

BMJ Open The SUPER study: protocol for a randomised controlled trial comparing follicle-stimulating hormone and clomiphene citrate for ovarian stimulation in intrauterine insemination

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ABSTRACT

Objective To study the effectiveness of four cycles of intrauterine insemination (IUI) with ovarian stimulation (OS) by follicle-stimulating hormone (FSH) or by clomiphene citrate (CC), and adherence to strict cancellation criteria.

Setting Randomised controlled trial among 22 secondary and tertiary fertility clinics in the Netherlands.

Participants 732 women from couples diagnosed with unexplained or mild male subfertility and an unfavourable prognosis according to the model of Hunault of natural conception.

Interventions Four cycles of IUI–OS within a time horizon of 6 months comparing FSH 75 IU with CC 100 mg. The primary outcome is ongoing pregnancy conceived within 6 months after randomisation, defined as a positive heartbeat at 12 weeks of gestation. Secondary outcomes are cancellation rates, number of cycles with a monofollicular or with multifollicular growth, number of follicles >14 mm at the time of ovulation triggering, time to ongoing pregnancy, clinical pregnancy, miscarriage, live birth and multiple pregnancy. We will also assess if biomarkers such as female age, body mass index, smoking status, antral follicle count and endometrial aspect and thickness can be used as treatment selection markers.

Ethics and dissemination The study has been approved by the Medical Ethical Committee of the Academic Medical Centre and from the Dutch Central Committee on Research involving Human Subjects (CCMO NL 43131-018-13). Results will be disseminated through peer-reviewed publications and presentations at international scientific meetings.

Trial registration number NTR4057.

BACKGROUND

More than 70 million couples worldwide fail to conceive within 1 year of regular unprotected intercourse.¹ At present, the first-line

Strengths and limitations of this study

- This is a multicentre randomised controlled trial.
- We aim to give cumulative pregnancy rates.
- This is an open-label study, which can be a limitation

treatment for couples diagnosed with unexplained or mild male factor subfertility is intrauterine insemination (IUI) with ovarian stimulation (OS).² OS aims to increase the number of dominant follicles per cycle, based on the concept that this will increase pregnancy rates.³

OS in the context of IUI for unexplained subfertility or mild male subfertility can be achieved with follicle-stimulating hormone (FSH) or with clomiphene citrate (CC). FSH is administered as a subcutaneous injection from cycle day 3, 4 or 5 until the ovulation trigger. CC is given orally during 5 days starting from cycle days 3 to 5. FSH appears to be the most effective regimen compared with CC in terms of pregnancy rate per couple.^{4 5} Pooling the results of seven randomised controlled trials (RCTs) among 556 patients, a Cochrane review found significantly increased pregnancy rates per couple in IUI–OS with FSH compared with IUI–OS with CC. The pregnancy rate per couple was 28% when using FSH and 19% when using CC (OR 1.8, 95% CI 1.2 to 2.7).⁴ On the basis of these results, the authors recommended FSH in IUI–OS.⁴ This advice overlooks the high multiple pregnancy rate of around 32% per conception cycle after FSH versus 8% per

conception cycle after CC.^{3–5} Multiple pregnancies are associated with an increased risk of serious neonatal and maternal morbidity.⁶

To reduce this risk, IUI–OS with strict cancellation criteria, that is, when more than three dominant follicles develop, has been suggested. An earlier study comparing IUI with FSH and strict cancellation criteria to IUI with CC showed a multiple pregnancy rate of 6% for similar cumulative ongoing pregnancy and live birth rates.⁷ Since this study was underpowered and the actual number of follicles at ovulation triggering was not reported, there is still no robust evidence on the effectiveness and safety of this strategy in IUI.

We propose to compare in a randomised, superiority trial the costs and effectiveness of IUI–FSH 75 IU and IUI–CC 100 mg and adherence to strict cancellation criteria. We will collect information on total number of follicles at ovulation triggering, cancellation rate and on biomarkers such as female age, body mass index (BMI), smoking status, antral follicle count (AFC) and endometrial aspect and thickness to identify any treatment selection markers to open up the possibility of a personalised approach.

