OXFORD

human reproduction

Human Reproduction, 2024, **39(6),** 1222–1230

https://doi.org/10.1093/humrep/deae071

Advance Access Publication Date: April 10, 2024

Original Article

Infertility

Hysterosalpingo-foam sonography versus hysterosalpingography during fertility work-up: an economic evaluation alongside a randomized controlled trial

Danah Kamphuis [1,2,*], Rik van Eekelen [2,3], Nienke van Welie [1,2,4], Kim Dreyer[1,2], Joukje van Rijswijk[1,2], Machiel H.A. van Hooff[5], Jan Peter de Bruin[6], Harold R. Verhoeve[4], Femke Mol [2,3], Wilhelmina M. van Baal[7], Maaike A.F. Traas[8], Arno M. van Peperstraten[9,10], Arentje P. Manger[11], Judith Gianotten[12], Cornelia H. de Koning[13], Aafke M.H. Koning[14], Neriman Bayram[15], David P. van der Ham[16], Francisca P.J.M. Vrouenraets[17], Michaela Kalafusova[18], Bob I.G. van de Laar[4], Jeroen Kaijser[19], Arjon F. Lambeek[20], Wouter J. Meijer[21], Frank J.M. Broekmans[10,22], Olivier Valkenburg[23], Lucy F. van der Voet[24], Jeroen van Disseldorp[25], Marieke J. Lambers[22], Rachel Tros[26], Cornelis B. Lambalk [1,2], Jaap Stoker [27], Madelon van Wely [2,3,28], Patrick M.M. Bossuyt[28], Ben Willem J. Mol[29,30], and Velja Mijatovic [1,2]

[1]Department of Reproductive Medicine, Amsterdam UMC location Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
[2]Amsterdam Reproduction and Development Research Institute, Amsterdam, The Netherlands
[3]Centre for Reproductive Medicine, Amsterdam UMC location Universitity of Amsterdam, Amsterdam, The Netherlands
[4]Department of Obstetrics and Gynaecology, OLVG, Amsterdam, The Netherlands
[5]Department of Obstetrics and Gynaecology, Franciscus Hospital, Rotterdam, The Netherlands
[6]Department of Obstetrics and Gynaecology, Jeroen Bosch Hospital, Den Bosch, The Netherlands
[7]Department of Obstetrics and Gynaecology, Flevo Hospital, Almere, The Netherlands
[8]Department of Obstetrics and Gynaecology, Gelre Hospitals, Apeldoorn, The Netherlands
[9]Department of Obstetrics and Gynaecology, Rivierenland Hospital, Tiel, The Netherlands
[10]Department of Reproductive Medicine and Gynaecology, University Medical Centre Utrecht, Utrecht, The Netherlands
[11]Department of Obstetrics and Gynaecology, Diakonessenhuis, Utrecht, The Netherlands
[12]Department of Obstetrics and Gynaecology, Spaarne Gasthuis, Haarlem, The Netherlands
[13]Department of Obstetrics and Gynaecology, Tergooi Medical Center, Hilversum, The Netherlands
[14]Department of Obstetrics and Gynaecology, Amstelland Hospital, Amstelveen, The Netherlands
[15]Department of Obstetrics and Gynaecology, Zaans Medical Centre, Zaandam, The Netherlands
[16]Department of Obstetrics and Gynaecology, Martini Hospital, Groningen, The Netherlands
[17]Department of Obstetrics and Gynaecology, Zuyderland Medical Center, Heerlen, The Netherlands
[18]Department of Obstetrics and Gynaecology, Refaja Hospital, Stadskanaal, The Netherlands
[19]Department of Obstetrics and Gynaecology, Ikazia Medical Center, Rotterdam, The Netherlands
[20]Department of Obstetrics and Gynaecology, IJsselland Hospital, Capelle aan den IJssel, The Netherlands
[21]Department of Obstetrics and Gynaecology, Gelre Hospitals, Zutphen, The Netherlands
[22]Department of Obstetrics and Gynaecology, Dijklander Hospital, Hoorn, The Netherlands
[23]Department of Reproductive Medicine, Maastricht University Medical Centre, Maastricht, The Netherlands
[24]Department of Obstetrics and Gynaecology, Deventer Hospital, Deventer, The Netherlands
[25]Department of Obstetrics and Gynaecology, Sint Antonius Hospital, Nieuwegein, The Netherlands
[26]Department of Obstetrics and Gynaecology, Amsterdam UMC location University of Amsterdam, Amsterdam, The Netherlands
[27]Department of Radiology and Nuclear Medicine, Amsterdam UMC location University of Amsterdam, Amsterdam, The Netherlands
[28]Department of Epidemiology & Data Science, Amsterdam Public Health, Amsterdam UMC, Amsterdam, The Netherlands
[29]Department of Obstetrics and Gynaecology, Monash University, Clayton, VIC, Australia
[30]Aberdeen Centre for Women's Health Research, University of Aberdeen, King's College, Aberdeen, UK

*Correspondence address. Department of Reproductive Medicine, Amsterdam UMC location Vrije Universiteit Amsterdam, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands. E-mail: d.kamphuis@amsterdamumc.nl https://orcid.org/0000-0002-2627-8591

ABSTRACT

STUDY QUESTION: What are the costs and effects of tubal patency testing by hysterosalpingo-foam sonography (HyFoSy) compared to hysterosalpingography (HSG) in infertile women during the fertility work-up?

SUMMARY ANSWER: During the fertility work-up, clinical management based on the test results of HyFoSy leads to slightly lower, though not statistically significant, live birth rates, at lower costs, compared to management based on HSG results.

WHAT IS KNOWN ALREADY: Traditionally, tubal patency testing during the fertility work-up is performed by HSG. The FOAM trial, formally a non-inferiority study, showed that management decisions based on the results of HyFoSy resulted in a comparable live

Received: May 19, 2023. **Revised:** January 29, 2024. **Editorial decision:** March 22, 2024.

birth rate at 12 months compared to HSG (46% versus 47%; difference −1.2%, 95% CI: −3.4% to 1.5%; $P = 0.27$). Compared to HSG, HyFoSy is associated with significantly less pain, it lacks ionizing radiation and exposure to iodinated contrast medium. Moreover, HyFoSy can be performed by a gynaecologist during a one-stop fertility work-up. To our knowledge, the costs of both strategies have never been compared.

