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Tubal flushing with oil-based or water-based contrast at hysterosalpingography for infertility: long-term reproductive outcomes of a randomized trial

Joukje van Rijswijk, M.D.,[a] Nienke van Welie, M.D.,[a] Kim Dreyer, M.D., Ph.D.,[a] Clarabelle T. Pham, B.Sc.,[b] Harold R. Verhoeve, M.D., Ph.D.,[c] Annemieke Hoek, M.D., Ph.D.,[d] Jan Peter de Bruin, M.D., Ph.D.,[e] Annemiek W. Nap, M.D., Ph.D.,[f] Machiel H. A. van Hooff, M.D., Ph.D.,[g] Mariëtte Goddijn, M.D., Ph.D.,[h] Angelo B. Hooker, M.D.,[i] Petra Bourdrez, M.D.,[j] Angelique J. C. M. van Dongen, M.D., Ph.D.,[k] Ilse A. J. van Rooij, M.D., Ph.D.,[l] Henrike G. M. van Rijnsaardt-Lukassen, M.D., Ph.D.,[m] Ron J. T. van Golde, M.D., Ph.D.,[n] Cathelijne F. van Heteren, M.D., Ph.D.,[o] Marie J. Pelinck, M.D., Ph.D.,[p] Annette E. J. Duijn, M.D.,[q] Mesrure Kaplan, M.D.,[r] Cornelis B. Lambalk, M.D., Ph.D.,[a] Velja Mijatovic, M.D., Ph.D.,[a] and Ben W. J. Mol, M.D., Ph.D.[s]

[a] Department of Reproductive Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; [b] College of Medicine and Public Health, Flinders University, Adelaide, Victoria, Australia; [c] Department of Obstetrics and Gynaecology, Onze Lieve Vrouwe Gasthuis, Amsterdam; the Netherlands; [d] Department of Reproductive Medicine and Gynaecology, University of Groningen, University Medical Centre Groningen, Hanzeplein, the Netherlands; [e] Department of Obstetrics and Gynaecology, Jeroen Bosch Hospital, Hertogenbosch, the Netherlands; [f] Department of Obstetrics and Gynaecology, Rijnstate Hospital, Arnhem, the Netherlands; [g] Department of Obstetrics and Gynaecology, Franciscus Hospital, Rotterdam, the Netherlands; [h] Centre for Reproductive Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; [i] Department of Obstetrics and Gynaecology, Zaans Medical Centre, Zaandam, the Netherlands; [j] Department of Obstetrics and Gynaecology, VieCuri Medical Centre, Venlo, the Netherlands; [k] Department of Obstetrics and Gynaecology, Hospital Gelderse Vallei, Ede, the Netherlands; [l] Department of Obstetrics and Gynaecology, Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands; [m] Department of Obstetrics and Gynaecology, Albert Schweitzer Hospital, Dordrecht, the Netherlands; [n] Department of Obstetrics and Gynaecology, Maastricht UMC, Maastricht, the Netherlands; [o] Department of Obstetrics and Gynaecology, Canisius Wilhelmina Hospital, Nijmegen, the Netherlands; [p] Department of Obstetrics and Gynaecology, Scheper Hospital, Emmen, the Netherlands; [q] Vrouwenkliniek Zuidoost, Amsterdam, the Netherlands; [r] Department of Obstetrics and Gynaecology, Röpcke-Zweers Hospital, Hardenberg, the Netherlands; and [s] Department of Obstetrics and Gynaecology, Monash University, Clayton, Victoria, Australia

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Reprint requests: Joukje van Rijswijk, M.D., Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Reproductive Medicine, De Boelelaan 1118, 1081 HV Amsterdam, the Netherlands (E-mail: j.vanrijswijk@amsterdamumc.nl).