OBJECTIVE

To study the effectiveness of four cycles of IUI–FSH 75 IU compared with IUI–CC 100 mg, and adherence to strict cancellation criteria, that is, when more than three dominant follicles develop.

METHODS

Study design

This study is a non-blinded, multicentre, superiority RCT in the Netherlands. Recruitment started on 5 June 2013. We expect to end the study on 1 August 2017. Trial registration number is NTR4057.

Study population

Inclusion criteria

We will study couples diagnosed with unexplained or mild male subfertility, in whom the woman is between 18 and 43 years and with at least one-sided tubal patency.

Unexplained subfertility is defined as a couple having 1 year of regular unprotected intercourse without conception, where the woman has a regular menstrual cycle and the man a prewash total motile sperm count (TMSC) of above 10 million.

Mild male subfertility is defined as prewash TMSC above 3 million and less than 10 million.

The following couples are eligible:

- ▶ Couples in whom the woman is under the age of 38 years with 12 months prognosis for natural conception according to the model of Hunault of <30%. This model encompasses female age, duration of subfertility, whether subfertility is primary or secondary, percentage of motile progressive sperm and referral status. It is readily available for all clinicians.⁸

- ▶ Couples in whom the woman is under the age of 38 years with 12 months prognosis for natural conception according to the model of Hunault of >30% after another 6 months of failed expectant management.
- ▶ Couples in whom the woman is at the age of 38 years or older regardless of their 12 months prognosis for natural conception.
- ▶ Women under the age of 35 years after 12 months of intracervical insemination (ICI) or IUI with donor sperm without OS.
- ▶ Women 35 years or older after 6 months of ICI or IUI with donor sperm without OS.

Exclusion criteria

Women with double-sided tubal pathology, polycystic ovary syndrome, irregular cycles or other endocrine disorders are not included.

Ethical considerations

Approval for this study is obtained from the Medical Ethical Committee of the Academic Medical Centre and from the Dutch Central Committee on Research Involving Human Subjects (CCMO NL 43131-018-13). Before randomisation, written informed consent was obtained in patients fulfilling the inclusion criteria.

Informed consent procedure

Women eligible for participation in the study are invited for additional counselling by a research nurse to ensure that they are fully informed on the nature of the study by means of both oral and written information. Women who agree to participate are asked to sign a written informed consent of which they receive a copy.

Randomisation

Randomisation is performed by accessing a web-based data system that is used for randomisation in clinical trials and will be performed centrally with the use of a permuted-block design. Couples are randomly allocated to either four cycles of IUI with subcutaneous injections of FSH at a dose of 75 IU or with CC tablets at a dose of 100 mg.

Interventions

Couples are treated until pregnancy occurs within a treatment time horizon of 6 months (figure 1).

In the first treatment cycle, all women are seen for a baseline visit with a transvaginal ultrasound on the third, fourth or fifth day of the menstrual cycle. At this baseline visit, the AFC will be measured.

Women are not allowed to start the treatment cycle if one or more ovarian cysts of >20 mm are seen, but may continue as soon as the cysts have disappeared.

In the experimental arm, women will receive IUI–FSH. The recruited women start with daily subcutaneous injections of 75 IU FSH on day 3, 4 or 5 of the menstrual cycle and continue these injections until the day of ovulation triggering. In the standard arm, women start with 100 mg CC on day 3, 4 or 5 of the menstrual cycle. The tablets