STUDY DESIGN, SIZE, DURATION: We performed an economic evaluation alongside the FOAM trial, a randomized multicenter study conducted in the Netherlands. Participating infertile women underwent, both HyFoSy and HSG, in a randomized order. The results of both tests were compared and women with discordant test results were randomly allocated to management based on the results of one of the tests. The follow-up period was twelve months.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We studied 1160 infertile women (18–41 years) scheduled for tubal patency testing. The primary outcome was ongoing pregnancy leading to live birth. The economic evaluation compared costs and effects of management based on either test within 12 months. We calculated incremental cost-effectiveness ratios (ICERs): the difference in total costs and chance of live birth. Data were analyzed using the intention to treat principle.

MAIN RESULTS AND THE ROLE OF CHANCE: Between May 2015 and January 2019, 1026 of the 1160 women underwent both tubal tests and had data available: 747 women with concordant results (48% live births), 136 with inconclusive results (40% live births), and 143 with discordant results (41% had a live birth after management based on HyFoSy results versus 49% with live birth after management based on HSG results). When comparing the two strategies—management based on HyfoSy results versus HSG results—the estimated chance of live birth was 46% after HyFoSy versus 47% after HSG (difference −1.2%; 95% CI: −3.4% to 1.5%). For the procedures itself, HyFoSy cost €136 and HSG €280. When costs of additional fertility treatments were incorporated, the mean total costs per couple were €3307 for the HyFoSy strategy and €3427 for the HSG strategy (mean difference €−119; 95% CI: €−125 to €−114). So, while HyFoSy led to lower costs per couple, live birth rates were also slightly lower. The ICER was €10 042, meaning that by using HyFoSy instead of HSG we would save €10 042 per each additional live birth lost.

LIMITATIONS, REASONS FOR CAUTION: When interpreting the results of this study, it needs to be considered that there was a considerable uncertainty around the ICER, and that the direct fertility enhancing effect of both tubal patency tests was not incorporated as women underwent both tubal patency tests in this study.

WIDER IMPLICATION OF THE FINDINGS: Compared to clinical management based on HSG results, management guided by HyFoSy leads to slightly lower live birth rates (though not statistically significant) at lower costs, less pain, without ionizing radiation and iodinated contrast exposure. Further research on the comparison of the direct fertility-enhancing effect of both tubal patency tests is needed.

STUDY FUNDING/COMPETING INTEREST(S): FOAM trial was an investigator-initiated study, funded by ZonMw, a Dutch organization for Health Research and Development (project number 837001504). IQ Medical Ventures provided the ExEm®-FOAM kits free of charge. The funders had no role in study design, collection, analysis, and interpretation of the data. K.D. reports travel-and speakers fees from Guerbet and her department received research grants from Guerbet outside the submitted work. H.R.V. received consulting—and travel fee from Ferring. A.M.v.P. reports received consulting fee from DEKRA and fee for an expert meeting from Ferring, both outside the submitted work. C.H.d.K. received travel fee from Merck. F.J.M.B. received a grant from Merck and speakers fee from Besins Healthcare. F.J.M.B. is a member of the advisory board of Merck and Ferring. J.v.D. reported speakers fee from Ferring. J.S. reports a research agreement with Takeda and consultancy for Sanofi on MR of motility outside the submitted work. M.v.W. received a travel grant from Oxford Press in the role of deputy editor for *Human Reproduction* and participates in a DSMB as independent methodologist in obstetrics studies in which she has no other role. B.W.M. received an investigator grant from NHMRC GNT1176437. B.W.M. reports consultancy for ObsEva, Merck, Guerbet, iGenomix, and Merck KGaA and travel support from Merck KGaA. V.M. received research grants from Guerbet, Merck, and Ferring and travel and speakers fees from Guerbet. The other authors do not report conflicts of interest.

TRIAL REGISTRATION NUMBER: International Clinical Trials Registry Platform No. NTR4746.

Keywords: infertility / tubal patency testing / hysterosalpingo-foam sonography (HyFoSy) / hysterosalpingography (HSG) / fertility work-up / live birth / cost-effectiveness analysis (CEA)

Introduction

Tubal pathology is one of the main underlying causes of infertility and affects between 11% and 30% of all women suffering infertility (Farquhar *et al.*, 2019; Anyalechi *et al.*, 2021). During the fertility work-up, it is therefore important to assess the patency of the fallopian tubes. Tubal patency can be assessed by a variety of tests (Saunders *et al.*, 2011). Laparoscopy with chromotubation is historically considered to be the reference test, as it can assess tubal patency and visualize pelvic anatomy at the same time, thus allowing simultaneous treatment (NICE, 2013). However, laparoscopy is an invasive and expensive procedure, it has shown to be less cost-effective compared to hysterosalpingography (HSG) (Verhoeve *et al.*, 2013), and therefore it is not the preferred test for women at low risk for tubal pathology (NICE, 2013; ASRM, 2020). HSG and hysterosalpingo-foam sonography (HyFoSy) are widely used alternatives for tubal patency testing. Both tests have a high and comparable diagnostic accuracy for evaluating tubal patency, compared to laparoscopy with chromotubation with a sensitivity of respectively 0.95 and 0.94 and a specificity of 0.93 and 0.92 (Broeze *et al.*, 2011; Maheux-Lacroix *et al.*, 2014; Alcázar *et al.*, 2020).

During HSG, the uterus and fallopian tubes are made visible on X-rays by infusing iodinated contrast medium into the uterine cavity. HSG has been considered as first-choice tubal patency test for decades (NICE, 2013; ASRM, 2020). Although HSG is less invasive than laparoscopy, it causes exposure to ionizing radiation and iodinated contrast medium, and women generally experience HSG as painful (Dreyer *et al.*, 2014; Engels *et al.*, 2021; Serrano Gonzalez *et al.*, 2022). To avoid these disadvantages of HSG, sonographic tubal patency methods have been introduced, such as HyFoSy. During HyFoSy, an echogenic foam is infused into the uterine cavity to evaluate patency of the fallopian tubes (Emanuel and Exalto, 2011). As HyFoSy is a more patient-friendly test than HSG, it has been argued that HSG should be replaced by sonographic tubal patency testing (Hamed *et al.*, 2009; Luciano *et al.*, 2011; Lim *et al.*, 2015; Lo Monte *et al.*, 2015). For many years, there were no studies that compared the diagnostic effectiveness of HyFoSy and HSG during fertility work-up. We recently reported the results of the FOAM trial, which compared clinical management based on the results of HyFoSy and HSG during fertility work-up, with ongoing pregnancy leading to live birth as primary outcome. This study showed that management

decisions based on the results of HyFoSy resulted in a comparable live birth rate at 12 months compared to HSG (46% versus 47%; difference −1.2%, 95% CI: −3.4% to 1.5%; $P = 0.27$) (van Welie *et al.*, 2022).

