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# Tubal flushing with oil-based contrast during hysterosalpingography versus tubal flushing by hysterosalpingo-foam sonography in infertile women undergoing fertility work-up: study protocol of a randomised controlled trial (FOil study)

Danah Kamphuis ,[1,2] Janette P M Huijser,[1,2] Nienke van Welie,[1,2] Harold R Verhoeve,[3] Esther Kuijper,[4] Jan Peter de Bruin,[5] Angelique J C M van Dongen,[6] Susanne C J P Gielen,[7] Guusje de Krom,[8] Femi Janse,[9] Carolien A M Koks,[10] Annemiek W Nap,[11] Johannes R Anema,[12] Judith E Bosmans,[13] Jaap Stoker,[14] Madelon van Wely,[2,15] Ben Willem J Mol ,[16] Velja Mijatovic,[1,2] Kim Dreyer[1,2]

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For numbered affiliations see end of article.

**Correspondence to**
Mrs Danah Kamphuis;
d.kamphuis@amsterdamumc.nl

## ABSTRACT

**Introduction** Hysterosalpingography (HSG) and hysterosalpingo-foam sonography (HyFoSy) are commonly used tubal patency tests during the fertility work-up. Besides its diagnostic purpose, HSG with oil-based contrast can also be applied for its fertility-enhancing effect, by tubal flushing. HyFoSy is considered as less painful compared with HSG, it lacks exposure to iodinated contrast medium and ionising radiation. The fertility-enhancing effects of HyFoSy are less studied and randomised controlled trials comparing pregnancy rates after HSG and HyFoSy are lacking. This study (FOil study) is initiated to compare the effectiveness of tubal flushing during HSG with oil-based contrast and HyFoSy.

**Methods and analysis** The FOil study is a nationwide, multicentre, open label, randomised controlled trial with a superiority design. Infertile women with an indication for tubal patency testing during their fertility work-up will be randomly assigned to HSG with oil-based contrast medium or HyFoSy. The primary outcome is conception within 6 months after randomisation leading to live birth. To demonstrate or refute an 8% difference in conception leading to live birth in favour of HSG with oil-based contrast, 1102 women will be included in the trial. A cost-effectiveness analysis from a societal perspective will be performed alongside the trial.

**Ethics and dissemination** The trial is approved by the Medical Ethics Review Committee of the Amsterdam University Medical Centers (Ref. No. 2022.0884, date: 17 March 2023) and by the boards of the participating hospitals. The findings will be disseminated in peer-reviewed journals and participants will be informed through the patient organisation.

**Trial registration number** NCT05882188.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first randomised controlled trial directly comparing the therapeutic effects of tubal flushing by hysterosalpingography (HSG) with oil-based contrast and hysterosalpingo-foam sonography (HyFoSy) in infertile women, which will contribute to the empowerment of patients and clinicians to make well-informed decisions weighing the pros and cons of each intervention.
⇒ A cost-effectiveness analysis (CEA) will be performed alongside the trial.
⇒ The safety of both tests will also be considered and compared (eg, risk of intravasation, thyroid dysfunction, infection).
⇒ Women with different causes of infertility are eligible to participate. These broad inclusion criteria ensure that the study results will be widely applicable in diverse settings, contributing to the relevance and impact of this study.
⇒ The alternative tubal patency test may be offered in case of inconclusive test results, this might introduce the possibility of crossover bias.

