ORIGINAL ARTICLE

# Oil-Based or Water-Based Contrast for Hysterosalpingography in Infertile Women

Kim Dreyer, M.D., Ph.D., Joukje van Rijswijk, M.D., Velja Mijatovic, M.D., Ph.D.,
Mariëtte Goddijn, M.D., Ph.D., Harold R. Verhoeve, M.D., Ph.D.,
Ilse A.J. van Rooij, M.D., Ph.D., Annemieke Hoek, M.D., Ph.D., Petra Bourdrez, M.D.,
Annemiek W. Nap, M.D., Ph.D., Henrike G.M. Rijnsaardt-Lukassen, M.D., Ph.D.,
Catharina C.M. Timmerman, M.D., Mesrure Kaplan, M.D., Angelo B. Hooker, M.D.,
Anna P. Gijsen, M.D., Ph.D., Ron van Golde, M.D., Ph.D.,
Cathelijne F. van Heteren, M.D., Ph.D., Alexander V. Sluijmer, M.D., Ph.D.,
Jan-Peter de Bruin, M.D., Ph.D., Jesper M.J. Smeenk, M.D., Ph.D.,
Jacoba A.M. de Boer, M.D., Ph.D., Eduard Scheenjes, M.D., Ph.D.,
Annette E.J. Duijn, M.D., Alexander Mozes, M.D., Marie J. Pelinck, M.D., Ph.D.,
Maaike A.F. Traas, M.D., Machiel H.A. van Hooff, M.D., Ph.D.,
Gijsbertus A. van Unnik, M.D., Cornelia H. de Koning, M.D., Ph.D.,
Nan van Geloven, Ph.D., Jos W.R. Twisk, Ph.D., Peter G.A. Hompes, M.D., Ph.D.,
and Ben W.J. Mol, M.D., Ph.D.

## ABSTRACT

**BACKGROUND**

Pregnancy rates among infertile women have been reported to increase after hysterosalpingography, but it is unclear whether the type of contrast medium used (oil-based or water-soluble contrast) influences this potential therapeutic effect.

**METHODS**

We performed a multicenter, randomized trial in 27 hospitals in the Netherlands in which infertile women who were undergoing hysterosalpingography were randomly assigned to undergo this procedure with the use of oil-based or water-based contrast. Subsequently, couples received expectant management or the women underwent intrauterine insemination. The primary outcome was ongoing pregnancy within 6 months after randomization. Outcomes were analyzed according to the intention-to-treat principle.

**RESULTS**

A total of 1119 women were randomly assigned to hysterosalpingography with oil contrast (557 women) or water contrast (562 women). A total of 220 of 554 women in the oil group (39.7%) and 161 of 554 women in the water group (29.1%) had an ongoing pregnancy (rate ratio, 1.37; 95% confidence interval [CI], 1.16 to 1.61; P<0.001), and 214 of 552 women in the oil group (38.8%) and 155 of 552 women in the water group (28.1%) had live births (rate ratio, 1.38; 95% CI, 1.17 to 1.64; P<0.001). Rates of adverse events were low and similar in the two groups.

**CONCLUSIONS**

Rates of ongoing pregnancy and live births were higher among women who underwent hysterosalpingography with oil contrast than among women who underwent this procedure with water contrast. (Netherlands Trial Register number, NTR3270.)

Infertility, which is defined as the inability to conceive after 1 year of unprotected intercourse, affects approximately one of every six couples who are trying to get pregnant.[1] Hysterosalpingography to assess tubal patency is part of the infertility evaluation in many cases. Although hysterosalpingography was introduced as a diagnostic test, it has been suggested that tubal flushing directly increases pregnancy rates in the months after hysterosalpingography.[2]

Many studies have shown a fertility-enhancing effect of hysterosalpingography with the use of oil contrast,[3] but few randomized, controlled trials have assessed this effect.[4-6] A meta-analysis of three trials showed higher rates of ongoing pregnancy after hysterosalpingography performed with oil contrast than after no intervention (odds ratio, 3.6; 95% confidence interval [CI], 2.1 to 6.3).[7]