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Objective: To determine the impact of oil-based versus water-based contrast on pregnancy and live birth rates ≤5 years after hysterosalpingography (HSG) in infertile women.
Design: A 5-year follow-up study of a multicenter randomized trial.
Setting: Hospitals.
Patient(s): Infertile women with an ovulatory cycle, 18–39 years of age, and having a low risk of tubal pathology.
Intervention(s): Use of oil-based versus water-based contrast during HSG.
Main Outcome Measure(s): Ongoing pregnancy, live births, time to ongoing pregnancy, second ongoing pregnancy.
Result(s): A total of 1,119 women were randomly assigned to HSG with oil-based contrast (n = 557) or water-based contrast (n = 562). After 5 years, 444 of 555 women in the oil group (80.0%) and 419 of 559 women in the water group (75.0%) had an ongoing pregnancy (relative risk [RR] 1.07; 95% confidence interval [CI] 1.00–1.14), and 415 of 555 women in the oil group (74.8%) and 376 of 559 women in the water group (67.3%) had live births (RR 1.11; 95% CI 1.03–1.20). In the oil group, 228 pregnancies (41.1%) were conceived naturally versus 194 (34.7%) pregnancies in the water group (RR 1.18; 95% CI 1.02–1.38). The time to ongoing pregnancy was significantly shorter in the oil group versus the water group (10.0 vs. 13.7 months; hazard ratio, 1.25; 95% CI 1.09–1.43). No difference was found in the occurrence of a second ongoing pregnancy.
Conclusion(s): During a 5-year time frame, ongoing pregnancy and live birth rates are higher after tubal flushing with oil-based contrast during HSG compared with water-based contrast. More pregnancies are naturally conceived and time to ongoing pregnancy is shorter after HSG with oil-based contrast.
Clinical Trial Registration Number: Netherlands Trial Register (NTR) 3270 and NTR6577(www.trialregister.nl). (Fertil Steril® 2020;114:155-62. ©2020 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Female infertility, hysterosalpingography, oil-based contrast medium, water-based contrast medium, ongoing pregnancy

Hysterosalpingography (HSG) is a commonly used outpatient clinic tubal patency test in which contrast medium is flushed through the uterine cavity and tubes, while taking radiographs (1). Traditionally oil-based contrast was used, but this was gradually replaced by water-based contrast in the 1970s due to presumed better imaging quality, higher safety, and lower costs (2).

We previously demonstrated in a large multicenter randomized controlled trial (3), the H2Oil trial (NTR 3270), that tubal flushing with oil-based contrast resulted in higher 6-month ongoing pregnancy rates than tubal flushing with water-based contrast (39.7% vs. 29.1%) (relative risk [RR] 1.37, 95% confidence interval [CI] 1.16–1.61), resulting in a 10% more live birth rate. A subsequent meta-analysis (4) of six randomized controlled trials, including the results of the H2Oil trial showing a significantly higher ongoing pregnancy rate after HSG with oil-based contrast compared with HSG with water-based contrast (odds ratio [OR] 1.47, 95% CI 1.12–1.93). Three studies (3, 5, 6) in the meta-analysis had a follow-up ≤6 months. The other three studies (7–9) had a follow-up between 9 and 39 months. Due to variable follow-up duration and limited evidence on fertility outcomes beyond 6 months, no adequate statistical analysis could be performed. A recently published network meta-analysis (10) confirmed the favorable effect of oil-based contrast at 6 months, and emphasized the need for studies addressing long-term follow-up.

In the present study a long-term follow-up of couples who participated in the H2Oil trial is given. We report on ongoing pregnancies and live births, as well as the way these pregnancies were conceived, and whether couples had a second child in the 5-year follow-up period.

MATERIALS AND METHODS

The H2Oil trial was a multicenter randomized clinical trial comparing oil-based and water-based contrast in women scheduled for HSG during their fertility work-up. Our investigator initiated follow-up study was registered in the Netherlands Trial Register as NTR 6577. The original H2Oil trial (NTR 3270) had ethical approval. This follow-up study was approved by the Institutional Review Board of the Amsterdam University Medical Centre—Vrije Universiteit University Medical Centre (reference 2017.221, dated 14 June 2017).