## INTRODUCTION

Globally, infertility is affecting an increasing number of couples in their reproductive years, and it has been indicated that approximately 15% of the couples face challenges in conceiving.[1 2] Infertility is defined as the inability to conceive after 12 months of unprotected sexual intercourse.[3] To identify the underlying cause, a fertility work-up can

be performed. As tubal pathology is one of the most prevalent causes of infertility, assessment of the patency of the fallopian tubes is considered as one of the cornerstones of the fertility work-up.[4 5]

Tubal patency assessment can be accomplished through a variety of diagnostic methods. While laparoscopy with chromopertubation remains the reference test, it is not the primary choice due to the inherent surgical risks, requirement of general anaesthesia and associated costs.[6] Alternative methods, such as hysterosalpingography (HSG) and hysterosalpingo-foam sonography (HyFoSy), are tubal patency tests that can be performed in an outpatient clinic setting.[7] Besides its diagnostic purpose, HSG can also be offered for its fertility-enhancing effect, by tubal flushing. Previous studies have shown that in women with unexplained infertility, the use of oil-based contrast during HSG results in more clinical pregnancies compared with no tubal flushing (OR: 3.54; 95% CI 2.08 to 6.02) or the use of water-based contrast (OR: 1.42; 95% CI 1.10 to 1.24).[8]

Compared with HSG, women experience HyFoSy as significantly less painful and also feel less anxious.[9–11] Moreover, it lacks exposure to ionising radiation and iodinated contrast medium. The latter can potentially lead to transient (subclinical) hypothyroidism, especially in women with subclinical hypothyroidism prior to HSG.[12–14] Another advantage of HyFoSy is the possibility for a one-stop fertility assessment, as tubal patency assessment can easily be combined with a regular transvaginal ultrasound. To date, randomised controlled trials on the therapeutic effects of tubal flushing by HyFoSy are lacking. Pregnancy rates after HyFoSy have only been reported in observational studies with limited sample sizes, lacking a control group. These studies reported widely varying pregnancy rates 6 to 12 months after HyFoSy from 11% to 55%.[15–20]

In order to determine the most preferable tubal patency test during fertility work-up, it is essential to assess the benefits and drawbacks of each test, including the potential fertility-enhancing effects and associated costs. Therefore, we set up the FOil study: a direct comparison between tubal flushing by HSG with oil-based contrast and HyFoSy in infertile women. An economic evaluation will be performed alongside the study.

## METHODS AND ANALYSIS

### Design

This will be an investigator initiated, multicentre, open label, randomised controlled trial with a superiority design. The study will be performed within the infrastructure of the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics & Gynaecology (NVOG Consortium 2.0) including district, teaching and university hospitals in the Netherlands (participating hospitals are listed in online supplemental file 2). An economic evaluation from a societal perspective will be performed alongside the trial.

### Participants and eligibility criteria

Infertile women with indication for tubal patency testing during their fertility work-up will be eligible to participate in the study. They should be aged between 18 and 42 years and sufficiently understand the Dutch and/or English language. Women will be excluded if they have a contrast iodine allergy, had a gynaecological procedure within the last 30 days or are known or suspected for reproductive tract neoplasia. The woman's partner or sperm donor should have a total motile sperm count higher than 3 million spermatozoa per millilitre.

### Recruitment and randomisation

Eligible women will be informed about the study and receive the participant information leaflet during an outpatient clinic visit. Afterwards, they will be contacted by a trained researcher for additional information. Women who are willing to participate, sign a consent form after they have been given a period of reflection of minimally 2 days. Partners or sperm donors will be asked to sign a consent form as well, allowing the researchers to have access to the semen analysis results. The particpant information leaflet and consent forms are available through the online supplemental file 3. Consenting women will be randomised 1:1 for tubal flushing with oil-based contrast (Lipiodol® Ultra Fluid) during HSG (HSG group) or for tubal flushing with ExEm® Foam during HyFoSy (HyFoSy group). Randomisation will be stratified per centre through the centrally web-based system Castor Electronic Date Capture (EDC, Amsterdam, the Netherlands) with the use of permuted block design (block size: 4, 6 or 8). Women will be randomly allocated to different study procedures, so blinding either the participants or clinicians is not possible. We do not expect that the lack of blinding will influence the study findings considering our primary outcome, conception leading to live birth, is an objective measurement.

