Tubal flushing with oil-based contrast during HSG in subfertile women: Is early flushing effective and cost-effective as compared to delayed flushing?

H2Oil-timing study

Version 1.6 February 2020

PROTOCOL TITLE **Tubal flushing with oil-based contrast during HSG in subfertile women: Is early flushing effective and cost-effective as compared to delayed flushing?**

Protocol ID	**METC Amsterdam UMC – location VUmc 2018.291** **NL62838.029.18**
Short title	**H2Oil-timing study**
EudraCT number	**2018-004153-24**
Version	**1.6**
Date	**04-02-2020**
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
HSG	**Hysterosalpingography/hysterosalpingogram**
IB	**Investigator's Brochure**
IC	**Informed Consent**
ICSI	**Intra Cytoplasmatic Sperm Injection**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
IUI	**Intra Uterine Insemination**
IVF	**In Vitro Fertilization**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
NVOG	**Dutch society of Obstetrics and Gynaecology (in Dutch: Nederlandse Vereeniging Obstetrie en Gynaecologie)**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**

TMSC	**Total Motile Sperm Count**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: We hypothesize that direct tubal flushing with oil-based contrast at HSG incorporated in the fertility work-up results in 10% more ongoing pregnancies and a shorter time to pregnancy compared to delayed tubal flushing 6 months after fertility work-up is completed in women at low risk for tubal pathology, which will lead to a reduction in the need for expensive fertility treatments like IVF and/or ICSI, and will therefore be an effective and cost effective strategy.

Objective: The aim of this study is to determine whether direct tubal flushing with oil-based contrast at HSG incorporated in the fertility work-up results in 10% more ongoing pregnancies and a shorter time to pregnancy, which will therefore be effective and cost-effective compared to delayed tubal flushing 6 months after fertility work-up is completed in women at low risk for tubal pathology.

Study design: We plan a multicentre randomized controlled trial with an economic analysis alongside it. Infertile women at low risk for tubal pathology will be randomized to direct tubal flushing with oil-based contrast incorporated in the fertility work-up or delayed tubal flushing 6 months after fertility work-up is completed.

Study population: Infertile women 18-38 years of age, who have a spontaneous menstrual cycle and at low risk for tubal pathology, undergoing fertility work-up.

Intervention (if applicable): Direct tubal flushing with oil-based contrast at HSG as part of the fertility work-up compared to delayed tubal flushing 6 months after the fertility work-up is completed.

Main study parameters/endpoints: The primary outcome is time to live birth, calculated from positive pregnancy test and within 12 months after randomization.

Our hypothesis is that tubal flushing at HSG with oil-based contrast incorporated in the fertility work-up will result in 10% more ongoing pregnancies and a shorter time to pregnancy, and thus reducing the need for ART and reducing costs.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: As we compare strategies (tubal flushing with oil-based contrast at HSG incorporated in the fertility work-up versus 6 months after completion of fertility work-up) that are already applied in current practice, no additional risks or burdens are expected from the study.

1. INTRODUCTION AND RATIONALE

Staying childless, due to the inability to conceive, is one of life's great misfortunes. Infertility, defined as the inability to conceive within 1 year of unprotected intercourse, affects 1 out of 6 couples trying to get pregnant[1]. The causes of infertility can be classified as anovulation, poor sperm quality and tubal pathology, with unexplained infertility as a large fourth segment.
Fertility work-up generally includes an assessment of the (ovulatory) cycle, a semen analysis and a tubal patency test. This evaluation of the tubes can be done by several different tests, including a diagnostic laparoscopy, a hysterosalpingo-foam sonography or a hysterosalpingography (HSG). An HSG is the most widely used outpatient method for tubal patency testing during the fertility work-up.

Although HSG was introduced as a diagnostic test, it has been hypothesized for decades that tubal flushing at HSG in general, and specifically with oil contrast, directly increases pregnancy rates[2]. However, the evidence for this fertility enhancement effect was lacking due to limited power of available studies.[3] Therefore, our group completed a large randomized clinical trial (H2Oil study) comparing oil contrast or water contrast in infertile women undergoing HSG. This landmark study, published in 2017 in the New England Journal of Medicine, showed that tubal flushing with oil-based contrast resulted in higher 6-month ongoing pregnancy rates than tubal flushing with water-based contrast (39.7% versus 29.1%) (RR 1.37, 95%CI 1.16-1.61). The subsequent live-birth rate was also significantly higher[4].

Our 2017 H2Oil study has changed the perspectives about the role of HSG in the fertility workup in infertile women and shifted the use of HSG from a diagnostic procedure towards a fertility enhancing procedure by tubal flushing with oil-based contrast medium[4]. The current Dutch guideline (2015) has not yet been updated following the results of the H2Oil study[4]. Consequently, some clinics perform an HSG in all infertile women while others follow the 2015 NVOG guideline and limit HSG to women at high risk for tubal pathology. HSG is usually offered after a waiting period of 6 months and no conception within these 6 months. This practice is switching since our study[4]. A recent survey among Dutch clinics showed that 70% of the Dutch fertility departments offered HSG, with the large majority of these clinics using oil-based contrast[5].