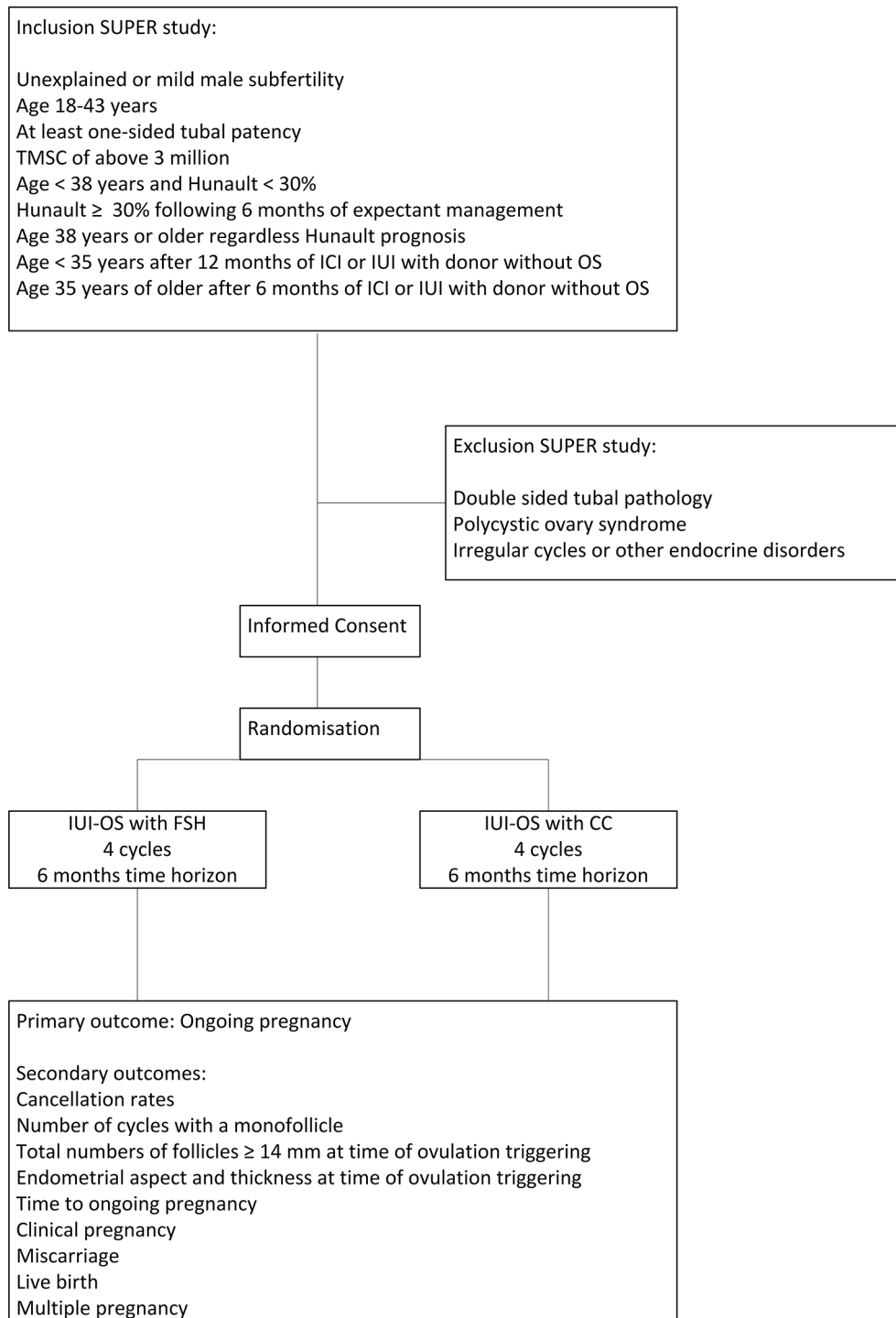


Figure 1 Flowchart of study. CC, clomiphene citrate; FSH, follicle-stimulating hormone; ICI, intracervical insemination; IUI, intrauterine insemination; OS, ovarian stimulation; TMSC, total motile sperm count.

are administered orally and stopped after 5 days of daily intake.

Growing follicles are monitored by transvaginal ultrasound and the subsequent insemination is planned if there is at least one dominant follicle with a mean diameter of 16–18 mm and a maximum of three follicles of 15 mm. Ovulation is triggered with 5000 IU hCG or 250 µg recombinant hCG.