### Intervention

Tubal flushing with oil-based contrast during HSG will be performed by a trained gynaecologist, fertility physician or physician assistant. Lipiodol® Ultra Fluid, Guerbet, Villipinte, France will be used as oil-based contrast medium during HSG. The contrast medium will be infused with the use of a cervical vacuum cup, Lipiodol® UF resistant balloon catheter or hysterophore. Up to 15 mL of oil-based contrast will be infused into the uterine cavity and fallopian tubes, and simultaneously the flow of the contrast will be visualised during fluoroscopy or on radiographs. The images will be assessed by a gynaecologist and/or radiologist.

### Control group

Tubal flushing with ExEm® Foam (Gedeon Richter Plc., Groot-Bijgaarden, Belgium) during HyFoSy will be performed by a trained gynaecologist, fertility physician, sonographer, or physician assistant according to local protocols. The clinicians are offered a training for

**Table 1** SPIRIT figure including all study activities

| | Study period | | | | | |
|---|---|---|---|---|---|---|
| | Enrolment | Allocation | | Post-allocation | | |
| Timepoint | *t-1* | *0* | *t1* | *t2* | *t3* | *t4* |
| Enrolment | | | | | | |
| Eligibility screen | X | | | | | |
| Informed consent | X | | | | | |
| Allocation | | X | | | | |
| Interventions | | | | | | |
| HSG with oil-based contrast | | | X | | | |
| HyFoSy with ExEm Foam | | | X | | | |
| Assessments | | | | | | |
| Demographics | | X | | | | |
| Thyroid function testing* | X | | | X | | |
| APAIS | | | X | | | |
| Pain score (VAS) | | | X | | | |
| Procedure and results | | | X | | | |
| Adverse events | | | X | | X | |
| iMCQ and iPCQ | | | | | X | |
| Treatments | | | | | X | |
| Pregnancies | | | | | X | |
| Pregnancy follow-up | | | | | | X |

t–1: prior to allocation, t1: day of intervention, t2: 1 month after tubal patency testing, t3: 6 months after randomisation, t4: after giving birth.
*No mandatory study intervention.
APAIS, Amsterdam Preoperative Anxiety and Information Scale; iMCQ, Medical Consumption Questionnaire; iPCQ, Productivity Cost Questionnaire; SPIRIT, Standard Protocol Items: Recommendations For Interventional Trials; VAS, Visual Analog Scale.

the performance of HyFoSy before the start of the study. During HyFoSy, approximately 5–10 cc of echogenic foam (created by mixing 5 cc ExEm gel with 5 cc sterile purified water) will be introduced through a little cervical balloonless applicator into the uterine cavity. During infusion of the foam into the uterine cavity, a two-dimensional transvaginal ultrasound will be performed, which will show the spread of the foam through the uterine cavity and fallopian tubes. The assessment will be done by the person who performed the procedure during the procedure itself. The type of ultrasound equipment and ultrasound settings depend on local protocols.

## Study procedures

All study procedures are summarised and presented in table 1. The allocated tubal flushing intervention will be performed after cessation of the menstrual bleeding or after progesterone-induced vaginal bleeding in women with ovulation disorders, during the follicular phase of the menstrual cycle. Women are allowed to take pain medication before the procedure (eg, paracetamol or naproxen). A few minutes before the procedure, participants will complete the modified Amsterdam Preoperative Anxiety and Information Scale questionnaire to score preprocedural anxiety as a confounder for experienced pain.[21] Procedural pain scores will be measured directly after the procedure using the Visual Analog Scale (range of scores from 0.0 to 10.0 cm). According to local protocols, antibiotics will be prescribed to women with suspicion of intra-abdominal adhesions or hydrosalpinx. Before and 1 month after tubal flushing, it is recommended to measure thyroid function (thyroid-stimulating hormone (TSH) and free thyroxine level (fT4)) to assess iodine contrast-induced (subclinical) hypothyroidism in both groups. The highest TSH level typically occurs 4 weeks after the HSG with oil-based contrast.[13] All women will be followed up for 6 months after randomisation, and if women get pregnant during this follow-up period, they will be followed up until after they have given birth. Women will receive a digital combined Medical Consumption Questionnaire (iMCQ) and Productivity Cost Questionnaire (iPCQ) 6 months after randomisation. These questionnaires are designed to measure healthcare consumption and estimating productivity losses.[22 23]