While our landmark trial proved that tubal flushing at HSG with oil-based contrast increases live-birth rates, the dilemma is now the timing of HSG relative to the (basic) fertility work-up. One issue is that in our NEJM trial the median duration of infertility of participating couples was 20 months. Currently, it is unclear whether direct tubal flushing (preferably after 12 months of unfulfilled child wish) with oil-based contrast medium is beneficial in comparison to delayed

tubal flushing (after 18 months of unfulfilled child wish). Direct tubal flushing at HSG with oil contrast incorporated in the fertility work-up might result in more ongoing pregnancies and a shorter time to pregnancy compared to delayed tubal flushing at HSG with oil-based contrast 6 months after completion of fertility work-up. If direct tubal flushing leads to more ongoing pregnancies and a shorter time to pregnancy, less women will need more expensive fertility treatments.

We expect 10% more ongoing pregnancies and a shorter time to pregnancy in the first 6 months following tubal flushing with oil-based contrast medium at HSG in the group of women that underwent direct tubal flushing as part of the fertility work-up versus delayed tubal flushing 6 months after completion of fertility work-up, and thus reducing the need for expensive fertility treatments and reducing costs. Therefore, direct tubal during HSG with oil contrast incorporated in the fertility workup would be a cost-effective strategy compared to delayed tubal flushing 6 months after completion of fertility work-up. There are no randomized studies comparing direct tubal flushing to delayed tubal flushing. This forces patients and their physicians to take decisions in uncertainty about the benefits and cost-effectiveness of direct tubal flushing in comparison with delayed tubal flushing.

2. OBJECTIVES

Primary Objective: Time to live birth, calculated from positive pregnancy test and within 12 months after randomization.

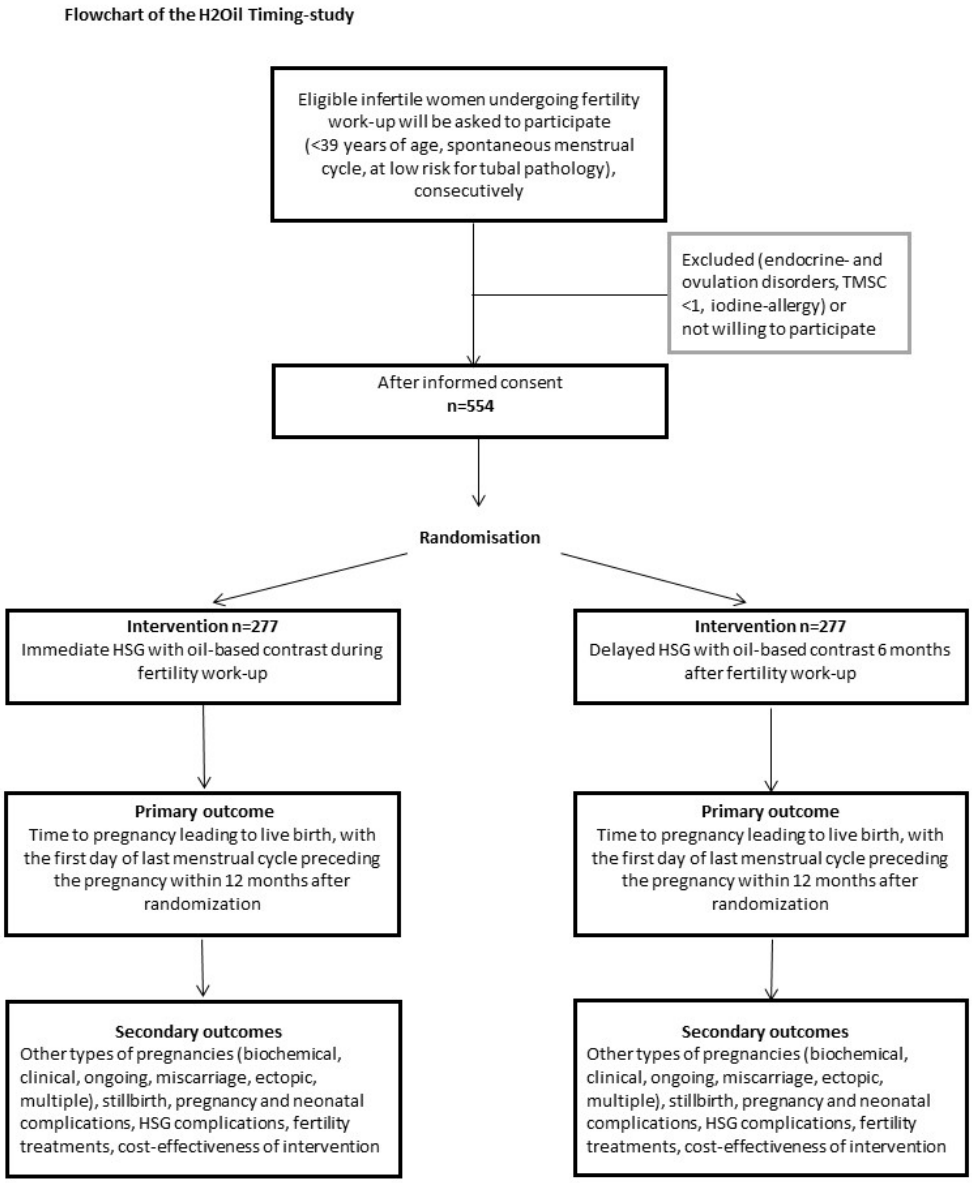
Secondary Objective(s):