Five randomized, controlled trials directly compared pregnancy rates after hysterosalpingography involving oil contrast with those after hysterosalpingography involving water contrast.[8-12] Four of these trials showed no significant difference in ongoing pregnancy rates associated with the two contrast mediums used,[8-10,12] but one trial showed a higher ongoing pregnancy rate after hysterosalpingography with oil contrast than with water contrast (odds ratio, 3.5; 95% CI, 2.0 to 6.0).[11] A meta-analysis including all five trials did not show significantly higher rates of pregnancy among women who underwent hysterosalpingography with oil contrast than among those who underwent this procedure with water contrast (odds ratio, 1.4; 95% CI, 0.8 to 2.5).[7] However, the included studies were considered to be of low quality, the method of randomization[9-11] and whether there was blinding of treatment assignments[8-12] were unclear, and some studies indicated that rates of loss to follow-up were as high as 21%.[8,10] Moreover, the largest trial, which included 533 participants, showed no significant difference in live-birth rates with the use of oil contrast as compared with water contrast.[12] In view of this uncertainty, we conducted a multicenter, randomized, controlled trial to compare ongoing pregnancy rates and other pregnancy outcomes among women who underwent hysterosalpingography with oil contrast with those among women who underwent this procedure with water contrast.

## METHODS

### TRIAL OVERSIGHT

The Water versus Oil (H2Oil) trial was approved by the ethics committee and institutional review board of the Academic Medical Center, Amsterdam, and by the board of directors of all participating hospitals. Trial oversight was provided by the ethics committee of the Academic Medical Center. In each of the participating centers, data monitoring in accordance with the Good Clinical Practice guidelines was performed by dedicated research nurses. All participants provided written informed consent. The first, second, and last authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol, which is available with the full text of this article at NEJM.org.

### TRIAL PARTICIPANTS

Participants in the H2Oil trial were recruited from 27 hospitals (4 academic, 12 teaching, and 11 nonteaching hospitals) in the Netherlands. Gynecologists in these hospitals collaborate in a nationwide consortium for women's health research (the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology; www.studies-obsgyn.nl).

Women were eligible to participate in the trial if they were between 18 and 39 years of age, had spontaneous menstrual cycles, and had been trying to conceive for at least 1 year and if there was an indication for evaluation of tubal patency by means of hysterosalpingography.[13] Exclusion criteria were known endocrine disorders (e.g., the polycystic ovary syndrome, diabetes, hyperthyroidism, and hyperprolactinemia), less than eight menstrual cycles per year, a high risk of tubal disease (as indicated by a history of pelvic inflammatory disease, previous chlamydia infection, or known endometriosis), iodine allergy (since the contrast mediums under study both contained iodine), and a total motile sperm count after sperm wash of less than 3 million sperm per milliliter in the male partner (or a total motile sperm count of <1 million sperm

per milliliter when an analysis after sperm wash was not performed).

## RANDOMIZATION AND TRIAL INTERVENTION

Potential participants were informed about the trial by their doctors or dedicated research nurses. After they provided written informed consent, the women were, preferably just before hysterosalpingography, randomly assigned in a 1:1 ratio to the use of oil contrast (Lipiodol Ultra-Fluid, Guerbet) (the oil group) or water contrast (Telebrix Hystero, Guerbet) (the water group). Randomization was performed by the doctors or research nurses with the use of a secured online randomization program (ALEA, FormsVision) with random block sizes of 2, 4, or 6, stratified according to hospital. This randomization program was overseen by an independent data manager. Owing to the difference in imaging between the use of oil-based contrast and water-based contrast, and, since our outcome of ongoing pregnancy was objective, the trial was not blinded with respect to participants and caregivers.

Hysterosalpingography was performed according to local protocols. The contrast medium could be infused into the uterus with the use of a cervical vacuum cup, metal cannula (hysterophore), or balloon catheter. During the infusion of approximately 5 to 10 ml of contrast medium, four to six radiographs that were obtained to evaluate the patency of both fallopian tubes were examined by a gynecologist or radiologist.