The subsequent fertility treatment depends on the results of the fertility work-up as well as the tubal patency test. Women with at least one-sided tubal patency will be treated according to their prognosis for natural conception within 1 year based on the prediction model of

Hunault.[24] In case of a favourable prognosis (≥30% chance of natural conception), women will be counselled for expectant management in accordance with the Dutch guideline.[25] Couples with an unfavourable prognosis (<30%) will be treated with up to six cycles intrauterine insemination (IUI) with mild ovarian hyper stimulation eventually followed by in vitro fertilisation (IVF). Women with suspected bilateral tubal pathology will be scheduled for diagnostic laparoscopy (DLS) or will directly be offered IVF. Calculation of Hunault score is not validated for women over 38 years of age. For these women, management will be based on local protocols. Women with ovulation disorders will start or continue with ovulation induction treatment possibly in combination with IUI. If the tubal patency test results are inconclusive, women will be offered treatment according to local protocols (eg, the alternative tubal patency test, DLS or expectant management).

## Outcome measures

The primary outcome measure is conception within 6 months after randomisation leading to live birth. Conception is defined as a positive pregnancy test, increase in human chorionic gonadotropin level or a pregnancy shown on sonographic examination. Live birth is defined as the birth of a live born baby beyond 24 weeks of gestation.

Secondary outcome measures include:

- Time to conception leading to live birth, calculated from the day of randomisation till the first moment the pregnancy test, can be positive (which is based on the first day of the last menstrual bleeding plus 28 days).
- Other pregnancy outcomes: number of clinical pregnancies (defined as gestational sac with or without heartbeat visible on sonographic examination), miscarriage (defined as presence of non-vitality on ultrasound or spontaneous loss of pregnancy before 16 weeks of gestation), ectopic pregnancy (defined as no intrauterine gestational sac with an ectopic mass on ultrasound or elevated serum HCG levels) and multiple pregnancy (defined as two or more vital intrauterine pregnancies at 12 weeks gestation).
- Societal costs.
- Number of adverse events (AEs) within 1 month after tubal flushing, for example, intravasation, infection, thyroid dysfunction.
- Procedural pain scores, measured by using the Visual Analogue Scale ruler (ranging from 0.0 cm to 10.0 cm) immediately after tubal flushing.
- Number of fertility treatment cycles within 6 months after randomisation.
- Number of pregnancy complications (eg, preterm birth, hypertensive pregnancy complications, gestational diabetes, stillbirth, placenta previa, intrauterine growth restriction, congenital anomalies).
- Pregnancy outcomes (duration of pregnancy, birth weight, sex of child).

## Data collection and management

Study data will be collected and entered into the web-based application Castor EDC. An anonymous, unique study number will be assigned to each participant. Only the local investigators will have access to the linkage of study numbers and personal data. Baseline characteristics and data on the tubal patency performance will be extracted from women's medical files. Data on fertility treatment and pregnancy will be extracted from their medical files or women will be contacted through telephone or digital questionnaire.