Study details and results have been published previously (3). In short, the H2Oil trial recruited 1,119 participants in a network of 27 hospitals in the Netherlands between February 3, 2012 and October 29, 2014 (3). Participating women were aged between 18 and 39 years, had an ovulatory cycle, and had a low risk on tubal pathology according to their medical history, without known endocrinologic disorders and a total motile sperm count after sperm wash of >3 million sperm/mL in the male partner. They were trying to conceive for ≥1 year and were scheduled for tubal patency testing with HSG at the end of the fertility work-up. After informed consent, couples were randomized for HSG with oil-based contrast or water-based contrast. In case of bilateral or unilateral patency at HSG, couples were counseled for management based on their prognosis for natural conception using the Hunault prognostic index (11). In case the prognosis for natural conception resulting in a live birth was ≥30% in the coming 12 months, couples were counseled for expectant management. When this prognosis was <30%, treatment with intrauterine insemination (IUI) with or without mild ovarian hyperstimulation was

performed. In case of no pregnancy after six IUI treatment cycles, in vitro fertilization (IVF) was offered to the couple. In case of bilateral tubal occlusion on HSG, confirmed at laparoscopy, or when the male partner had unexpectedly a very poor semen quality at repeated semen analysis, couples were advised to start IVF or IVF with intracytoplasmic sperm injection (ICSI).

Data collection

For this follow-up study of the H2Oil trial, data regarding fertility treatments and pregnancies were obtained from the electronic medical records of the H2Oil trial participants. In addition to these data all H2Oil participants received an information letter regarding the follow-up study (including an informed consent form) from their treating physician to collect supplementary information to their medical record. After receiving the signed informed consent form, a questionnaire was sent to the participating women by mail or e-mail. The questionnaire contained questions regarding pregnancies and fertility treatments (IUI, IVF, or IVF with ICSI). Women who did not respond were sent a reminder after 2 weeks, and if needed they were contacted by telephone. Data were handled confidentially and anonymously. The handling of personal data was in comply with the Dutch Personal Data Protection Act.

Study outcomes

The main outcome of this long-term follow-up study was ongoing pregnancy, defined as a viable pregnancy at ultrasound beyond 12 weeks of gestation. Other outcomes were biochemical pregnancy (defined as a positive pregnancy test or an increase in human chorionic gonadotropin combined with menstrual bleeding and absence of ultrasound visible pregnancy), clinical pregnancy (defined as an ultrasound visible gestational sac), live birth (defined as a live birth after 24 weeks of gestation), miscarriage (defined as the presence of nonviability on ultrasound or spontaneous loss of pregnancy before 12 weeks of gestation), ectopic pregnancy (defined as an embryo implants outside the uterine cavity), and multiple pregnancy (defined as a positive heartbeat of at least two fetuses on ultrasound). We also compared the time to pregnancy resulting in an ongoing pregnancy (calculated from the first day of the last menstrual period plus 4 weeks). We also recorded received fertility treatments, mode of conception and the aim and ability to have a second ongoing pregnancy after HSG.

Statistical analysis

Demographic characteristics of the study population were summarized using the appropriate descriptive statistics. Categorical data were reported as absolute numbers and percentages. Normally distributed continuous variables were summarized as means with standard deviations and non-normally distributed continuous variables as medians with interquartile ranges (IQR). All analyses were performed on an intention-to-treat basis. Time to ongoing pregnancy was compared between the use of oil-based and water-based contrast using the log-rank test with the cumulative ongoing pregnancy rates over time visualized by means of Kaplan-Meier curves. A hazard ratio (HR) with 95% CI was reported as the effect size. Proportions of dichotomous outcomes were compared using the χ^2 test with relative risks (RRs) and 95% CI calculated as effect-size. Continuous outcomes were compared using the independent *t*-test or Mann-Whitney *U* test as appropriate.

For all outcome variables, we reported the number of participants for whom the outcome was available. A P value $<.05$ was considered to indicate statistical significance. Stata version 15 (StataCorp 2017. Stata statistical software: release 15—StataCorp LLC) was used to create the Kaplan-Meier curves. The IBM Statistical Package for Social Sciences (SPSS) version 22.0 was used for all other statistical analyses.

RESULTS

Between February 3, 2012, and October 29, 2014, 1,119 women were randomized for the use of HSG with oil-based contrast (n = 557) or water-based contrast (n = 562) (Supplemental Fig. 1, available online). The baseline characteristics and HSG results were comparable between study groups (Supplemental Tables 1 and 2, available online).