Subsequently, couples received expectant management or the women underwent intrauterine insemination. Expectant management was indicated when the predicted likelihood of natural conception within 12 months after hysterosalpingography, as based on the prognostic model of Hunault,[14,15] was 30% or greater. Intrauterine insemination was offered when this likelihood was less than 30%, when mild male infertility (defined as a total motile sperm count between 1 million and 3 million sperm per milliliter) was present, or after a period of expectant management without natural conception. Intrauterine insemination was initiated after a minimum of 2 months of expectant management after hysterosalpingography and could be performed with or without mild ovarian hyperstimulation, according to local protocols. Mild ovarian hyperstimulation, aiming for two or three follicles, was achieved with clomiphene citrate or exogenous gonadotropins.
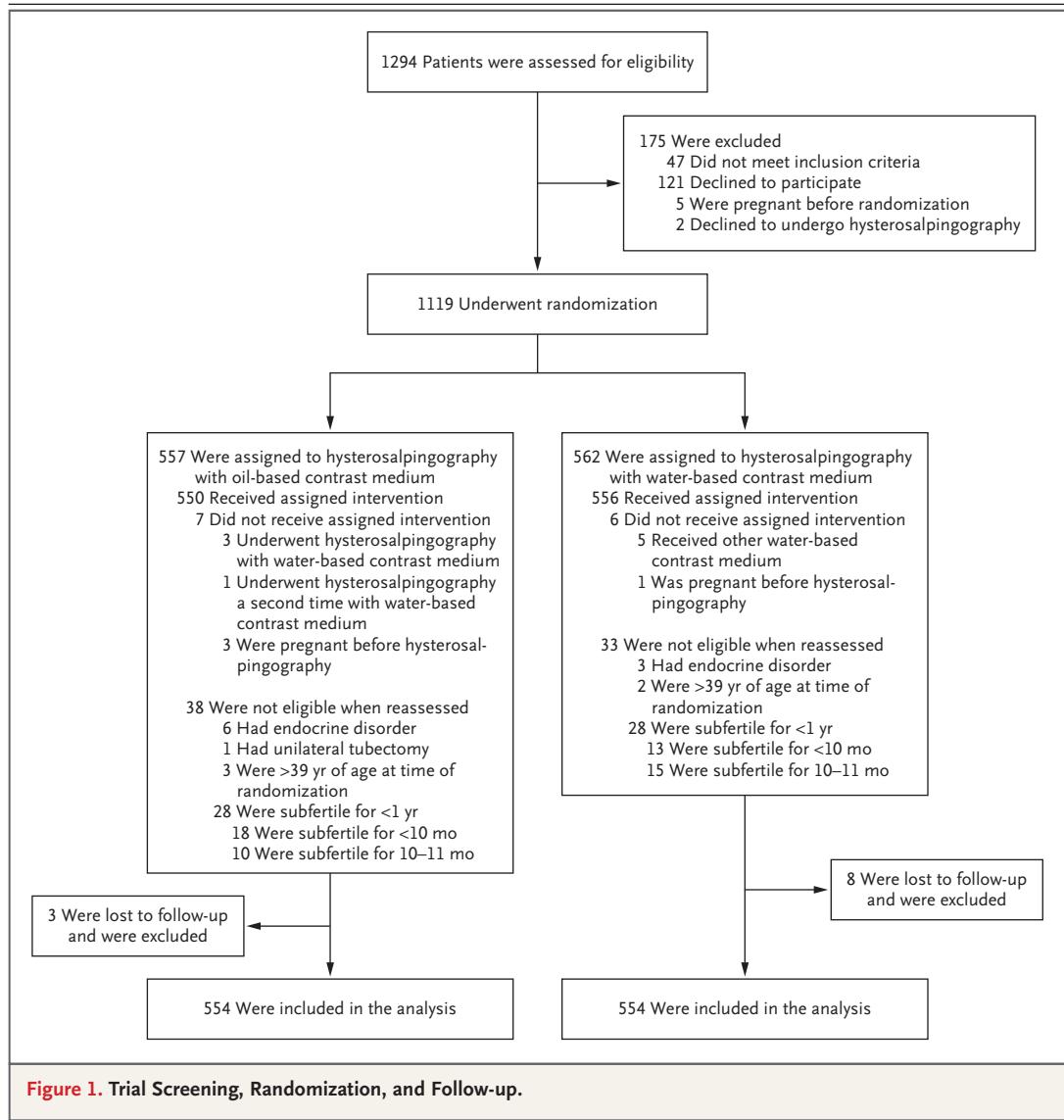
## OUTCOME MEASURES