## Safety monitoring

For this study, we consider intravasation of the contrast medium, pelvic inflammatory disease, thyroid dysfunction and any other AE, which could be related to the tubal flushing method on appropriate judgement by the investigator as an AE. All AEs which occur between the first study-related procedure and 1 month after will be reported. If an AE results in death, is life-threatening, requires hospitalisation or results in persistent or significant disability, the event will be classified as serious AE (SAE). These events will be reported through the web portal ToetsingOnline to the accredited ethics committee within a period of 15 days after the first knowledge of the SAE or in case of life-threatening event within a period of 7 days. All (S)AEs will be followed until they have ablated or until a stable situation has been reached. For this study, an independent data safety monitoring board will evaluate the safety of participants during the study by assessing the (S)AE line listing once a year. Since the trial compares two interventions used routinely in clinical practice, an interim analysis is not planned. Data will be collected and processed in accordance with the General Data Protection Regulation (EU) 2016/679. Data will be stored for 15 years after the study has been completed. Data monitoring will be performed by a certified clinical research associate. This study will be conducted in accordance with the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and acts.

## Sample size calculation

We hypothesise that a difference of 8% in conception leading to live birth rate in favour of tubal flushing with oil-based contrast during HSG will be effective. To detect or refute this increase in live births, a total of 1102 women (551 women per group) should be randomised with a power of 80% and an alpha of 0.05. We included 2% lost to follow-up. The sample size is based on Lindborg *et al* who demonstrated a live birth rate of 29% after tubal flushing by hysterosalpingo contrast sonography (HyCoSy).[26]

## Statistical analysis

The effectiveness analyses will be done by intention to treat principle including all randomised women. Differences in conception leading to live birth rates between

the two groups will be expressed as crude and adjusted risk ratio using log-linear binomial regression and as absolute risk difference, with associated 95% CIs. For the primary outcome measurement, subgroup analyses will be performed for the different types of subfertility (unexplained infertility, ovulation disorder, high risk for tubal pathology, age above 38 years). We also plan a per protocol analysis to provide insight into the effect of both tubal flushing methods among those who strictly adhered to the study protocol.

The secondary outcome measurements will be reported as means and SDs (normally distributed data) or medians and ranges (non-parametrical data) in case of continuous data. Categorical data will be reported as percentages. For the comparison of numerical and continuous outcomes between the two groups, the student t-test or Mann-Whitney U test will be used. For dichotomous outcomes, the difference between two proportions will be calculated by using the $\chi^2$ of Fishers exact test. Time to event (conception leading to live birth) will be calculated and compared using Kaplan-Meier analysis with a log-rank test.

For missing data, losses to follow-up and protocol violation, a worst-case scenario analysis will be attempted to explore the effect of these factors on the study findings. In a sensitivity analysis, we will use imputation methods for missing data to explore the effect of missing data on the study findings. IBM SPSS Statistics V.28.0 and R software (R Project for Statistical Computing) will be used for statistical analyses.

### Economic evaluation

The aim of the economic evaluation will be to relate the incremental costs of tubal flushing during HSG with oil-based contrast in comparison with tubal flushing by HyFoSy to the incremental health effects. The CEA will be performed from a societal and healthcare perspective according to Dutch guidelines with a time horizon of 6 months after randomisation. Cost categories that will be included are healthcare costs; lost productivity costs (absenteeism from paid and unpaid work, and presenteeism—being present at work, but not able to fully function); and patient costs (informal care and other care services paid for by patients themselves).[27] Healthcare costs include costs for tubal patency testing and additional fertility treatments and also other healthcare costs such as visits to the general practitioner or medication use. Costs will be measured from a societal perspective using web-based questionnaires based on the iMCQ and iPCQ at 6 months after randomisation.[22 23] Valuation will be done according to Dutch costing guidelines using Dutch standard costs.[28]