In both interventions, the total number of follicles, their diameters and the endometrial aspect and thickness are measured at the final ultrasound before ovulation triggering and registered. Ovulation triggering is withheld if more than three follicles with a diameter of >15 mm are seen or five follicles with a diameter of 12 mm. In this case, the couples are also strictly advised to have protected or no intercourse. IUI is scheduled 36–42 hours after ovulation triggering. On the day of insemination, the partner

will provide a semen sample after a minimum of 2 days of sexual abstinence. The semen is processed according to local protocol. In case of donor sperm treatment, donor semen is thawed and processed according to local protocol.

Women who are not pregnant are scheduled for the next insemination cycle. In case of monofollicular growth or cancellation of the cycle because of the growth of more than three follicles above 14mm, the dose is adjusted in the subsequent cycle. It is known that IUI with monofollicular growth does not contribute to pregnancy outcomes compared with expectant management⁽⁹⁾. If monofollicular development occurred, the dose of recombinant FSH was increased by 37.5 IU, and in case of CC, the dose was increased by 50 mg in the next cycle. If a cycle was cancelled due to multifollicular growth, the dose of rFSH was decreased by 37.5 IU, and in case of CC, the dose was decreased by 50 mg in the next cycle.

OUTCOME MEASURES

Primary outcome measure

The primary outcome is conception leading to ongoing pregnancy, defined as a positive heartbeat at 12 weeks of gestation. Only conceptions that occur within the first 6 months after randomisation will count for the assessment of the primary endpoint.

Secondary outcome measure

Secondary outcomes are cancellation rates, number of cycles with a monofollicular and multifollicular growth, total number of follicles >14mm at the time of ovulation triggering, time to ongoing pregnancy, clinical pregnancy rate, miscarriage rate, live birth rate and multiple pregnancy rate. We will also assess patients' preference and costs. We will collect information on biomarkers such as female age, duration and type of subfertility, TMSC, Hunault score, BMI, smoking status, ethnicity and AFC and endometrial aspect and thickness.

Background and demographic characteristics

We will present the baseline measurements including female age, duration of subfertility, diagnosis of subfertility, parity, semen quality and referral status.

Data analysis

On the basis of a superiority design, the analysis of all outcomes will be done on an intention-to-treat basis.

Baseline data and outcome data are summarised separately. For continuous variables, we examine the distribution of the observations, and if normally distributed, we summarise them as means with SDs. If they are not normally distributed, medians and IQRs are reported. For dichotomous data, we provide proportions (or percentages). In addition to the baseline and outcome data, we also summarise the recruitment numbers, those lost to follow-up, protocol violations and other relevant data.

We will analyse a maximum of four cycles of IUI–OS performed within a time horizon of 6 months after randomisation.

The effectiveness of IUI–FSH versus IUI–CC is expressed as a rate ratio for ongoing pregnancy with corresponding 95% CIs. A formal test of the difference in ongoing pregnancy rate will be performed using χ^2 test statistics.

The effectiveness over time is evaluated in life tables and differences in ongoing pregnancy over time are evaluated by the log-rank test. Further dichotomous outcomes are analysed using the Fishers exact test or χ^2 test as appropriate. For continuous outcomes, we use t-test if the observations in each trial arm are normally distributed, and if non-normally distributed, then Mann-Whitney U test is used. Although p values are reported, the focus is on providing 95% CIs around point estimates, as these are more useful in interpreting the findings of the trial.

If randomisation fails to achieve balanced groups, we will perform secondary analyses in which we adjust for unbalanced prognostic factors using procedures such as logistic regression. If the primary unadjusted analysis and secondary adjusted analysis are discordant, we will give greater weighting to the primary analysis in the interpretation of trial findings.

For issues such as loss to follow-up, missing data and protocol violations, we attempt sensitivity ('worst-case scenario') analyses to explore the effect of these factors on the trial findings. The effect of baseline characteristics on the primary outcome is explored using logistic regression analysis. We will construct Kaplan-Meier curves expressing time to ongoing pregnancy.