We received the questionnaires from 273 (49.0%) of 557 women in the oil-based contrast group and 270 (48.0%) of 562 women in the water-based contrast group. We had follow-up data from 1,114 women (555 in the oil group and 559 in the water group) after reviewing all medical files and questionnaires. We could not get follow-up information in two women in the oil group and three women in the water group, therefore we considered these women as lost to follow-up. The median duration of the follow-up was comparable for both groups (oil-based contrast group: 45.3 months, IQR, 26.9–57.8 months; water-based contrast group: 46.7 months, IQR, 23.6–57.5 months) ($P = .82$).

A total of 221 (39.8%) of the women (555) who were randomly assigned to the oil-based contrast group and 196 (35.1%) of the women (559) who were randomly assigned to the water-based contrast group received no further treatment (Table 1). Comparable percentages of women in the oil-based contrast group and the water-based contrast group underwent IUI (with or without mild ovarian hyperstimulation) alone (192/555 [34.6%] and 191/559 [34.2%]) (RR 1.01, 95% CI 0.86–1.19; $P = .88$), IUI followed by IVF or IVF with ICSI (126/555 [22.7%] and 152/559 [27.2%]) (RR 0.84, 95% CI 0.68–1.03; $P = .08$), or IVF or IVF with ICSI alone (14/555 [2.5%] and 16/559 [2.9%]) (RR 0.88, 95% CI 0.43–1.79; $P = .73$). The total number of couples who received IVF or IVF with ICSI (either immediately or after unsuccessful IUI) was 140 (25.2%) versus 168 (30.1%) (RR 0.84, 95% CI 0.69–1.01; $P = .07$).

Outcomes

An ongoing pregnancy occurred in 444 (80.0%) women (of 555) in the oil-based contrast group versus 419 (75.0%) women (of 559) in the water-based contrast group (RR 1.07, 95% CI 1.00–1.14; $P = .04$) (Table 2). There were 415 women (74.8%) in the oil-based contrast group versus 376 women

TABLE 1

Number of couples starting fertility treatment after hysterosalpingography.

Characteristic	Oil-based contrast group (n = 555)	Water-based contrast group (n = 559)	Relative risk (95% CI)	*P* value
No treatment	221 (39.8)	196 (35.1)	1.14 (0.98–1.32)	.10
IUI	192 (34.6)	191 (34.2)	1.01 (0.86–1.19)	.88
IUI followed by IVF or IVF with ICSI	126 (22.7)	152 (27.2)	0.84 (0.68–1.03)	.08
IVF or IVF with ICSI	14 (2.5)	16 (2.9)	0.88 (0.43–1.79)	.73
Other[a]	2 (0.4)	4 (0.7)	0.50 (0.09–2.74)	.42

Note: Values are n (%) unless specified otherwise. All *P* values are two-sided. CI = confidence interval; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; IUI = intrauterine insemination.
[a] Other treatment such as ovulation induction with clomiphene citrate.

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(67.3%) in the water-based contrast group with a documented live birth (RR 1.11, 95% CI 1.03–1.20; $P = .006$). Miscarriage and ectopic pregnancy rates were comparable between the groups (Table 2).

The median time to ongoing pregnancy was 10.0 months (95% CI 8.5–11.5) in the oil-based contrast group versus 13.7 months (95% CI 11.7–15.8) in the water-based contrast group (HR 1.25, 95% CI 1.09–1.43; $P = .001$) (Fig. 1). In the oil-based contrast group, 228 of 555 (41.1%) ongoing pregnancies were conceived naturally versus 194 of 559 (34.7%) in the water-based contrast group (RR 1.18, 95% CI 1.02–1.38; $P = .03$). There were slightly more pregnancies after IUI in the oil-based contrast group and slightly less pregnancies after IVF or IVF with ICSI (Table 2).

As pregnancies established through IVF or IVF with ICSI occur independent of the condition of the fallopian tube, thus denying the potential effect of tubal flushing, we also analyzed ongoing pregnancies that were established without IVF or IVF with ICSI and median time to onset of ongoing pregnancy after censoring time to conception when IVF or IVF with ICSI pregnancy was established. In the oil-based contrast group, 354 of 555 (63.8%) ongoing pregnancies were conceived without the need for IVF or IVF with ICSI versus 310 of 559 (55.5%) ongoing pregnancies in the water-based contrast group (RR 1.15, 95% CI 1.04–1.27; $P = .005$). The mode of conception was unknown in three pregnancies that occurred in the water-based contrast group. Time to ongoing pregnancy was 10.8 months (95% CI 9.2–12.9) in the oil-based contrast group versus 16.8 months (95% CI 13.5–24.4) in the water-based contrast group (HR 1.28, 95% CI 1.10–1.50; $P = .001$) (Fig. 2).