All statistical analyses will be done according to the intention-to treat principle. Missing cost and effect data will be imputed using multiple imputation according to the Multivariate Imputation by Chained Equations algorithm. Rubin's rules will be used to pool the results from the different multiply imputed datasets. Linear regression analyses will be used to estimate cost and effect differences between intervention and control while adjusting for confounders if necessary. Incremental cost-effectiveness ratios (ICERs) will be calculated by dividing the difference in the mean total costs between the treatment groups by the difference in mean effects between the treatment groups. Bias-corrected and accelerated bootstrapping with 5000 replications will be used to estimate 95% CIs around the cost differences and statistical uncertainty surrounding the ICERs. Uncertainty surrounding the ICERs will be graphically presented on cost-effectiveness planes. Cost-effectiveness acceptability curves will also be estimated showing the probability that the intervention is cost-effective in comparison with control for a range of different ceiling ratios, thereby showing decision uncertainty.[29]

### Implementation problem analysis

We will conduct an implementation problem analysis based on the Model of Fleuren, resulting in an implementation strategy.[30] In this problem analysis, interviews with all stakeholders will take place, in order to get insight into barriers and facilitators for implementation of study results to select evidence-based and implementation strategies tailored to barriers and facilitators. Based on the findings, an implementation plan will be drafted including guideline implementation based on the study results at an early phase and to advise the guideline development group in adding tools to the guideline to overcome barriers found and to stimulate a fast incorporation of guidelines, especially as key persons in guideline development take part in this study. The supposed study will be conducted within the infrastructure of the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics & Gynaecology (NVOG Consortium V.2.0).

### Patient and public involvement

Patients and representatives of patient organisations were actively involved in the development of the used preferred outcomes in fertility research.[31] Furthermore, the Dutch patient organisation for infertile couples (Freya) was actively involved in the design and the evaluation of the feasibility of this study. A survey among Freya members was released to gather information about their willingness to participate in the proposed study. The results showed that the majority of the women would be willing to participate. Freya has also reviewed the study protocol and the patient information leaflet. Eventually, a lay summary including the results of the study will be disseminated among the members of Freya to inform infertile women on the results of the study.

## DISCUSSION

In recent years, HyFoSy has emerged as a feasible and less painful alternative to traditional HSG assessment of tubal patency during fertility work-up.[16 32 33] While the diagnostic advantages of HyFoSy over HSG are evident, it is

essential to assess the potential fertility-enhancing effects of either of the tests and the associated costs as well. Up to now, the fertility-enhancing effects of tubal patency testing by HSG with oil-based contrast and HyFoSy have never been directly compared. In this randomised controlled trial, we aim to compare live births following tubal flushing by HSG with oil-based contrast and HyFoSy during fertility work-up.

This study builds on our previous randomised trial (FOAM trial) showing that, during fertility work-up, management based on the results of either HyFoSy or HSG resulted in comparable live birth rates.[10] In the FOAM trial, women underwent both tubal patency tests, and therefore we were not able to assess the potential therapeutic effects of either of the tests. Additionally, we will perform an economic evaluation alongside this study to relate the costs of tubal flushing during HSG with oil-based contrast in comparison with HyFoSy to the difference in effect in terms of ongoing pregnancies. To provide a complete picture of costs associated with infertility work-up, we will perform the CEA from a societal perspective. The CEA of the FOAM trial showed that management based on the results of HyFoSy is associated with slightly lower live birth rates (although not statistically significant), at slightly lower costs compared with management based on the results of HSG.[34] If tubal flushing by HSG results in more pregnancies than HyFoSy, then it would be likely that less women will need expensive fertility treatments, resulting in HSG being less costly than HyFoSy. If HSG is more effective than HyFoSy, and also more costly, then it would be relevant to calculate the costs for an additional live birth. Another potential strength is that we include women with different types of infertility in this study, therefore the results will be widely applicable in infertility care. Eventually, the results of this study should be implemented in the current fertility guidelines on tubal patency assessment and treatment. To get insight into barriers and facilitators for implementation of the study, we will conduct a implementation problem analysis. This study has several potential limitations. Clinicians in the Netherlands have extensive experience in the performance and interpretation of tubal patency testing by HSG. HyFoSy, on the other hand, is a less common performed test and possibly clinicians will have a learning curve of the performance of HyFoSy. However, in our previous FOAM study 24 hospitals in The Netherlands participated and got familiar with the performance and interpretation of HyFoSy. Nevertheless, we will offer a training for the performance of HyFoSy before the start of the study. Additionally, given the nature of both tubal patency tests, the study cannot be blinded. Since our primary outcome, pregnancy leading to live birth, is objective, we do not expect that the results will largely be affected by the open-label character of the study.