Since healthcare costs are increasing, cost-effectiveness is becoming ever more relevant in healthcare (OECD, 2023). Before adjusting fertility work-up guidelines and implementing HyFoSy as first-choice diagnostic tubal patency test, it may be relevant to compare the costs as well as the effects of HyFoSy and HSG. We here report a cost-effectiveness analysis of tubal patency testing by HyFoSy and HSG during fertility work-up, performed alongside the FOAM trial.

Materials and methods

The FOAM trial was a multicenter prospective, comparative study with a randomized design, performed in the Netherlands between May 2015 and January 2019 (van Welie *et al.*, 2022). In this study, the effectiveness of clinical management based on the results of tubal patency testing by HyFoSy and HSG during fertility work up was compared. The study was approved by the Institutional Review Board of the Amsterdam UMC, location VU Medical Centre (No. 2014.454), the National Central Committee on Research involving Human Subjects (CCMO, The Netherlands; No. NL50484.029.14), and the local board of directors of the participating hospitals. The study is registered in the International Clinical Trials Registry Platform (No. NTR4746).

Study design

The protocol of the FOAM trial, including a description of this economic evaluation, has been published previously (van Rijswijk *et al.*, 2018b). In summary, eligible and consenting women underwent both tubal patency tests in a randomly assigned order (HyFoSy-HSG or HSG-HyFoSy). The results of both tests were compared and assessed as concordant, inconclusive, or discordant. In case of discordant test results, women were randomly allocated to management based on the results of either HyFoSy or HSG.

Study group, procedures, and outcomes

Infertile women were eligible if they were between 18 and 41 years of age and scheduled for tubal patency testing. The male partner or sperm donor should have normal or mildly impaired semen quality with a total post washed motile sperm count above 3×10^6 per milliliter. Women known with endometriosis, anovulatory cycles not responding to ovulation induction, and/or allergy to iodinated contrast medium were not invited.

Eligible and consenting women underwent both tubal patency tests in the follicular phase of their cycle. During HyFoSy, 5–10 cc of echogenic foam (created by mixing 5 cc ExEm®-gel with 5 cc sterile purified water (IQ Medical Ventures BV, Rotterdam, The Netherlands)) was infused through a special catheter with cervical cannula into the uterine cavity, while a transvaginal ultrasound was made. This ultrasound showed whether the foam passed through the fallopian tubes into the abdominal cavity, thereby demonstrating patency of the tubes or not. During HSG, contrast medium (oil- or water-based, according to local protocols) was infused into the uterine cavity through a special HSG-balloon catheter, cervical vacuum cup, or hysterophore. During infusion of the contrast medium, approximately four to six radiographs were taken to evaluate the patency of the fallopian tubes. The evaluation was done by a gynaecologist and/or radiologist. Due to the design of the study, neither of the clinicians nor participating couples were blinded, however HyFoSy and HSG were performed by different clinicians who were not informed about the results of the other test.

Subsequent clinical fertility management was either based on the results of both tests in women with concordant or inconclusive test results or based on the results of the randomly assigned test in women with discordant test results. In women with at least one patent fallopian tube, expectant management for a minimum of 6 months or IUI was offered, depending on their prognosis for natural conception based on the Hunault model (Hunault *et al.*, 2004). After six failed IUI cycles, women were offered IVF. In women with bilateral occlusion, IVF was offered or diagnostic laparoscopy with chromotubation was performed to confirm tubal occlusion and if confirmed, IVF was offered. Women with ovulation disorders and tubal patency continued using ovulation induction with or without IUI according to the local protocols.

The primary outcome was ongoing pregnancy leading to live birth within 12 months after randomization. Ongoing pregnancy was defined as an intrauterine pregnancy with a fetal heartbeat on ultrasound examination between 10 and 12 weeks of gestation. Live birth was defined as a live birth after 24 weeks of gestation. Secondary outcomes considered in this economic evaluation were ongoing pregnancy rate, miscarriage rate, ectopic pregnancy rate, and multiple pregnancy rate.

Economic evaluation

The economic evaluation was performed from a healthcare (direct medical costs) and societal (direct and indirect medical costs) perspective and expressed in European currency (Euro), in line with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines (McGhan *et al.*, 2009) and following the Consolidated Health Economic Evaluation Reporting Standards statement (Husereau *et al.*, 2022).

From a healthcare perspective, we considered all costs associated with achieving live births in the primary analysis: tubal patency testing, fertility treatments, and costs associated with pregnancy and childbirth. Costs associated with pregnancy and childbirth included costs for miscarriage, ectopic pregnancy, and birth (singleton and multiple). The Dutch Health Care Authority has not assigned a standard price for HyFoSy. The unit price for HyFoSy was therefore estimated by including the costs to perform a transvaginal ultrasound and the costs of the ExEm®-Foam and catheter. The costs for HSG were according to the Dutch Health Care Authority plus the mean costs for water- and oil-based contrast medium (retrieved from the Dutch Formulary for medication (Hakkaart-Van Roijen, 2016) and Guerbet, respectively). The costs for fertility treatments and pregnancy losses (miscarriages and ectopic pregnancies) were obtained from the costs as retrieved by an expert panel on cost-effectiveness from the Dutch Consortium for Research in Women's Health. The expert panel, consisting of gynaecologists, economists, and a methodologist, determined the actual per unit medical costs from resources that are being used in fertility studies within our consortium from two university hospitals and one general hospital. For the costs of a singleton and multiple pregnancy and birth, we used the study of Lukassen *et al.* (2004).

From a societal perspective, we added costs due to productivity loss to all other mentioned costs. Productivity loss due to absenteeism from work during fertility treatment were calculated using Dutch governmental guidelines (Hakkaart-Van Roijen, 2016). All prices were standardized for the year 2018 using consumer price index data. The unit costs that were included in this economic evaluation are presented in Table 1.

Data on resource use were collected from the individual case record forms of the clinical trial. For each woman, the number of subsequent fertility treatments and pregnancy outcome within twelve months after inclusion was reported.

Statistical analysis

For the analysis, we created two datasets for the 1026 participating women: one in which all would only have HyFoSy and HyFoSy based management and a second in which all would only have HSG and would follow HSG based management. We calculated the weighted average of all live births for women with concordant, inconclusive, and discordant test results, in which only the one with discordant results (n = 143) contributed to a difference between the two strategies in terms of management costs. For the women with at least one inconclusive test results, we included the costs for the initial (inconclusive) test and the alternative other test.

The incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in mean total costs by the difference in chance of live birth. We bootstrapped the costs and effects for 5000 samples with replacement to obtain the 95% confidence intervals (95% CI) of skewed costs and effects. We reported the results from bootstrapping in the cost-effectiveness plane with the four quadrants that represent the four possible conclusions (HyFoSy-based management is more effective, but also more expensive than HSG based management; HyFoSy-based management is less effective and less expensive; HyFoSy-based management is less effective and more expensive; and HyFoSy-based management is more effective and less expensive).

We used the bootstrap samples to construct a cost-effectiveness acceptability curve (CEAC) following Fenwick *et al.* (2004). In CEACs, we vary the willingness-to-pay threshold from €0 to €100 000. The purpose of the CEAC is to show the probability that HyFoSy-based management would be considered cost-effective at these varying thresholds, defined as the proportion of bootstrap samples where the ICER was below the threshold value. This reflects the uncertainty around cost-effectiveness even when bootstrap samples cross quadrants.

Sensitivity analyses

We first repeated the previously mentioned economic evaluation in the discordant patient group (instead of the overall 1026 women), as although this group can in practice not be found without conducting both tests on a patient, this subgroup is the driving force behind the difference in the overall group.

Second, to evaluate the influence of costs associated with pregnancy and childbirth on the results, we repeated the analysis but now excluded these costs. As the primary goal of fertility treatment is to achieve live births, these costs as consequences of those live births could be considered as secondary, less important, or even warranted.

Third, to evaluate the influence of the societal costs on cost-effectiveness, we conducted the same analysis in which we added costs for productivity loss due to hospital visits during their fertility treatment according to Dutch guidelines as well (Hakkaart-Van Roijen, 2016).

Fourth, as HSG can be performed with either water-based or oil-based contrast medium and this leads to considerable differences in price, sensitivity analyses were undertaken for the price of HSG with exclusively water-based contrast (€160) or oil-based contrast (€400).

Results

Study group and effectiveness outcome

Between May 2015 and January 2019, 1160 women were included; a total number of 1026 women underwent both tubal patency tests and had data available (the flowchart of the FOAM trial is presented in Supplementary Fig. S1). The baseline characteristics for the entire study group and the two arms in those randomized after discordant results were comparable (Supplementary Table S1). Seven hundred and forty-seven (73%) women had concordant test results, 143 (14%) women had discordant test results, and 136 (13%) women had at least one inconclusive test result, meaning either HyFoSy or HSG had failed. Of the 143 women with discordant test results, 105 gave consent and were randomly assigned to clinical management guided by either the results of HyFoSy or HSG. The live birth rate in women with

Table 1. Unit costs for the different direct medical cost categories: tubal patency tests, fertility treatment, pregnancy/birth and the indirect medical costs.

	Unit costs in Euro[a]	Reference
Tubal patency testing		
Hysterosalpingo-foam sonography[b]	136	Dutch hospitals and IQ Medical Ventures
Hysterosalpingography[c]	280	Dutch Health Care Authority
Fertility treatment		
Ovulation induction[d]	391	Dutch hospitals
IUI without mild ovarian hyperstimulation	346	Dutch hospitals
Hormonal stimulated IUI	347	Dutch hospitals
IVF	1450	Dutch hospitals
ICSI	1803	Dutch hospitals
Cryo cycle	372	Dutch hospitals
Pregnancy/birth		
Singleton	3298	Lukassen *et al.* (2004)
Multiple	17 427	Lukassen *et al.* (2004)
Miscarriage[e]	97	Dutch hospitals
Indirect medical costs		
Productivity loss—female (per hour)	32	CBS
Productivity loss—male (per hour)	38	CBS

CBS, Statistics Netherlands.
[a] Prices of the year of 2018.
[b] HyFoSy costs were estimated based on the costs for transvaginal ultrasound and the costs for the ExEm®-foam and catheter (€62.10 and €70.00, respectively).
[c] HSG costs were calculated by averaging the costs of water- and oil-based contrast medium (€168.21 and €399.90, respectively).
[d] Ovulation induction costs were calculated by averaging the costs for ovulation induction by Clomiphene Citrate and gonadotrophines (€198.43 and €583.15, respectively).
[e] Costs for miscarriage were based on the mean costs for spontaneous miscarriage, medical treatment and curettage.

concordant test results was 48% (361/747) and 40% (55/136) in women with inconclusive test results. For women with discordant test results allocated to clinical management based on the results of HyFoSy, live birth rate was 41% (22/54) and 49% (25/51) for women allocated to management based on the results of HSG. This resulted in a difference in live birth of −8% (95% CI: −27% to 10%). When these results were extrapolated to the entire study group, management based on the results of either HyFoSy or HSG was estimated to lead to a live birth rate of respectively 46% (474/1026) and 47% (486/1026) (difference −1.2%; 95% CI: −3.4% to 1.5%; $P = 0.27$). Miscarriage, ectopic pregnancy, and multiple pregnancy rates were low and not significantly different for both groups. Additional information on the subsequent fertility treatment after tubal patency testing is presented in Supplementary Table S2.

Economic evaluation

In the entire study group, considering the costs in those with concordant, inconclusive, and discordant results, the average total costs for tubal patency testing, fertility treatments, pregnancy, and childbirth were €3307 (95% CI: €3104–€3523) for management based on the results of HyFoSy and €3427 (95% CI: €3223–€3642) for management based on the results of HSG, giving a mean difference of €−119 (95% CI: €−125 to €−114).

So, while HyFoSy-based management led to lower costs per couple, live birth rates were also slightly lower, although this was not statistically significant. This yielded an ICER of €10 042, meaning that by using HyFoSy instead of HSG we would save €10 042 per each additional live birth lost. Vice versa, additional costs of €10 042 on HSG are incurred per additional live birth.

In Fig. 1, we report the bootstrap samples in the cost-effectiveness plane. Of all samples 81.1% appeared in the south-west (HyFoSy-based management is less expensive but also less effective) and 18.9% of the samples appeared in the south-east (HyFoSy-based management is less expensive and more effective). Because of crossing quadrants, simple 95% CIs of the ICER cannot be interpreted.

The CEAC in Fig. 2 provides more information on the uncertainty surrounding the cost-effectiveness, as the ICER is difficult to interpret when crossing quadrants. We found that at willingness to pay of €5000 per additional live birth, HyFoSy-based management was cost-effective in 81.6% of bootstrap samples compared to HSG-based management, which decreased further to 32.4% for a willingness to pay threshold of €20 000 and 24.8% for a willingness to pay threshold of €40 000.