Biomarker study

We will classify female age, BMI, duration of subfertility, TMSC and Hunault score as continuous variables and endometrial thickness at start cycle, type of subfertility (primary or secondary) and smoking status (yes or no) as binary variables. For each potential treatment selection marker, we will explore the association between the factor and ongoing pregnancy after IUI–FSH and IUI–CC and will test for factor–treatment interaction. For continuous factors, we will plot ongoing pregnancy chance as a function of the prognostic factor in a Subpopulation Treatment Effect Pattern Plot (STEPP).^{10 11} STEPP is a non-parametric approach allowing for investigation of patterns of treatment effect heterogeneity in subgroups of the factor that is being studied. For binary factors, we will develop logistic regression models and calculate the p value of factor–treatment interaction. In a sensitivity analysis, we will also perform the same analyses using ongoing pregnancy rate as main effectiveness outcome.

Given the exploratory nature of our analysis, we will use a more liberal p value of 0.1.¹² All analyses will be performed based on the intention-to-treat principle. We will use R for Windows (Version 3.0.1; R Foundation for Statistical Computing, Vienna, Austria); STEPP analyses will be done by package 'stepp' (<https://cran.r-project.org/web/packages/stepp/stepp.pdf>) and evaluation of

the performance of binary factors by the package ‘Treatment Selection’.¹³

Economic evaluation

We will perform an economic analysis from a healthcare perspective alongside the clinical trial. We make a distinction between direct costs (costs like medical interventions and other healthcare costs like medical appliances) and indirect costs (costs of productivity loss or time loss costs). We analyse a cost-minimization or cost-effectiveness analysis depending on the outcome of ongoing pregnancy rates in both groups. We present the cost-effectiveness of each strategy as cost per ongoing pregnancy and costs per live birth. We explore the robustness of the results for various assumptions and parameter estimates in sensitivity analysis outcomes and we express these in incremental cost-effectiveness ratio graphs and cost-effectiveness acceptability curves. The economic evaluation will be reported in a separate paper.

Power calculation

The study is designed as a superiority trial. We assume that the ongoing pregnancy rate after four cycles will be 25% following CC treatment and we aim to be able to prove an absolute difference of 10% following FSH.¹⁴ With a two-sided alpha of 5% and a beta of 20%, 329 couples per group are required. Accounting for 10% dropout extra, we need to include 732 women.

DISCUSSION

In couples diagnosed with unexplained or mild male subfertility, the first-line treatment is IUI with OS. OS can be achieved with FSH or CC. On the basis of the available evidence, FSH appears to be the most effective medication in terms of the pregnancy rate per couple compared with CC. The disadvantage is the risk of multiple pregnancies and its associated maternal and neonatal complications. A way to reduce the risk of multiple pregnancies is to hold on to strict cancellation criteria. A cycle will be cancelled when three or more dominant follicles develop. Within this strategy, it is unclear whether OS should be done with FSH or with CC. The objective of this multicentre RCT is to determine the costs and effectiveness of IUI–FSH 75 IU and IUI–CC 100 mg, and adherence to strict cancellation criteria.

ETHICS AND DISSEMINATION

The study has been approved by the Medical Ethical Committee of the Academic Medical Centre and from the Dutch Central Committee on Research involving Human Subjects (CCMO NL 43131-018-13). Results will be disseminated through peer-reviewed publications and presentations at international scientific meetings.

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Contributors ND is responsible for the overall logistical aspects of the trial and drafted the paper. MHM, FvdV and MvW designed the trial and were responsible for the development of the protocol. ND, CK, JG, JpdB, BJC, DPvdH, NFK, MHAHV, FB, KF, CAHJ, JMRvW, JvD, M Twisk, M Traas, MFGV, MJP, JV, DAMP, DESB, HRV, CFvH, BWJM, SR, MHM and MvW contributed to the protocol included patients and approved the final version of the paper.

Competing interests None declared.

Ethics approval Approved by METC AMC Amsterdam.

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