- Live birth
- Clinical pregnancy
- Ongoing pregnancy
- Miscarriage
- Ectopic pregnancy
- Multiple pregnancy
- Complications following HSG (infection, intravasation)
- Pregnancy outcomes (f.e. birth weight)
- Pregnancy complications
- Stillbirth
- Thyroid function of the woman (before and 1 month after HSG)
- Neonatal outcomes
- Additional fertility treatments (Intra-uterine insemination, IVF, IVF/ICSI)
- Costs within 12 months after randomization
- Thyroid function of neonate (determined by heelprick)

3. STUDY DESIGN

We plan an multicenter randomized controlled trial with an economic analysis alongside it. Infertile women below 39 years of age, who have a spontaneous menstrual cycle and at low risk for tubal pathology, who undergo fertility work-up, will be randomized to direct tubal flushing at HSG with oil-based contrast incorporated in the fertility work-up or delayed tubal flushing 6 months after completion of the fertility work-up (if they did not conceive within the 6 month waiting time). 554 women (277 per arm) will be included in the study.

Figure 1: Flowchart



4. STUDY POPULATION

4.1 Population (base)

We will study infertile women aged between 18 and 38 years of age, who have a spontaneous menstrual cycle and with a perceived low risk for tubal pathology, undergoing fertility work-up will be included.

4.2 Inclusion criteria

In order to be eligible to participate in this study, women must meet all of the following criteria:
- Between 18- and 38 years of age
- Spontaneous menstrual cycle
- Perceived low risk for tubal pathology
- Undergoing fertility work-up

4.3 Exclusion criteria

- Women with known endocrine disorders (e.g. the polycystic ovary syndrome, diabetes, hyperthyroidism and hyperprolactinemia) except for well managed hypothyroidism prior to the fertility work, as defined by TSH level between 0.3 and 2.5 mIU/l
- Ovulation disorders defined as less than eight menstrual cycles per year
- Iodine allergy
- Male subfertility defined as a post-wash total motile sperm count < 1 x10^6 spermatozoa/ml or a pre-wash total motile sperm count <3 x 10^6 spermatozoa/ml
- Not willing or able to sign the consent form
- Insufficient ability to talk and/or read Dutch or English language

4.4 Sample size calculation

Sample size calculation was done in PASS 15.0.6 (NCSS Statistical Software LCC, Utah, USA). Time-to-Event method was used for our sample size calculation, based on the study of Dreyer et al., 2017[4]. Primary outcome is time to pregnancy leading to a live birth within a time horizon of 12 months. A two-sided logrank test with an overall sample size of 554 subjects achieves 90% power at a 0.05 significance level to detect a hazard ratio of 1.39. The expected cumulative live birth rate is 0.53 with a median time to event of 11 months in the control group. The expected cumulative live birth rate is 0.65 in the treatment group with a median time to event of 8 months. Accrual time is 36 months, total time is 48 months and it is assumed that 0.32% of the couples switch from one group to the other group.

5. TREATMENT OF SUBJECTS

Women will be randomized for tubal flushing with oil-based contrast medium at HSG incorporated in the fertility work-up (direct TF) or tubal flushing at HSG with oil-based contrast medium after a waiting time of 6 months after completion of fertility work-up (delayed TF at HSG).

5.1 Investigational product/treatment

Experimental intervention:
Tubal flushing at HSG with Lipiodol® (oil-based contrast medium) (max. 15mL) incorporated in the fertility work-up (direct TF)

Control:
Tubal flushing at HSG with Lipiodol® (oil-based contrast medium) (max. 15mL) after a 6 months waiting period after completion of fertility work-up. (delayed TF)

HSG:
HSG will be done in the follicular phase of the cycle. During HSG a maximum amount of 15cc of oil-based contrast medium will be infused into the uterine cavity through a cervical vacuum cup, a metal cannula (hysterophore) or a special HSG-balloon catheter. The contrast medium contains Iodine and will be visible on radiography. During instillation of the contrast medium, 4-6 radiographs will be taken to see if the fallopian tubes are patent. Test results of the HSG will be classified as normal, one-sided tubal pathology or double-sided tubal pathology.