In the oil-based contrast group, 166 of 555 (29.9%) women had a second ongoing pregnancy versus 155 of 559 (27.7%) women in the water-based contrast group (RR 1.08, 95% CI 0.90–1.30; $P = .42$). Supplemental Table 3 shows the mode of conception for the second ongoing pregnancies. In both groups, the median time to a second ongoing pregnancy was not reached. The estimated second ongoing pregnancy rates at 5 years was 47% in the oil-based contrast group and 45% in the water-based contrast group (HR 1.10, 95% CI 0.88–1.37; $P = .39$) (Supplemental Fig. 2, available online).

DISCUSSION

This follow-up study of the H2Oil trial shows that during a 5-year period there was significantly higher ongoing pregnancy and live birth rates and a shorter time to ongoing pregnancy in favor of oil-based contrast in infertile women undergoing HSG compared with the use of water-based contrast. Also, significantly more pregnancies were conceived without the use of fertility treatments in the oil-based contrast group compared with those in the water-based contrast group. We did not find statistically significant

TABLE 2

Fertility outcomes of first pregnancy.

Characteristic	Oil-based contrast group (n = 555)	Water-based contrast group (n = 559)	Risk ratio (95% CI)	*P* value
Ongoing pregnancy	444 (80.0)	419 (75.0)	1.07 (1.00–1.14)	.04
Mode of conception[a]				
Natural	228 (41.1)	194 (34.7)	1.18 (1.02–1.38)	.03
IUI	126 (22.7)	116 (20.8)	1.09 (0.88–1.37)	.43
Total non-IVF	354 (63.8)	310 (55.5)	1.15 (1.04–1.27)	.005
IVF or IVF with ICSI	90 (16.2)	106 (19.0)	0.86 (0.66–1.10)	.23
Live birth[b]	415 (74.8)	376 (67.3)	1.11 (1.03–1.20)	.006
Miscarriage[c]	68 (12.3)	82 (14.7)	0.84 (0.62–1.13)	.24
Ectopic pregnancy	7 (1.3)	11 (2.0)	0.64 (0.25–1.64)	.35
Multiple pregnancies	9 (1.6)	17 (3.0)	0.53 (0.24–1.19)	.12

Note: Values are n (%) unless specified otherwise. All *P* values are two-sided. CI = confidence interval; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; IUI = intrauterine insemination.
[a] Missing: water-based contrast group, 3.
[b] 9 versus 10 pregnancies were intrauterine pregnancy loss, partus immaturus, or ended because of congenital abnormalities. Data on live birth of 20 versus 33 pregnancies is missing.
[c] Miscarriage presented as the amount of women with at least one miscarriage.

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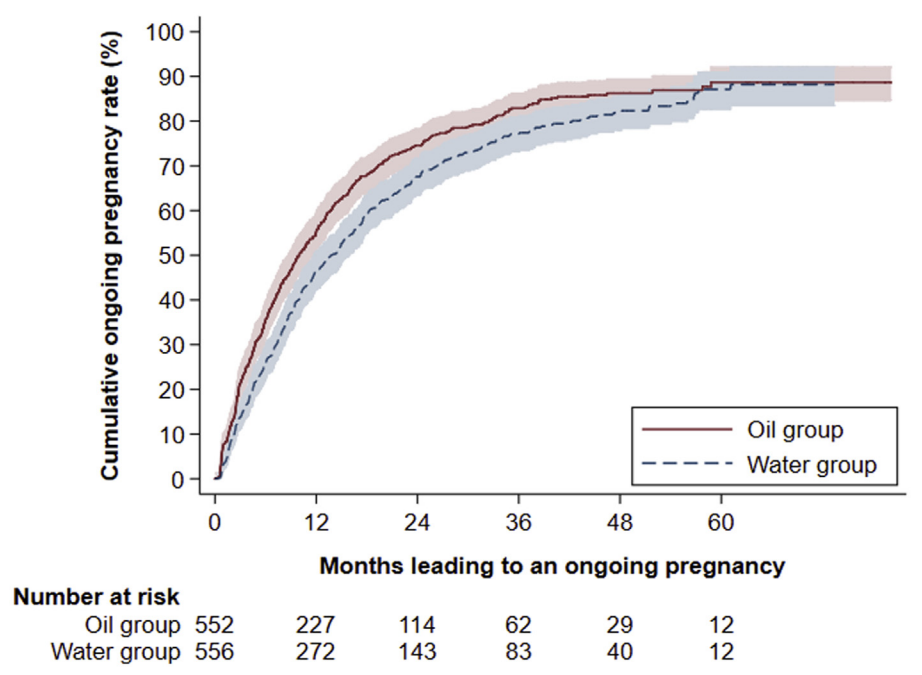
FIGURE 1