The primary outcome measure was ongoing pregnancy, defined as a positive fetal heartbeat on ultrasonographic examination after 12 weeks of gestation, with the first day of the last menstrual cycle for the pregnancy within 6 months after randomization. Secondary outcome measures were clinical pregnancy (defined as a gestational sac detected on ultrasonography), live birth (defined as a live birth after 24 weeks of gestation), miscarriage (defined as the absence of a fetal heartbeat on ultrasonography or spontaneous loss of pregnancy before 12 weeks of gestation), ectopic pregnancy (defined as an embryo implanted outside the uterine cavity), and pain scores after hysterosalpingography, measured by means of the Visual-Analogue Scale for Pain (scores range from 0.0 to 10.0 cm, with higher scores indicating more severe pain).

Costs were a prespecified secondary outcome, but this analysis is not included in this article. 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).

## STATISTICAL ANALYSIS

We calculated that the trial would need to include 1080 women (540 in each group) to obtain a power of 80%, with an alpha error of 5%, to detect a difference of 7 percentage points between the trial groups in rates of ongoing pregnancies. This difference was considered by the clinical investigators to be clinically meaningful, over an anticipated control rate of 18% after hysterosalpingography.[10,11] Since the trial compared two interventions used routinely in clinical practice and was expected to recruit quickly, an interim analysis was not performed.

Categorical data were reported as absolute numbers and percentages. Normally distributed continuous variables were summarized as means with standard deviations, and nonnormally distributed continuous variables were reported as medians with interquartile ranges. Apart from

**Figure 1. Trial Screening, Randomization, and Follow-up.**

conventional baseline data, we also compared the likelihood of natural conception within 12 months after hysterosalpingography (calculated with the use of the prognostic model of Hunault) in the two trial groups after completion of the fertility workup to see whether the chance of getting pregnant was similar in the two groups.[14,15]

All data were analyzed according to the intention-to-treat principle. Univariate rate ratios or relative risks and 95% confidence intervals were calculated for the primary and other binary outcome measures, and the chi-square test was used to assess statistical significance. Continuous outcomes were analyzed with the use of an independent t-test or the Mann–Whitney U-test as appropriate. We used Kaplan–Meier curves with a log-rank test to compare the groups with respect to the time to pregnancy resulting in an ongoing pregnancy. Two-sided P values of less than 0.05 were considered to indicate statistical significance. No adjustment was made for multiple comparisons. SPSS software, version 22.0 (IBM), and R software, version 3.3.1 (R Project for Statistical Computing), were used for statistical analyses.

**Table 1. Baseline Characteristics of the Trial Participants.***

| Characteristic | Oil Group (N = 554) | Water Group (N = 554) |
|---|---|---|
| Age | | |
|     Median (IQR) — yr | 32.8 (30.1–35.7) | 33.0 (29.9–35.7) |
|     Age group — no./total no. (%) | | |
|         18–35 yr | 379/553 (68.5) | 382/552 (69.2) |
|         >35 yr | 174/553 (31.5) | 170/552 (30.8) |
| Body-mass index† | | |
|     Median (IQR) | 23.0 (20.8–26.4) | 22.8 (20.8–25.5) |
|     >30.0 — no./total no. (%) | 61/509 (12.0) | 43/499 (8.6) |
| Primary infertility — no. (%) | 373 (67.3) | 374 (67.5) |
| Median duration of infertility (IQR) — mo | 19.8 (16.0–26.3) | 19.6 (15.4–27.4) |
| Median duration of menstrual cycle (IQR) — days | 28 (27–30) | 28 (28–30) |
| Race — no. (%)‡ | | |
|     White | 409 (73.8) | 415 (74.9) |
|     Nonwhite | 57 (10.3) | 61 (11.0) |
|     Unknown | 88 (15.9) | 78 (14.1) |
| Current smoker — no. (%)§ | 77 (13.9) | 95 (17.1) |
| Previous surgery — no. (%) | | |
|     Large-loop excision of the transformation zone or conization of the cervix | 22 (4.0) | 25 (4.5) |
|     Myoma or polyp resection or cystectomy | 3 (0.5) | 5 (0.9) |
|     Tubal surgery | 2 (0.4) | 0 |
|     Intestinal surgery | 33 (6.0) | 37 (6.7) |
| Median total motile sperm count in male partner (IQR) — million/ml | 55.0 (19.0–126.9) | 54.7 (21.7–111.1) |

* There were no significant differences (P<0.05) between the two groups in any of the baseline characteristics. IQR denotes interquartile range.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race was reported by the clinicians.
§ Data on maternal smoking were missing for 36 women in the oil group and 26 women in the water group.