The planned fertility treatment will be based on the results of the fertility work-up. Women with patent tubes at HSG will be treated according to their prognosis for natural conception based on the model of Hunault[6]. In case the prognosis for natural conception within 12 months ≥30% women will be counselled for expectant management. In case the prognosis is <30%, women will be treated with Intra-Uterine Insemination (IUI) eventually followed by IVF. In case of suspected uni- or bilateral tubal occlusion or pathology, women will be scheduled for Diagnostic Laparoscopy (DLS) according to the local protocol, followed by IVF in case bilateral tubal occlusion is conformed. In case of uni- or bilateral tubal patency during DLS the subsequent fertility treatment will also be based on the Hunault prognosis for natural conception.[6]

5.2 Use of co-intervention (if applicable)

Antibiotic will be prescribed (f.e. Doxycylin 200mg BDS for 7 days) to women with suspicion of intra-abdominal adhesions or hydrosalpinx following HSG, according to the local protocols of the participating centres.

5.3 Escape medication (if applicable)

Not applicable.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of product

The investigational product is an oil-based contrast medium, Lipiodol® (Guerbet). Lipiodol® is a solution of ethyl esters of iodized fatty acids of poppy seed oil equivalent to 480mg I/ml and is a licensed contrast agent in the Netherlands (RVG 02806, see SmPC D2). The maximum amount of Lipiodol® per HSG procedure is 15 ml. Based on the H2Oil study the medium volume of contrast medium used in HSG procedures was 8-9 ml per participant[6].

6.2 Summary of findings from non-clinical studies

This section is not applicable. Both contrast media are routinely used in daily practice and there is more than 50 years of experience with both contrast media in humans.

6.3 Summary of findings from clinical studies

Recently, a meta-analysis of six RCT's (N=2,562) was published. This meta-analysis showed that the use of oil-based contrast medium at HSG was associated with significantly higher rates of ongoing pregnancy compared with the use of water based contrast medium at HSG (OR 1.47, 95% CI 1.12–1.93), based on moderate-quality evidence. Three trials reported live birth, but they were not pooled owing to extreme statistical heterogeneity There was no difference in incidence of miscarriage (OR 0.83, 95% CI 0.56–1.24) or ectopic pregnancy (OR 0.65, 95% CI 0.18–2.36) between oil-based contrast medium and water-based contrast medium groups[7].

Our study group recently submitted a network meta-analysis regarding the effectiveness of tubal flushing with different contrast media on fertility outcomes, we concluded that tubal flushing with oil-based contrast increases short-term (6 months) clinical pregnancy rate and may increase live birth rate compared to tubal flushing with water-based contrast and no tubal flushing, but it is not certain whether such potential superiority persists after 6 months. The effect of oil-based contrast has not been evaluated outside HSG[8].

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6.4 Summary of known and potential risks and benefits

The fertility enhancing mechanism of HSG with oil-based contrast, as showed in the above described Systematic Reviews, is the most important benefit in our study population (infertile women wishing to conceive).

However, several safety concerns on tubal flushing have been raised. Firstly, venous intravasation occurs in approximately 2-7% cases in HSG[9-11], and occurs more frequently when using oil-based contrast. While intravasation can potentially result in pulmonary embolism and even death, no deaths have been reported since the 1960s[12] which is probably related to the introduction of fluoroscopy screening during HSG. Moreover, no cases of embolism were reported in the published RCTs (including the H2Oil study). Secondly, the concern about the thyroid function of mother and child is based on the effects of iodinated contrast media[13,14] and a longer persisting time of oil-based contrast in the pelvis[15]. Maternal hypothyroidism can occur after tubal flushing with oil-based contrast[14], especially in women with subclinical hypothyroidism before HSG[16]. With regards to neonatal

safety, one Japanese studied infants born to mothers who had become pregnant after undergoing HSG with oil-based contrast. Five out of 212 infants tested positive during congenital hypothyroidism screening (2.4%), this frequency was higher than the recall rate among first congenital hypothyroidism screening results (0.7%) in Tokyo, Japan. However, iodine-rich seaweed consumption in Japan can also be a cause of excessive iodine exposure[13]. It is also important to mention that according to the RIVM in the Netherlands, the congenital hypothyroidism (CH) background rate is much lower (0.05%) compared to the background rate in Japan (0.7%). In addition, the median dosage of oil contrast used in the thyroid dysfunction group was significantly higher than compared to the normal thyroid function group (20 ml versus 8 ml, p = 0.033)[13]. For this current study, the maximum of oil contrast will be 15 ml (as per SmPC).
To evaluate CH after HSG with oil or water contrast we conducted a retrospective cohort study (METc Amsterdam UMC – location VUmc 2018.463). We are currently working on this project. However, we anticipate a very low chance of thyroid problems in the neonate.

Thirdly, pelvic infection is another potential safety concern. Data from the included trials in our network meta-analysis indicated it is a rare event and there is insufficient evidence to show a difference between different contrasts.
See also SmPCs under section D2 of the research file, paragraph 4.4, 4.6 and 4.8.