Kaplan-Meier survival curve of the time to the first ongoing pregnancy. Data on six participants (3 in the oil-based contrast group and 3 in the water-based contrast group) were not included because information on the first day of the last menstrual period before an ongoing pregnancy was missing for these participants.

van Rijswijk. Oil or water at HSG: long-term outcomes. Fertil Steril 2020.

differences in the occurrence of miscarriage, ectopic pregnancy, or a second child after tubal flushing during HSG with oil-based contrast compared with the use of water-based contrast.

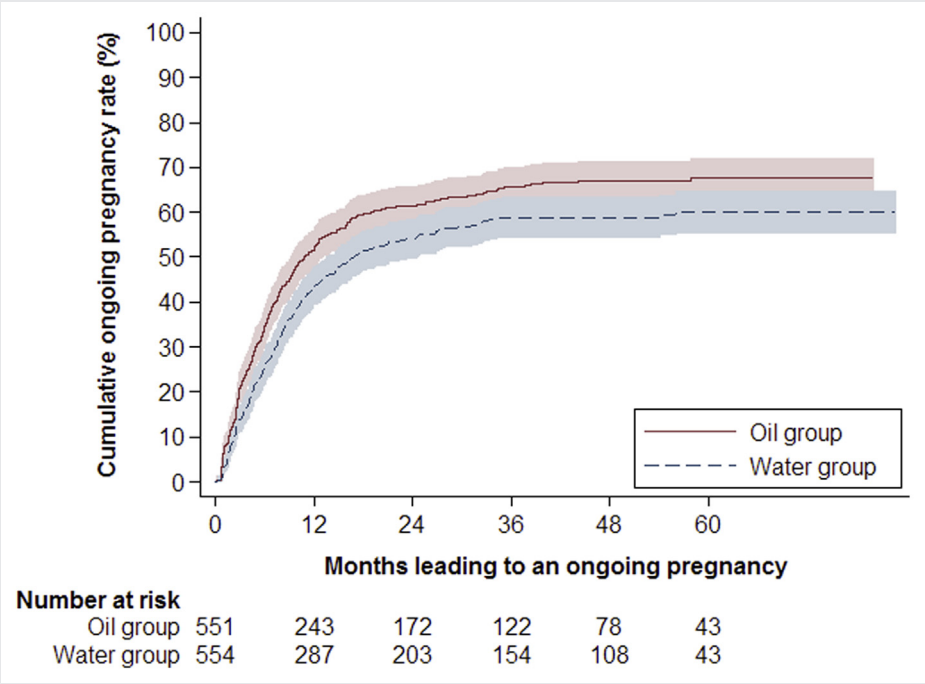
Our results are in line with the findings of two recent systematic reviews (4, 10) showing a significantly higher number of ongoing pregnancies, with 6 months follow-up, in favor of oil-based contrast with no difference in occurrence of miscarriages or ectopic pregnancies between contrast groups. However, there was insufficient evidence of a difference in clinical pregnancy or live birth within 12 months after HSG between the use of oil-based contrast and water-based contrast (10). Available evidence supports the short-term (6 months) fertility enhancing effects of oil-based contrast, but it is uncertain whether such effects would persist after 6 months. The follow-up study of the H2Oil trial is the first study to demonstrate significantly higher ongoing pregnancy and live birth rates after HSG in favor of the use of oil-based contrast compared with the use of water-based contrast. Despite comparable numbers of couples starting IVF or IVF with ICSI in the long-term follow-up period, more ongoing pregnancies were conceived naturally after an HSG with oil-based contrast. These long-term outcomes are an important contribution to the available evidence and they demonstrate that the beneficial effect of tubal flushing with oil-based contrast medium is sustained during a period of ≤ 5 years.