## RESULTS

### TRIAL PARTICIPANTS

Between February 3, 2012, and October 29, 2014, a total of 1294 infertile women were screened for eligibility in the trial, of whom 1240 met the inclusion criteria and 1119 provided written informed consent (Fig. 1). Among these 1119 women, 557 were randomly assigned to hysterosalpingography with the use of oil contrast and 562 were assigned to hysterosalpingography with the use of water contrast. At 6 months after randomization, data on the primary outcome, ongoing pregnancy, were available for 1108 of 1119 women (99.0%). Since the number of missing values was very low, we did not impute missing data, and we report on 1108 women (554 women in each group). A total of 71 women (38 women in the oil group and 33 in the water group) did not meet the inclusion criteria after assignment, mostly because of a period of infertility of slightly less than 1 year (Fig. 1); these women were included in the analyses.

The baseline characteristics were similar in the two groups (Table 1). A total of 787 women underwent hysterosalpingography on the day of randomization; the remaining women underwent hysterosalpingography more than 1 day (inter-

**Table 2. Results of Fertility Evaluation and Treatment.***

| Variable | Oil Group (N = 554) | Water Group (N = 554) | P Value† |
|---|---|---|---|
| **Results of fertility evaluation** | | | |
| Idiopathic or mild male infertility — no. (%) | 486 (87.7) | 490 (88.4) | 0.71 |
| Tubal-factor infertility — no. (%) | 49 (8.8) | 43 (7.8) | 0.64 |
| Other cause — no. (%) | 31 (5.6) | 28 (5.1) | 0.69 |
| Median prognostic index (IQR) — %‡ | 35.43 (26.61–45.38) | 35.77 (26.76–45.82) | 0.45 |
| **Treatment after hysterosalpingography** | | | |
| Expectant management | | | |
| ≥6 mo — no. (%) | 323 (58.3) | 317 (57.2) | 0.72 |
| Followed by intrauterine insemination — no. (%) | 99 (17.9) | 82 (14.8) | 0.16 |
| Without hyperstimulation — no. (%) | 45 (8.1) | 32 (5.8) | 0.13 |
| With hyperstimulation — no. (%) | 52 (9.4) | 46 (8.3) | 0.53 |
| Without hyperstimulation and with hyperstimulation — no. (%) | 2 (0.4) | 4 (0.7) | 0.42 |
| Duration of expectant management (IQR) — mo | 4 (3–5) | 4 (3–5) | 0.54 |
| Intrauterine insemination — no. (%) | | | |
| All patients who underwent only intrauterine insemination | 116 (20.9) | 140 (25.3) | 0.09 |
| Without hyperstimulation | 32 (5.8) | 46 (8.3) | 0.10 |
| With hyperstimulation | 77 (13.9) | 82 (14.8) | 0.67 |
| Without hyperstimulation and with hyperstimulation | 7 (1.3) | 12 (2.2) | 0.25 |
| Intrauterine insemination followed by IVF or ICSI | 5 (0.9) | 5 (0.9) | 1.00 |
| IVF or ICSI — no. (%) | 8 (1.4) | 7 (1.3) | 0.80 |
| Other treatment such as ovulation induction with clomiphene citrate — no. (%) | 3 (0.5) | 3 (0.5) | 1.00 |
| Operation — no./total no. (%) | | | |
| Laparoscopy | 34/550 (6.2) | 34/549 (6.2) | 0.99 |
| Hysteroscopy | 24/550 (4.4) | 23/549 (4.2) | 0.89 |