Sensitivity analyses

The cost-effectiveness planes and CEACs of the sensitivity analyses are shown in Supplementary Figs S2, S3, S4, S5, S6, S7, S8, S9, S10, and S11.

First, in the subgroup with discordant test results (analysis 1), which is the subgroup which contributed to a difference between the two strategies in terms of management costs, the average total costs were €2823 (95% CI: €2335–€3300) for HyFoSy-based management and €3544 (95% CI: €2599–€4670) for HSG-based management, giving a mean (bootstrap) difference of €−722 (95% CI: €−1895 to €348). As before, the live birth rates were 40.7% after HyFoSy and 49.4% after HSG, giving a mean difference of −8.6% (95% CI: −27.6 to 10.2). HyFoSy was on average less expensive and less effective than HSG resulting in an ICER of €8349. We show the cost-effectiveness plane in Supplementary Fig. S2 and the cost-effectiveness acceptability curve in Supplementary Fig. S3.

Second, in the sensitivity analysis excluding the costs associated with pregnancy and childbirth, results were similar to the primary analysis (analysis 2).

Third, in the sensitivity analysis using the societal perspective (analysis 3), we found that the results were similar to the ones in the primary analysis.

Fourth and final, in the sensitivity analysis including costs if all HSG procedures were conducted with either water-based (analysis 4A) or oil-based contrast medium (analysis 4B), we found lower (€1062) and higher (€19 525) ICERs, respectively, compared to the primary analysis. There was still a considerable amount of uncertainty surrounding ICERs as shown in the CEACs such that overall conclusions were similar to the primary analysis.

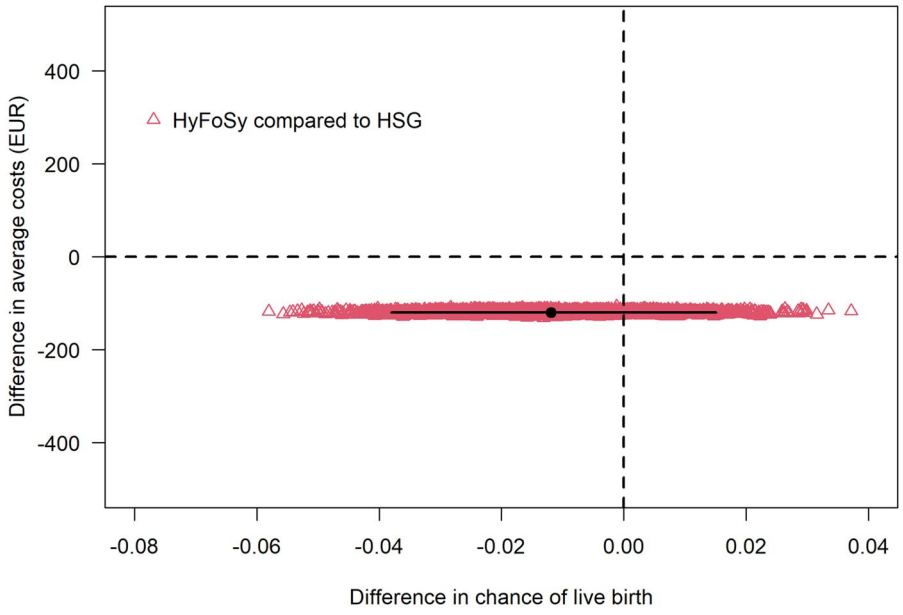

Figure 1. Cost-effectiveness plane showing differences in costs and proportions of live birth in all bootstrap samples. HyFoSy, hysterosalpingo-foam sonography (HyFoSy-based management); HSG, hysterosalpingography (HSG-based management).

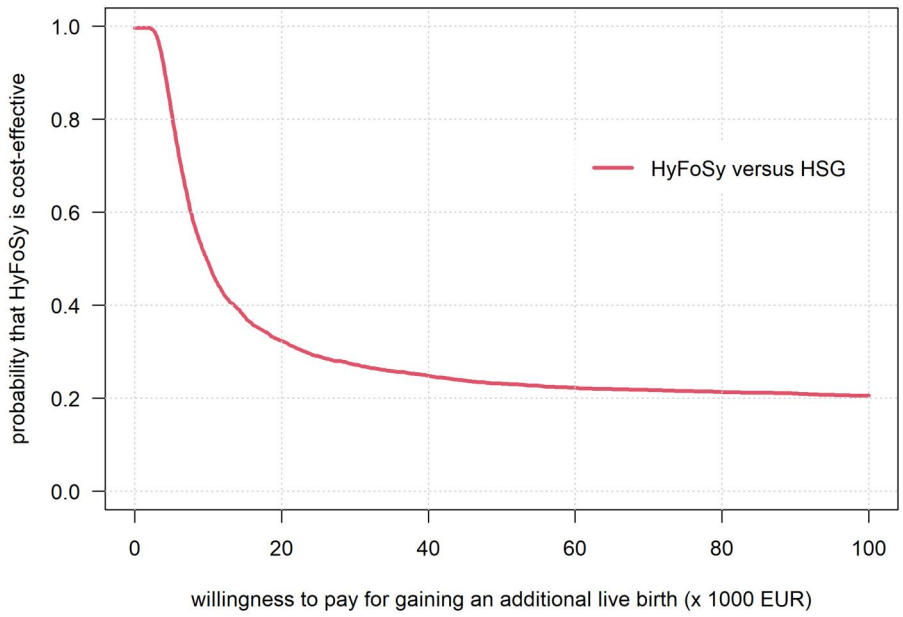

Figure 2. Cost-effectiveness acceptability curve showing the proportion of bootstrap samples (y-axis) that were found cost-effective when compared to a range of threshold monetary values (x-axis). HyFoSy, hysterosalpingo-foam sonography (HyFoSy-based management); HSG, hysterosalpingography (HSG-based management).

Discussion

Principal findings

We here report results of an economic evaluation, performed alongside the FOAM trial. In women scheduled for tubal patency testing during their fertility work-up, clinical management based on the results of HyFoSy leads to slightly lower live birth rates (though not statistically significant) at slightly lower costs compared to management based on the results of HSG. This yielded an ICER of €10 042, meaning that by using HyFoSy instead of HSG, we would save €10 042 per additional live birth lost. There was considerable uncertainty around the ICER.