To our knowledge, the proposed study will be the first randomised trial comparing tubal flushing by HSG with oil-based contrast and HyFoSy. The results of this study will give policymakers insights in the most cost-effective strategy for tubal patency testing and will support clinicians and infertile couples to make a well-informed decision on the most suitable tubal patency test.

## Ethics and dissemination

The study has been approved by the Medical Ethics Review Committee of the Amsterdam University Medical Centers (reference number 2022.0884, date: 17 March 2023) and by the boards of the participating hospitals. All study amendments to the protocol will be noted to the Medical Ethics Review Committee. The study is prospectively registered on ClinicalTrials.gov. and the trial registration data set is available through online supplemental file 1. The findings will be disseminated in peer-reviewed journals and participants will be informed through the patient organisation.

**Author affiliations**
[1]Reproductive Medicine, Amsterdam UMC location Vrije Universiteit, Amsterdam, The Netherlands
[2]Amsterdam Reproduction and Development Research Institute, Amsterdam, The Netherlands
[3]Obstetrics and Gynaecology, OLVG, Amsterdam, The Netherlands
[4]Obstetrics and Gynaecology, Spaarne Gasthuis, Haarlem, The Netherlands
[5]Obstetrics and Gynaecology, Jeroen Bosch Hospital, 's-Hertogenbosch, The Netherlands
[6]Obstetrics and Gynaecology, Gelderse Vallei Hospital, Ede, The Netherlands
[7]Obstetrics and Gynaecology, Franciscus Hospital, Rotterdam, The Netherlands
[8]Obstetrics and Gynaecology, Zuyderland Medical Center, Heerlen, The Netherlands
[9]Obstetrics and Gynaecology, Rijnstate, Arnhem, The Netherlands
[10]Obstetrics and Gynaecology, Maxima Medical Center, Veldhoven, The Netherlands
[11]Obstetrics and Gynaecology, Radboud University Medical Center, Nijmegen, The Netherlands
[12]Public and Occupational Health, Amsterdam UMC location Vrije Universiteit, Amsterdam, The Netherlands
[13]Department of Health Sciences, Faculty of Science, Amsterdam Public Health, research institute, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
[14]Radiology and Nuclear Medicine, Amsterdam UMC location University of Amsterdam, Amsterdam, The Netherlands
[15]Centre for Reproductive Medicine, Amsterdam UMC location University of Amsterdam, Amsterdam, The Netherlands
[16]Obstetrics and Gynaecology, Monash University, Melbourne, Victoria, Australia

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**Contributors** DK, NvW, HRV, JPdB, CAMK, AWN, HA, JB, JS, MvW, BWM, VM, KD contributed to the grant application and the design of this study. DK and JH are responsible for the logistic coordination of the study and the acquisition of the data. HRV, EK, JPdB, AvD, SCJP, GdK, FJ are local investigators of participating sites and are responsible for recruitment of participants. KD acted as guarantor. All authors critically revised and approved this manuscript.

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**Competing interests** DK reports support from Guerbet. MvW is coordinating editor of the Cochrane Gynaecology and Fertility Group and member of the Cochrane thematic group Reproductive Health. HV is a member of the advisory board of Ferring Ltd, member of the ESHRE unexplained infertility guideline development group, and chairman of the Dutch unexplained infertility guideline development

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**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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**ORCID iDs**
Danah Kamphuis http://orcid.org/0000-0002-2627-8591
Ben Willem J Mol http://orcid.org/0000-0001-8337-550X

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