6.5 Description and justification of route of administration and dosage

The HSG will be performed by a gynaecologist, attending-gynaecologist or fertility doctor according to local protocols. HSG will be done in the follicular phase of the cycle. During HSG a maximum amount of max 15 ml of oil-based contrast medium will be infused into the uterine cavity through a cervical vacuum cup, a metal cannula (hysterophore) or a special HSG-balloon catheter. The oil-based contrast medium contains Iodine and will be visible on radiography. All HSGs will be made with real time fluoroscopic imaging. During instillation of the contrast medium, 4-6 radiographs will be taken to see if the fallopian tubes are patent. Test results of the HSG will be classified as normal, one-sided tubal pathology or double-sided tubal pathology. The HSG procedure will be aborted if intravasation occurs, in order to minimize the risk of oil embolism. The maximum amount of contrast medium is 15 ml. Based on the H2Oil study the medium volume of oil-based contrast medium used in HSG procedures will be 8-9 mL per participant[6].

6.6 Dosages, dosage modifications and method of administration

The investigational product is an oil-based contrast medium, Lipiodol® (Guerbet). Lipiodol® is a solution of ethyl esters of iodized fatty acids of poppy seed oil equivalent to 480mg I/ml and is a licensed contrast agent in the Netherlands (RVG 02806, see SmPC D2). The maximum amount of Lipiodol® per HSG procedure is 15 ml. Based on the H2Oil study the medium volume of contrast medium used in HSG procedures was 8-9 ml per participant[6].
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6.7 Preparation and labelling of Investigational Medicinal Product

The Investigational Medicinal Product will not be prepared and labelled according to EU GMP annex 13 regulations. Labelling as an IMP is not deemed necessary, because the IMP will not be dispensed to the patient and administration is performed by a trained physician. We will ensure the IMP is produced and handled according to GMP and GDP regulations. Lipiodol Ultra Fluid® is produced by a GMP approved manufacturer and is authorized in the Netherlands. The contrast medium is licensed for the indication (Hysterosalpingography) used in this study, see also SPC's under section D2 of the research file. An HSG with Lipiodol is normal and standard care in the Netherlands[28]. Lipiodol Ultra Fluid® is distributed by a GMP/GDP pharmaceutical company (Guerbet) stored at constant room temperature in the hospital pharmacy. Dispensing to the radiology department is documented and the contrast media are stored at constant room temperature with air conditioning, in a locked and secured room at the radiology department according to the storage conditions in the SmPC par 6.4.

6.8 Drug accountability

The contrast medium will not be prescribed for the individual patient. The (attending) gynaecologist will state in the medical file of the patient that "the patient is eligible to participate in this study" and states that "the patient will undergo an HSG with Lipiodol® during fertility work-up or 6 months after fertility work-up based on randomization outcome". The (attending) gynaecologist communicates this with the researcher or research nurse of this study. The researcher or research nurse will also check whether the patient is eligible to participate in this study. Randomization will be done by either the (attending) gynaecologist, researcher or research nurse (depending per local center and delegation log). The (attending) gynaecologist will perform the HSG with Lipiodol® in concordance with the randomization. Lipiodol® will only be used once during HSG and will be distributed from the pharmacy to the radiology department. The use of contrast media is standard care, which is used in daily patient care, there the logistics will be according to standard procedures. Before opening a research site the local procedures will be checked for GDP compatibility.
To ensure traceability and accurate documentation of the intervention the (attending-) gynaecologist and investigator will note the RVG-number, batch number, expiration date and volume of used contrast in the register form in the CRF. Drug accountability will be monitored via the CRF based on study number. There will be a monitor plan for all participating centers to check drug traceability and accountability. Together with the CRB of the Amsterdam UMC location VUmc we will ensure the monitoring of the participating centers.

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

The primary outcome is time to live birth, calculated from positive pregnancy test and within 12 months after randomization.

7.1.2 Secondary study parameters/endpoints (if applicable)

- Live birth
- Clinical pregnancy
- Ongoing pregnancy
- Miscarriage
- Ectopic pregnancy
- Multiple pregnancy
- Complications following HSG (infection, intravastion)
- Pregnancy outcomes (f.e. birth weight)
- Pregnancy complications
- Stillbirth
- Thyroid function of the woman (before and 1 month after HSG)
- Neonatal outcomes
- Additional fertility treatments (Intra-uterine insemination, IVF, IVF/ICSI)
- Costs within 12 months after randomization
- Thyroid function of neonate (determined by heelprick)

7.1.3 Other study parameters (if applicable)

The basic parameters which will be monitored are the following: Women's age, ethnicity, medical history, referral status, cycle duration, use of medications, intoxications, BMI.

