reproductive Medicine, Radboud University Medical Centre, Nijmegen. C.A.H. Janssen, MD PhD, Department of Obstetrics and Gynaecology Groene Hart Hospital, Gouda. J.M. Rijn-van Weert, MD PhD, Department of Obstetrics and Gynaecology Noord West Groep Alkmaar, Alkmaar. J. van Disseldorp, Department of Obstetrics and Gynaecology, St. Antonius hospital Nieuwegein, Nieuwegein. M. Twisk, MD PhD, Department of Obstetrics and Gynaecology MC Zuiderzee, Lelystad. M.A.F. Traas, MD PhD, Department of Obstetrics and Gynaecology Gelre Hospital, Apeldoorn. M.F.G. Verberg, MD PhD, Fertility Clinic Twente. M.J. Pelinck, MD PhD, Department of Obstetrics and Gynaecology Scheper Hospital, Emmen. J. Visser, MD PhD, Department of Obstetrics and Gynaecology Amphia, Breda D.A.M. Perquin, MD PhD, Department of Obstetrics and Gynaecology Medical Centre Leeuwarden, Leeuwarden. D.E.S. Boks, MD PhD, Department of Obstetrics and Gynaecology, Spaarne Hospital, Hoofddorp. H.R. Verhoeve, MD PhD. Department of Obstetrics and Gynaecology, OLVG Amsterdam-Oost. C.F. van Heteren, MD PhD. Department of Obstetrics and Gynaecology, Canisius Wilhelmina Hospital, Nijmegen. A. Sluijmer, MD PhD. Department of Obstetrics and Gynaecology Wilhelmina Hospital, Assen. B.W.J. Mol, Prof. Monash University, Monash Medical Centre, Australia. F. van der Veen, Prof. Center for Reproductive Medicine, Academic Medical Center, Amsterdam. M.H. Mochtar, MD PhD Centre for Reproductive Medicine, Academic Medical Center, Amsterdam.

Authors' roles

N.D. is responsible for the overall logistical aspects of the trial and drafted the paper. M.M., Fv.dV. and M.W. designed the trial and were responsible for the development of the protocol. All authors contributed to the protocol and approved the final version of the article.

Funding

Dutch Organization for Health Research and Development (ZonMw) (Health Care Efficiency Research; project number 80-83600-98-10192). The Eudract number for this trial is 2013-001034-18.

Conflict of interest

Prof. Dr. B.W.J. Mol reports consultancy for Merck, ObsEva and Guerbet and is supported by a NHMRC Practitioner Fellowship (GNTI082548). The other authors declare that they have no competing interests.

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