Strengths and limitations

The primary outcome of this study was ongoing pregnancy leading to live birth, the most relevant outcome for couples during their fertility work-up. We performed two sensitivity analyses to also evaluate the influence of the costs for contrast media used on the cost-effectiveness, as the costs for HSG are mainly driven by the type of contrast medium (oil-based contrast medium is approximately 12 times more expensive than water-based contrast medium). As a consequence, this had a considerable influence on our results given that the costs of the tests was the primary difference between strategies. The FOAM trial included women with numerous causes of infertility, therefore the results of this study may be widely applicable within fertility care. Analyses were performed from two perspectives: a healthcare perspective including direct medical costs only and a societal perspective including direct and indirect medical costs.

A limitation of this study is the number of inconclusive HyFoSy test results, which was higher than anticipated. This situation could partly be explained by the fact that HyFoSy was a relatively new method for assessing tubal patency and that clinicians may not have mastered performing HyFoSy, despite the mandatory training before start of the study. Another explanation can be that HyFoSy is an operator dependent test, which makes it more difficult to assess the sonographic images once the test is performed. In the situation of inconclusive test results, an alternative tubal patency test should be performed which involves additional costs. We expect that once HyFoSy is more established in daily practice, clinicians' experience will grow, resulting in a reduced number of inconclusive tests. We observed a significant uncertainty surrounding ICER comparing both tubal patency strategies. This uncertainty predominantly concerned the uncertainty surrounding the difference in live birth rate for both tubal patency strategies. Due to the design of the study, women underwent both tubal patency tests, which made it impossible to compare the potential fertility enhancing effect of either test. The fertility enhancing effect of HSG with oil-based contrast has widely been studied and confirmed (Fang *et al.*, 2018; Wang *et al.*, 2020). For HyFoSy, only small and observational studies reported on pregnancy outcomes and such effect has not been confirmed yet (Emanuel *et al.*, 2012; Exacoustos *et al.*, 2015; Tanaka *et al.*, 2018). If either of the tests appears to be more effective, this can potentially lead to a reduction in expensive fertility treatments. Finally, in this analysis, costs were used based on Dutch standards, given that the study was conducted in the Netherlands. It is important to note that the costs related to fertility care can differ across countries, especially the costs for oil-based contrast medium used during HSG, thus limiting the generalizability of the study findings to other countries.

Relation to other studies

To our knowledge, this is the first economic evaluation that compared clinical management based on the results of tubal patency testing by HyFoSy and HSG during fertility work-up. Van Rijswijk *et al.* performed a cost-effectiveness analysis on the comparison of tubal patency testing by HSG with oil-based versus water-based contrast medium. They showed that HSG with oil-based contrast medium is cost-effective compared to water-based contrast medium if the society is willing to pay $8198 for an additional live birth (van Rijswijk *et al.*, 2018a). Subsequently, they performed a long-term cost-effectiveness analysis over a 5-year follow-up period showing that HSG with oil-based contrast medium resulted in more live births at comparable costs compared to HSG with water-based contrast medium, and therefore using oil-based contrast medium during HSG was the dominant

strategy (van Welie et al., 2021). These studies showed that even though HSG with oil-based contrast medium incurred higher costs than water-based contrast medium, oil-based contrast medium was eventually less expensive thanks to the cost savings on fertility treatments. Furthermore, these results underline the importance of comparing the direct fertility enhancing effect of tubal patency tests. van Kessel et al. (2022) performed a cost-effectiveness analysis comparing tubal patency testing by HSG (with either water- or oil-based contrast medium) and transvaginal hydrolaparoscopy (THL) during fertility work-up. They showed that THL resulted in a higher live birth rate, at lower costs. The main driver for the lower costs for THL were the lower number of additional laparoscopies and fertility treatments. In the FOAM trial, HSG was performed with either water- or oil-based contrast medium, and no distinction between both contrast media was made, therefore the effect of either of the contrast media on live birth chance remains unknown.

Future implications

To determine the most effective treatment approach, it is essential to evaluate the cost-effectiveness of diagnostic tests in relation to the societal value placed on achieving an additional live birth (referred to as the willingness to pay). The ESHRE Capri Workgroup illuminated the challenges of performing cost-effectiveness analyses in infertility care. It is difficult to capture the value of infertility care in quality adjusted life years (QALYs), the standard metric used when comparing clinical interventions. QALYs represent an additional year in perfect health and not an additional healthy live birth, which is the primary aim of infertility care (Group ECW, 2015). Besides cost-effectiveness, we have to consider other aspects of the tests as well. HSG represents a higher burden for both patient and clinician than HyFoSy: it is experienced as significantly more painful (based on Visual Analogue Scale; 5.4 cm versus 3.1 cm; $P < 0.001$ (van Welie et al., 2022)) and causes exposure to ionizing radiation and iodinated contrast medium. HyFoSy can be easily performed by a gynaecologist or fertility doctor allowing a one-stop fertility work-up with no need for the radiology department and staff. However, the direct fertility enhancing effects of the two tests have never been compared. To determine the preferred first choice tubal patency test during fertility work-up a head-to-head comparison of tubal patency testing by HyFoSy and HSG with oil-based contrast medium would be required.

Conclusion

In summary, this study showed that in infertile women with indication for tubal patency testing during their fertility work-up, clinical management based on the test results of HyFoSy leads to slightly lower, though not statistically significant, live birth rates, at lower costs, compared to management based on HSG results. This comparison resulted in an ICER of €10 042, meaning that by using HyFoSy instead of HSG we would save €10 042 per additional live birth lost. Although there was considerable uncertainty around the ICER, the more valuable we consider a live birth to be, the less likely it is that the HyFoSy strategy would be cost-effective compared to the HSG strategy. Importantly, the direct fertility enhancing effect of both tubal patency tests is not incorporated in this conclusion as women underwent both tubal patency tests in this study.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Acknowledgements

The authors thank the women who participated in the trial, the hospitals, the research nurses, and other staff who contributed to this trial. We thank Prof. Dr Fulco van der Veen for his contribution in designing this study. Furthermore, we thank the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology (NVOG Consortium; www.zorgevaluatienederland.nl) for logistic support, and Marijke M.C. van Nispen (database development) and the staff of the Clinical Research Unit of the Amsterdam UMC, location Academic Medical Centre for their help with the randomization program and the online database during this trial.