7.1.4 Data/analysis and presentation/synthesis

Step 1: Summarizing trial data

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

Step 2: Inter-group comparisons

The analysis of all outcomes will be done on an intention-to-treat basis. The effectiveness of a fertility work-up with a strategy of direct tubal flushing at HSG versus a strategy of delayed tubal flushing at HSG will be expressed as a rate for live birth with corresponding 95% confidence intervals. We will compare the time to pregnancy in both groups using Kaplan-Meier analysis. Dichotomous outcomes will be analyzed using either Fisher Exact of chi-square as appropriate. Categorical data will also be analyzed using chi-square. For continuous outcomes we will use t-test if the observations in each trial arm are normally distributed, and if non-normally distributed, then Mann-Whitney-U test will be employed. Although p-values will be reported, the focus will be on providing 95% confidence intervals around point estimates as these are more useful in interpreting the findings of the trial. As the analysis of all outcomes will be done on an intention-to-treat basis, all women randomized will be followed up until the occurrence of an ongoing pregnancy within 12 months after inclusion.

Step 3: Adjustments and sensitivity analysis

If randomization fails to achieve balanced groups, then we will perform secondary analyses in which we will adjust for unbalanced prognostic factors using procedures such as (multiple) logistic regression analyses. If the primary 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 losses to follow-up, missing data and protocol violations, we will attempt sensitivity ("worst-case scenario") analyses to explore the effect of these factors on the trial findings. As a secondary analysis, we will adjust tor missing data using imputation techniques to explore the effects of such imputations on the trial findings. The effect of baseline characteristic on the primary outcome will be explored using (multiple) logistic regression analyses. In sub analyses the association between age, semen quality and ongoing pregnancy will be evaluated.

7.1.5 Cost-effectiveness Analysis (CEA)

General considerations:

The aim of the economic evaluation is to relate the incremental costs of direct tubal flushing at HSG with oil contrast during fertility work-up (intervention) in comparison with delayed tubal flushing at HSG with oil contrast 6 months after fertility work-up (control) to the incremental health effects. Both a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA) will be performed from a societal and healthcare perspective according to Dutch guidelines with a time horizon of 12 months[18]. Because the time horizon of the economic evaluation is 12 months, discounting is not necessary.

Measurement and valuation of costs:

Costs will be measured from a societal perspective using internet questionnaires based on the iMPCQ after 6 and 12 months of follow-up. Cost categories that will be included are:
1) healthcare costs (primary and secondary care, complementary care and home care);
2) lost productivity costs (absenteeism from paid and unpaid work, and presentism);
3) patient costs (informal care and other care services paid for by patients themselves).

Valuation will be done according to Dutch costing guidelines[19]. For the valuation of health care utilization, lost productivity and informal care Dutch standard costs will be used. Medication use will be valued using prices of the Royal Dutch Society for Pharmacy. Patient and family costs other than informal care will be valued using self-reported prices. For the valuation of absenteeism from paid work, the friction cost approach will be used.

Patient outcome analysis:
Our primary effectiveness outcome is time to birth of child within a time horizon of one year. Cost will include delivery cost. We will also determine costs until a conception leading to an ongoing pregnancy. 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 MICE algorithm developed by van Buuren[20]. Rubin's rules will be used to pool the results from the different multiply imputed datasets. Bivariate 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 effect between the treatment groups. Bias-corrected and accelerated bootstrapping with 5000 replications will be used to estimate 95% confidence intervals around the cost differences and statistical uncertainty surrounding the ICERs. Uncertainty surrounding 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[21].

7.1.6 Budget impact analysis (BIA)

General consideration BIA:
A budget impact analysis (BIA) will be conducted from the perspective of health-care decision makers according to the Dutch guidelines and the recommendations from Sullivan et al[19,22]. In the BIA, data from the clinical study and the cost-effectiveness analysis regarding the differences in costs and health outcomes will be combined with national prevalence and incidence data to extrapolate the findings to a time horizon of 5 years. The BIA will be conducted from the societal and government perspective (Budget Kader Zorg). Dutch standard costs for the societal perspective and actual NZA tariffs for the
government perspective.

Cost-analysis:

The budget analyses will differentiate between incidental and structural cost (savings), and take into account budgetary consequences of changes within these cost components. Both resource use and annual costs will be presented for both perspectives. Sensitivity analyses will be performed for subgroups of patients, providing budget information for relevant subgroups to decision makers. In addition, sensitivity analyses will address the impact of variations of the main assumptions and input parameters for the BIA for each of the applied perspectives.

7.2 Randomisation, blinding and treatment allocation

Consenting eligible women will be randomized for tubal flushing with oil-based contrast incorporated in the fertility work-up (direct tubal flushing) or delayed tubal flushing with oil-based contrast 6 months after completion of fertility work-up. Randomization is stratified per centre, will be performed after baseline data have been entered in a centrally web-based system (CASTOR) with the use of permuted block design. Owing to the nature of the intervention and since our primary outcome of live birth is objective, the trial is not blinded with respect to participants and caregivers. Women who decline randomization will be offered the standard treatment in the participating clinic.
The HSG images will be judged by a gynaecologist and/or radiologist according to local protocol, and a conclusion and advised treatment will be given depending on the results and the prognosis on a natural conception based on the model of Hunault[6] or other local protocol.