Strengths and limitations

This follow-up study is based on a large robust randomized controlled trial. The lost to follow-up number was lower than in the original H2Oil trial (5 vs. 11 in the original trial), due to more available information retrieved from the medical file as well as the returned questionnaires.

Our follow-up study has some limitations. We collected the long-term follow-up data in retrospect from medical files and additional questionnaires, this introduces possible ascertainment and selection bias. Variable durations of follow-up were found; however, the mean duration of follow-up was comparable between the groups, which allowed us to compare the absolute pregnancy rates. Information on live births is missing in 20 ongoing pregnancies in the oil-based contrast group versus 33 in the ongoing pregnancies in the water-based contrast group for two reasons. First, there was no response to our request to fill in the questionnaires and second, the participants were still pregnant while completing the questionnaire and/or during the review of the medical file. Nonetheless, ongoing pregnancy was the main outcome of this study, and is suggested as a proxy for live birth (12). Therefore, we believe it is unlikely that these missing data influence the results. Furthermore, in the H2Oil trial we included women up to the age of 39 years, without known endocrinological disorders and with a low risk of tubal pathology. Therefore, the results of this study cannot be generalized to all infertile women who do not share these features.

FIGURE 2



Kaplan-Meier survival curve of the time to the first ongoing pregnancy censored for in vitro fertilization or in vitro fertilization with intracytoplasmic sperm injection pregnancies. Data on nine participants (4 in the oil-based contrast group and 5 in the water-based contrast group) were not included because information on the first day of the last menstrual period before an ongoing pregnancy was missing for these participants.

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Implications

Tubal flushing with oil-based contrast in comparison with water-based contrast shows a sustained favorable effect on ongoing pregnancies and live births. It also reduces the time to ongoing pregnancy significantly with an average difference of 3.7 months, and when censoring for IVF or IVF with ICSI conceived pregnancies the difference in time to pregnancy is even longer. Waiting for 4 months can be a burden for couples trying to conceive. In addition, in the present-day society in which women starting a family at an older age, 4 months makes a difference in their chance of completing their family. Furthermore, more women will have a spontaneous pregnancy, which could implicate a decrease in the need for IVF treatment resulting in a decrease in health-care costs. A cost-effectiveness analysis of this follow-up study is needed to answer this question. There is a benefit beyond 6 months for infertile women to undergo an HSG with oil-based contrast, in terms of time to pregnancy and more natural conceptions. However, the exact duration of the fertility enhancing effect remains uncertain. A previous analysis (13) tried to identify women who benefit from an HSG with oil-based contrast. However, the treatment effect appeared to be independent of characteristics of the couple. To determine which women benefit and for how long, remains uncertain. When aiming for a second child, no clear benefit of oil-based contrast was found. The number of women was small, and the median time to ongoing pregnancy could not be calculated. Further research is needed.

Independent of the type of contrast used, tubal flushing itself has a treatment effect (10, 14). The underlying mechanism of the fertility enhancing effect of flushing during HSG and the reason for oil-based contrast being more effective compared with water-based contrast is largely unknown. Various studies suggest an immunobiological effect of the oil-based contrast on the endometrium and the peritoneum (15–20) or enhancement of the tubal ciliary activity, improvement of cervical mucus, and iodine-induced bacteriostatic action on mucus membranes (21). Another potential explanation is a mechanical effect on the proximal tube. During tubal patency testing debris or mucus plugs could be flushed out of the fallopian tubes (22–24). A previous study (24) found higher ongoing pregnancy rates in women who experienced mild-to-severe pain during HSG, which could support the hypothesis that small mucus plugs or debris is flushed away from the proximal parts of otherwise healthy fallopian tubes. Future studies using experimental set-ups have to address the effect of variation in the build-up of pressure within the fallopian tube, resulting from the chemical and physical characteristics of the contrast medium applied.