Authors' roles

K.D., M.v.W., P.M.M.B., J.S.S., B.W.J.M., and V.M. designed the trial. D.K. coordinated the economic evaluation of the trial and oversaw drafting the manuscript. R.v.E. performed the statistical analysis and interpreted the results for this economic evaluation. He also participated in the manuscript drafting. N.v.W. and J.v.R. coordinated the FOAM trial and oversaw collecting the data. N.v.W., J.v.R., K.D., C.B.L., M.v.W., P.M.M.B., J.S.S., B.W.J.M., and V.M. participated in the analysis, manuscript drafting, and supervision of the work. M.H.A.v.H., J.P.d.B., H.R.V., F.M., W.M.v.B., M.A.F.T., A.M.v.P., A.P.M., J.G., C.H.d.K., A.M.H.K., N.B., D.P.v.d.H., F.P.J.M.V., M.K., B.I.G.v.d.L., J.K., A.F.L., W.J.M., F.J.M.B., O.V., L.F.v.d.V., J.v.D., M.J.L., and R.T. recruited and counselled participants of this study as local investigators. All authors read, edited, and approved the final manuscript.

Funding

The FOAM trial was an investigator-initiated study, funded by ZonMw, a Dutch organization for Health Research and Development (837001504). ZonMw funded the whole project. IQ Medical Ventures provided the ExEm® FOAM kits free of charge. The funders had no role in study design, collection, analysis and interpretation of the data.

Conflict of interest

K.D. reports travel and speakers fees from Guerbet and her department received research grants from Guerbet outside the submitted work. H.R.V. received consulting and travel fee from Ferring. A.M.v.P. reports received consulting fee from DEKRA and fee for an expert meeting from Ferring, both outside the submitted work. C.H.d.K. received travel fee from Merck. F.J.M.B. received a grant from Merck and speakers fee from Besins Healthcare. F.J.M.B. is a member of the advisory board of Merck and Ferring. J.v.D. reported speakers fee from Ferring. J.S.S. reports a research agreement with Takeda and consultancy for Sanofi on MR of motility outside the submitted work. M.v.W. received a travel grant from Oxford Press in the role of deputy editor for *Human Reproduction* and participates in a DSMB as independent methodologist in obstetrics studies in which she has no other role. B.W.J.M. received an investigator grant from NHMRC GNT1176437. B.W.J.M. reports consultancy for ObsEva, Merck, Guerbet, iGenomix, and Merck KGaA and travel support

from Merck KGaA. V.M. received research grants from Guerbet, Merck, and Ferring and travel and speakers fee from Guerbet. The other authors do not report conflicts of interest.

References

Alcázar JL, Martinez A, Duarte M, Welly A, Marín A, Calle A, Garrido R, Pascual MA, Guerriero S. Two-dimensional hysterosalpingo-contrast-sonography compared to three/four-dimensional hysterosalpingo-contrast-sonography for the assessment of tubal occlusion in women with infertility/subfertility: a systematic review with meta-analysis. *Hum Fertil (Camb)* 2020;**25**:43–55.

Anyalechi GE, Wiesenfeld HC, Kirkcaldy RD, Kissin DM, Haggerty CL, Hammond KR, Hook EW, 3rd, Bernstein KT, Steinkampf MP, Geisler WM. Tubal factor infertility, in vitro fertilization, and racial disparities: a retrospective cohort in two US clinics. *Sex Transm Dis* 2021;**48**:748–753.

ASRM. Evidence-based treatments for couples with unexplained infertility: a guideline. *Fertil Steril* 2020;**2**:305–322.

Broeze KA, Opmeer BC, Coppus SF, Van Geloven N, Alves MF, Anestad G, Bhattacharya S, Allan J, Guerra-Infante MF, Den Hartog JE *et al.* Chlamydia antibody testing and diagnosing tubal pathology in subfertile women: an individual patient data meta-analysis. *Hum Reprod Update* 2011;**17**:301–310.

Dreyer K, Out R, Hompes PG, Mijatovic V. Hysterosalpingo-foam sonography, a less painful procedure for tubal patency testing during fertility workup compared with (serial) hysterosalpingography: a randomized controlled trial. *Fertil Steril* 2014;**102**:821–825.

Emanuel MH, Exalto N. Hysterosalpingo-foam sonography (HyFoSy): a new technique to visualize tubal patency. *Ultrasound Obstet Gynecol* 2011;**37**:498–499.

Emanuel MH, van Vliet M, Weber M, Exalto N. First experiences with hysterosalpingo-foam sonography (HyFoSy) for office tubal patency testing. *Hum Reprod* 2012;**27**:114–117.

Engels V, Medina M, Antolín E, Ros C, Amaro A, De-Guirior C, Manzour N, Sotillo L, De la Cuesta R, Rodríguez R *et al.* Feasibility, tolerability, and safety of hysterosalpingo-foam sonography (hyfosy). multicenter, prospective Spanish study. *J Gynecol Obstet Hum Reprod* 2021;**50**:102004.

Exacoustos C, Tiberio F, Szabolcs B, Romeo V, Romanini E, Zupi E. Can tubal flushing with hysterosalpingo-foam sonography (HyFoSy) media increase women's chances of pregnancy? *J Minim Invasive Gynecol* 2015;**22**:S238.

Fang F, Bai Y, Zhang Y, Faramand A. Oil-based versus water-based contrast for hysterosalpingography in infertile women: a systematic review and meta-analysis of randomized controlled trials. *Fertil Steril* 2018;**110**:153–160.e153.

Farquhar CM, Bhattacharya S, Repping S, Mastenbroek S, Kamath MS, Marjoribanks J, Boivin J. Female subfertility. *Nat Rev Dis Primers* 2019;**5**:7.

Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves—facts, fallacies and frequently asked questions. *Health Econ* 2004;**13**:405–415.

Group ECW. Economic aspects of infertility care: a challenge for researchers and clinicians. *Hum Reprod* 2015;**10**:2243–2248.

Hakkaart-Van Roijen LV, Bouwmans C, Kanters T, Tan S. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg (versie 2016) | Publicatie | Zorginstituut Nederland, 2016.

Hamed HO, Shahin AY, Elsamman AM. Hysterosalpingo-contrast sonography versus radiographic hysterosalpingography in the evaluation of tubal patency. *Int J Gynaecol Obstet* 2009;**105**:215–217.

Hunault CC, Habbema JD, Eijkemans MJ, Collins JA, Evers JL, Te Velde ER. Two new prediction rules for spontaneous pregnancy leading to live birth among subfertile couples, based on the synthesis of three previous models. *Hum Reprod* 2004;**19**:2019–2026.

Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, Caulley L, Chaiyakunapruk N, Greenberg D, Loder E, *et al.*; CHEERS 2022 ISPOR Good Research Practices Task Force. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. *BMJ* 2022;**376**:e067975.

Lim SL, Jung JJ, Yu SL, Rajesh H. A comparison of hysterosalpingo-foam sonography (HyFoSy) and hysterosalpingo-contrast sonography with saline medium (HyCoSy) in the assessment of tubal patency. *Eur J Obstet Gynecol Reprod Biol* 2015;**195**:168–172.

Lo Monte G, Capobianco G, Piva I, Caserta D, Dessole S, Marci R. Hysterosalpingo contrast sonography (HyCoSy): let's make the point!. *Arch Gynecol Obstet* 2015;**291**:19–30.

Luciano DE, Exacoustos C, Johns DA, Luciano AA. Can hysterosalpingo-contrast sonography replace hysterosalpingography in confirming tubal blockage after hysteroscopic sterilization and in the evaluation of the uterus and tubes in infertile patients? *Am J Obstet Gynecol* 2011;**204**:79.e1–e75.e71.

Lukassen HG, Schonbeck Y, Adang EM, Braat DD, Zielhuis GA, Kremer JA. Cost analysis of singleton versus twin pregnancies after in vitro fertilization. *Fertil Steril* 2004;**81**:1240–1246.

Maheux-Lacroix S, Boutin A, Moore L, Bergeron ME, Bujold E, Laberge P, Lemyre M, Dodin S. Hysterosalpingosonography for diagnosing tubal occlusion in subfertile women: a systematic review with meta-analysis. *Hum Reprod* 2014;**29**:953–963.

McGhan WF, Al M, Doshi JA, Kamae I, Marx SE, Rindress D. The ISPOR good practices for quality improvement of cost-effectiveness research task force report. *Value Health* 2009;**12**:1086–1099.

NICE. National Institute for Health and Care Excellence (NICE); fertility problems: assessment and treatments. 2013. https://www.nice.org.uk/guidance/cg156 (1 May 2023, date last accessed).

OECD. Organisation for Economic Co-operation and Development. OECD Health Statistics, 2023. https://www.oecd.org/els/health-systems/health-data.htm (1 May 2023, date last accessed).

Saunders RD, Shwayder JM, Nakajima ST. Current methods of tubal patency assessment. *Fertil Steril* 2011;**95**:2171–2179.

Serrano Gonzalez L, Perez-Medina T, Bueno Olalla B, Royuela A, De La Cuesta MLR, Saez de la Mata D, Dominguez-Franjo E, Calles-Sastre L, Engels V. Is hysterosalpingo-foam sonography (HyFoSy) more tolerable in terms of pain and anxiety than hysterosalpingography (HSG)? A prospective real-world setting multicentre study. *BMC Womens Health* 2022;**22**:41.

Tanaka K, Chua J, Cincotta R, Ballard EL, Duncombe G. Hysterosalpingo-foam sonography (HyFoSy): Tolerability, safety and the occurrence of pregnancy post-procedure. *Aust N Z J Obstet Gynaecol* 2018;**58**:114–118.

van Kessel MA, Pham CT, Tros R, Oosterhuis GJE, Kuchenbecker WKH, Bongers MY, Mol BWJ, Koks CAM. The cost-effectiveness of transvaginal hydrolaparoscopy versus hysterosalpingography in the work-up for subfertility. *Hum Reprod* 2022;**37**:2768–2776.

van Rijswijk J, Pham CT, Dreyer K, Verhoeve HR, Hoek A, de Bruin JP, Nap AW, Wang R, Lambalk CB, Hompes PGA *et al.* Oil-based or water-based contrast for hysterosalpingography in infertile

women: a cost-effectiveness analysis of a randomized controlled trial. *Fertil Steril* 2018a;**110**:754–760.

van Rijswijk J, van Welie N, Dreyer K, van Hooff MHA, de Bruin JP, Verhoeve HR, Mol F, Kleiman-Broeze KA, Traas MAF, Muijsers G et al The FOAM study: is hysterosalpingo foam sonography (HyFoSy) a cost-effective alternative for hysterosalpingography (HSG) in assessing tubal patency in subfertile women? Study protocol for a randomized controlled trial. *BMC Womens Health* 2018b; **1**:64.

van Welie N, Pham CT, van Rijswijk J, Dreyer K, Verhoeve HR, Hoek A, de Bruin JP, Nap AW, van Hooff MHA, Goddijn M, *et al.*; H2Oil Study Group. The long-term costs and effects of tubal flushing with oil-based versus water-based contrast during hysterosalpingography. *Reprod Biomed Online* 2021;**42**:150–157.

van Welie N, van Rijswijk J, Dreyer K, van Hooff MHA, Bruin JP, Verhoeve HR, Mol F, van Baal WM, Traas MAF, van Peperstraten AM *et al.* Can hysterosalpingo-foam sonography replace hysterosalpingography as first-choice tubal patency test? A randomized non-inferiority trial. *Hum Reprod* 2022;**37**:969–979.

Verhoeve HR, Moolenaar LM, Hompes P, van der Veen F, Mol BW. Cost-effectiveness of tubal patency tests. *BJOG* 2013;**120**:583–593.

Wang R, Watson A, Johnson N, Cheung K, Fitzgerald C, Mol BWJ, Mohiyiddeen L. Tubal flushing for subfertility. *Cochrane Database Syst Rev* 2020;**10**:Cd003718.

Human Reproduction, 2024, 39, 1222–1230
https://doi.org/10.1093/humrep/deae071
Original Article

1 STEP AHEAD

SAGE 1-Step™ GM-CSF medium

Put your patients one step ahead

- SAGE 1-Step™ GM-CSF medium is the first single-step culture and transfer medium containing the GM-CSF cytokine and Hyaluronan.
- GM-CSF supports embryo-endometrial communication for improved implantation and chances of pregnancy.[1]
- Provides an additional treatment option for patients with a previous failed treatment cycle.[2]

Upgrade your lab with innovation that matters.

Click to explore

CooperSurgical®

1. Hardy, K. & Spanos, S. (2002) Growth factor expression and function in the human and mouse preimplantation embryo. J Endocrinol 172: 221-236.
2. Sipahi, M., Mümüşoğlu, S. et al. (2021). The impact of using culture media containing granulocyte-macrophage colony-stimulating factor on live birth rates in patients with a history of embryonic developmental arrest in previous in vitro fertilization cycles. Journal of the Turkish German Gynecological Association, 22(3), 181–186.