7.3 Study procedures

Eligible women for participation in the study will be counselled during their regular outpatient clinic visit by the (attending) gynaecologist or fertility doctor. To ensure that they are fully informed on the nature of the study, they will receive written information (Participant Information Form, section E of this research file). If they do not object to telephone contact, the researcher will call the potential participant to answer any questions and to discuss the informed consent procedure. Women who agree to participate will be asked to sign a written informed consent of which they will receive a copy. In cases where women don't have a follow-up appointment scheduled, they will send a digital copy of their signed informed consent form and email this to the researcher after which randomization will take place. In these instances it is possible that the researcher signs the original copy of the informed consent form after the date of randomization.

Consenting eligible women will be randomized for direct or delayed tubal flushing at HSG with oil-based contrast. Randomization is stratified per center, will be performed after baseline data have been entered in a centrally web-based system (CASTOR) with the use of permuted block design. Owing to the nature of the intervention and since our primary outcome of live birth is objective, the trial is not blinded with respect to participants and caregivers. The following patients' characteristics of all patients will be assessed after randomisation: a complete medical history, referral status, BMI, smoking, ethnicity and cycle

duration. Women who decline randomization will be offered the standard treatment in the participating clinic.

Intervention:
Women randomized to direct tubal flushing will undergo an HSG with oil contrast as part of the initial fertility work-up.

Usual care/comparison:
Women randomized to delayed tubal flushing at HSG with oil contrast will be performed 6 months after the initial fertility work-up.

HSG:
Women will be asked to fill out the anxiety questionnaire prior to the HSG to assess fear or anxiety for the procedure. Directly after the procedure women will be asked to report the pain they experienced on a Visual Analogue Scale (VAS).
HSG will be done in the follicular phase of the cycle. During HSG a maximum amount of 15cc of oil-based contrast medium will be infused into the uterine cavity through a cervical vacuum cup, a metal cannula (hysterophore) or a special HSG-balloon catheter. The contrast medium contains Iodine and will be visible on radiography. During instillation of the contrast medium, 4-6 radiographs will be taken to see if the fallopian tubes are patent. Test results of the HSG will be classified as normal, one-sided tubal pathology or double-sided tubal pathology.
The planned fertility treatment will be based on the results of the fertility work-up. Women with patent tubes at HSG will be treated according to their prognosis for natural conception based on the model of Hunault.[6] In case the prognosis for natural conception within 12 months ≥30% women will be counselled for expectant management. In case the prognosis is <30%, women will be treated with Intra-Uterine Insemination (IUI) eventually followed by IVF. In case of suspected uni- or bilateral tubal occlusion or pathology, women will be scheduled for Diagnostic Laparoscopy (DLS) according to the local protocol, followed by IVF in case bilateral tubal occlusion is conformed. In case of uni- or bilateral tubal patency during DLS the subsequent fertility treatment will also be based on the Hunault prognosis for natural conception.[6]

Follow-up:
All women will receive questionnaires regarding medical care (iMCQ) and production loss (iPCQ) after 6 and 12 months. Furthermore, after 12 months all women will receive a questionnaire regarding received fertility treatments, pregnancy(-ies) and live births. All women randomized will be followed up until the occurrence of an ongoing pregnancy within 12 months after inclusion and until life birth if an ongoing pregnancy has occurred.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.4.1 Specific criteria for withdrawal (if applicable)

Not applicable.

7.5 Replacement of individual subjects after withdrawal

According to our power calculation we need to include 554 patients, in case of withdrawal we will replace these patients with new inclusions.

7.6 Follow-up of subjects withdrawn from treatment

Patients who have been withdrawn from treatment will not be followed-up.

7.7 Premature termination of the study

Both the investigator and the Sponsor reserve the right to terminate the study for safety reasons of the subjects of if the trial becomes scientifically meaningless.

8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 AEs, SAEs and SUSARs

8.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation; *except hospitalization for labour, diagnostic laparoscopy, vacuum curettage in case of an incomplete miscarriage or ovarian hyper stimulation syndrome (OHSS) during IVF.*
- results in persistent or significant disability or incapacity;
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.
According to literature, the SAE's that are seen after an HSG are related to infection or allergic reacting, both of which are expected to occur within several days to two weeks after the procedure. In this study the abovementioned SAE's will be reported up until 1 month after the HSG. Additionally, adverse neonatal outcomes such as a congenital anomaly or birth defect will be reported as SAE.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events. SAEs that result in death or are life threatening should be reported expedited.

All investigators of the participating hospitals will directly report the serious adverse events to the Sponsor of this study. The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

8.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

8.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

8.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

8.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

A DSMB will not be installed since the product and intervention used in this study are registered for the given indication and used in clinical practice for years.