In conclusion in infertile women with unexplained or mild male factor infertility undergoing HSG, the use of oil-based contrast versus water-based contrast results in a higher 5-year ongoing pregnancy rate, a reduction in the median time to ongoing pregnancy, and an increase in the chance of a natural conception. All infertile women with unexplained

or mild male factor infertility should be offered an HSG with oil-based contrast.

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H2Oil Study Group Members: Anna P. Gijsen, M.D. (Department of Obstetrics and Gynaecology, Elkerliek Hospital, Helmond), Ph.D., Cornelia H. de Koning, M.D. (Department of Obstetrics and Gynaecology, Tergooi Hospital, Blaricum), Ph.D., Marieke J. Lambers, M.D. (Department of Obstetrics and Gynaecology, Dijklander Hospital, Hoorn), Ph.D., Frédérique Lichtenbeld, B.Sc. (Department of Reproductive Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands), Alexander Mozes, M.D. (Department of Obstetrics and Gynaecology, Amstelland Hospital, Amstelveen), Alexander V. Sluijmer, M.D. (Department of Obstetrics and Gynaecology, Wilhelmina Hospital, Assen), Ph.D., Jesper M.J. Smeenk, M.D. (Department of Obstetrics and Gynaecology, Elisabeth-TweeSteden Hospital, Tilburg), Ph.D., Catharina C.M. Timmerman, M.D.(Department of Obstetrics and Gynaecology, Bravis Hospital, Roosendaal), Maaike A.F. Traas, M.D. (Department of Obstetrics and Gynaecology, Gelre Hospitals, Apeldoorn), Rachel Tros, M.D. (Department of Obstetrics and Gynaecology, Amsterdam UMC, Vrije Universiteit Amsterdam–location Louwesweg, Amsterdam), and Gijs A. van Unnik, M.D.(Department of Obstetrics and Gynaecology, Alrijne Hospital, Leiden), the Netherlands.

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Lavado de trompas con medio de contraste liposoluble o hidrosoluble en la histerosalpingografía por infertilidad: resultados reproductivos a largo plazo en un ensayo aleatorizado

Objetivo: Determinar el impacto del uso de contrastes liposolubles versus hidrosolubles sobre las tasas de embarazo y nacidos vivos ≤ 5 años post-histerosalpingografía (HSG) en mujeres infértiles.

Diseño: Estudio de seguimiento a 5 años en un estudio multicéntrico aleatorizado.

Entorno: Hopitalario.

Paciente(s): Mujeres infértiles con ciclos ovulatorios, de edades entre 18 y 39 años y con bajo riesgo de patología tubárica.

Intervención(es): Uso de contraste liposoluble versus hidrosoluble durante la HSG.

Medidas de resultado(s) principal(es): Embarazo en curso, nacidos vivos, tiempo hasta conseguir el embarazo, segundo embarazo en curso.

Resultado(s): Se aleatorizaron un total de 1,119 mujeres asignándose a HSG con medio liposoluble (n=557) o hidrosoluble (n=562). Transcurridos 5 años, 444 de 555 mujeres en el grupo liposoluble (80%) y 419 de 559 en el grupo hidrosoluble (75%) consiguieron embarazo en curso (riesgo relativo [RR] 1.07; Intervalo de Confianza del 95% [[CI] 1.00-1.14] y 415 de 555 mujeres en el grupo liposoluble (74.8%) y 376 de 559 mujeres en el grupo hidrosoluble (67.3%) tuvo nacidos vivos (RR 1.11; 95% CI 1.03-1.20). En el grupo hidrosoluble, 228 embarazos (41.1%) se concibieron espontáneamente vs 194 (34.7%) en el grupo hidrosoluble (RR 1.18; 95% CI 1.02-1.38). El tiempo para conseguir el embarazo fue significativamente menor en el grupo liposoluble versus el grupo hidrosoluble (10.0 vs 13.7 meses; hazard ratio 1.25; 95% CI 1.09-1.43). No se encontraron diferencias en la consecución de un segundo embarazo en curso.

Conclusión(es: En un periodo de 5 años, las tasas de embarazo en curso y nacidos vivos son mayores después del lavado tubárico con contraste liposoluble durante la HSG comparado con el lavado con contraste hidrosoluble. Un mayor número de embarazos se conciben espontáneamente y el tiempo para lograr un embarazo en curso es menor después de la HSG con contraste liposoluble.