9. STATISTICAL ANALYSIS

9.1 Primary study parameter(s)

The primary outcome is time to live birth, calculated from positive pregnancy test and within 12 months after randomization. The primary analysis will be performed in the intention-to-treat population. Differences in time to live-birth will be analyzed using Kaplan Meier analysis and tested with the log-rank test. The treatment groups will be compared by the 95% two sided confidence interval for the difference between the intervention (HSG incorporated in fertility work up) and the control group (HSG 6 months after fertility work up). The primary analysis will be repeated in the per protocol population.

9.2 Secondary study parameter(s)

All secondary outcomes (listed in section 8) will be compared in the intention-to-treat and the per protocol population. For numerical and continuous outcomes, 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-square of Fishers exact test.
For the cost effectiveness analyses a Cost Effectiveness Analysis (CEA) and Budget Impact Analysis (BIA) will be performed. For detailed information about the CEA and BIA see grant application ZonMw (section K of this research file).

9.3 Other study parameters

In case of continuous data, group results are presented as means and standard deviations (normally distributed data) or medians and ranges (non-parametrical data). In case of categorical data number with percentages will be used. These statistics will be provided for the intention to treat (ITT) and per protocol (PP) groups.

9.4 Interim analysis (if applicable)

Not applicable.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts. The study protocol will be submitted to the ethics committee.

10.2 Recruitment and consent

Eligible patients will be informed about the study by the gynaecologist, the attending resident or the fertility doctor. The patients will also obtain written information about the study. Subsequently, the investigator, supervising gynaecologist, the attending registrar or fertility doctor must explain to each subject the nature of this study, its purpose, procedures, expected duration and the potential risks and benefits involved in study participation along with any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that withdrawal of consent will not affect her right to the most appropriate medical treatment or affect the doctor relationship. This informed consent should be given by means of a standard written statement. It should be written so as to be easily understood by the subject. The subject should be given enough time to read and understand the statement herself before signing her consent and dating the document. In case the subject wants more information, an independent doctor is available to answer her questions. The subject should receive a copy of the written statement once signed.

10.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

10.4 Benefits and risks assessment, group relatedness

The potential benefit of direct tubal flushing with oil-based contrast during fertility work-up is a shorter time to pregnancy.

10.5 Compensation for injury

The Amsterdam UMC – location VUmc has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.
1. € 650.000,-- (i.e. six hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 5.000.000,-- (i.e. five million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 7.500.000,-- (i.e. seven million five hundred thousand Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.6 Incentives (if applicable)

Not applicable.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

Informed Consents (IC) will be stored in a locked closet on the medical researchers' room (or in the ISF on the local research nurses' room) which is locked if the medical researcher or local research nurse is not there. Randomisation will be done in a web-based registration system (Castor Electronic Data Capture, Ciwit BV, Amsterdam, The Netherlands, 2016) with the use of permuted block design and is stratified per center. The study code is a meaningless generated number and will not be based on the patient's initials or birth date. Data will be handled coded and confidentially according to the Good Clinical Practice (GCP) guideline and General Data Protection Regulation (GDPR) (in Dutch: Algemene verordening Gegevensbescherming (AVG)).

The Trial Master File (TMF) or Investigator Site File (ISF) will be stored with a password on the hard disk of the local Obs&Gyn department of the participating center. Only the medical researcher and principal investigator have access to the TMF on the hard disk at the Amsterdam UMC – location VUmc, and are able to identify the link between study number and participant. The Investigator Site is available for the local investigator and research nurse. Data will be handled confidentially, with the link between the participant and study code only available to the local investigator and research nurse in the participating center. All data will be collected by study number in a web-based registration system (Castor Electronic Data Capture, Ciwit BV, Amsterdam, The Netherlands, 2016). Data will be stored for a maximum of 25 years after the study has been completed. Afterwards all data will be deleted. Data will only be shared with other researchers in case of valid and relevant requests, and a coded database will be shared without any linkage to individual participants.

11.2 Monitoring and Quality Assurance

An independent monitor from the Clinical Research Bureau (CRB) of the Amsterdam UMC – location VUmc will have access to the data and source documents of the trial. Monitoring will be performed in compliance with Good Clinical Practice (GCP) and other rules and regulations in order to achieve high quality research and secure patient safety.

11.3 Amendments

All amendments will be notified to the METC and to the competent authority.

11.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.5 Start of study

The start of this study will be communicated to the METC.

11.6 Temporary halt and (prematurely) end of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.
The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.7 Public disclosure and publication policy

No specific arrangements will be made between any sponsors and the investigator concerning the public disclosure and publication of the research data. The principle investigator will publish the results of the study as soon as appropriate. The results of the study will be disclosed unreservedly as mentioned in the statement on publication policy of the CCMO (www.ccmo.nl).

12. STRUCTURED RISK ANALYSIS

12.1 Potential issues of concern

Not applicable: use of registered products used within the indication and not in combination with other products.

12.2 Synthesis

Since we compare timing of an examination used in daily practice for years we do not expect additional risks compared to the standard practice outside the study. See also previous literature in section K of this research file.

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