\* ICSI denotes intracytoplasmic sperm injection, and IVF in vitro fertilization.
† All P values are two-sided.
‡ The probability of natural conception within 12 months after hysterosalpingography (calculated with the use of the prognostic model of Hunault) is shown.[14,15]

quartile range, 2 to 10) after randomization. Hysterosalpingography showed bilateral tubal patency in 477 of 554 women randomly assigned to oil contrast (86.1%) and in 491 of 554 women randomly assigned to water contrast (88.6%) (rate ratio, 0.97; 95% CI, 0.93 to 1.02) (Table S1 in the Supplementary Appendix, available at NEJM.org). Bilateral tubal occlusion occurred in 9 women in the oil group (1.6%) and in 13 women in the water group (2.3%) (relative risk, 0.69; 95% CI, 0.30 to 1.61).

A total of 58.3% of the women who were randomly assigned to oil contrast and 57.2% of the women who were randomly assigned to water contrast received expectant management (Table 2). Similar percentages of women in the oil group and the water group underwent intrauterine insemination (39.7% and 41.0%, respectively), in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) (2.3% and 2.2%), laparoscopy (6.2% in each group), and hysteroscopy (4.4% and 4.2%). Indications for IVF or ICSI, laparoscopy, and hysteroscopy are summarized in Table S2 in the Supplementary Appendix.

**Table 3. Outcomes of the Trial.**

| Outcome | Oil Group (N = 554) | Water Group (N = 554) | Rate Ratio (95% CI)* | P Value† |
|---|---|---|---|---|
| Ongoing pregnancy — no. (%) | 220 (39.7) | 161 (29.1) | 1.37 (1.16–1.61) | <0.001 |
| Clinical pregnancy — no. (%) | 251 (45.3) | 194 (35.0) | 1.29 (1.12–1.50) | 0.001 |
| Miscarriage — no. (%) | 29 (5.2) | 31 (5.6) | 0.94 (0.57–1.53) | 0.79 |
| Ectopic pregnancy — no. (%) | 2 (0.4) | 2 (0.4) | 1.00 (0.14–7.07) | 1.00 |
| Live birth ≥24 wk of gestation — no./total no. (%) | 214/552 (38.8) | 155/552 (28.1) | 1.38 (1.17–1.64) | <0.001 |
| Stillbirth — no./total no. (%) | 4/552 (0.7) | 4/552 (0.7) | 1.00 (0.25–3.98) | 1.00 |
| Twin live birth ≥24 wk of gestation — no./total no. (%) | 2/552 (0.4) | 3/552 (0.5) | 0.67 (0.11–3.97) | 0.66 |
| Median duration of pregnancy (IQR) — wk | 39.9 (38.8–40.9) | 39.9 (38.5–40.6) | | 0.14 |
| Median pain score on visual-analogue scale (IQR)‡ | 4.8 (3.0–6.4) | 5.0 (3.0–6.7) | | 0.28 |

* All rate ratios and 95% confidence intervals are univariate.
† All P values are two-sided.
‡ The pain score was measured immediately after hysterosalpingography. Scores on the Visual-Analogue Scale for Pain range from 0.0 to 10.0 cm, with higher scores indicating more severe pain.

## OUTCOMES

The primary outcome, ongoing pregnancy, occurred in 220 of 554 women (39.7%) randomly assigned to oil contrast and in 161 of 554 women (29.1%) randomly assigned to water contrast (rate ratio, 1.37; 95% CI, 1.16 to 1.61; P<0.001). The median time to the onset of pregnancy was 2.7 months (interquartile range, 1.5 to 4.7) in the oil group and 3.1 months (interquartile range, 1.6 to 4.8) in the water group (P=0.44) (Fig. 2).

Of the 220 ongoing pregnancies in the oil group, 162 (73.6%) were naturally conceived, 15 (6.8%) were conceived after intrauterine insemination without mild ovarian hyperstimulation, 39 (17.7%) were conceived after intrauterine insemination with mild ovarian hyperstimulation, and 4 (1.8%) were conceived after embryo transfer following IVF or ICSI. Of the 161 ongoing pregnancies in the water group, 117 (72.7%) were naturally conceived, 16 (9.9%) were conceived after intrauterine insemination without mild ovarian hyperstimulation, 26 (16.1%) were conceived after intrauterine insemination with mild ovarian hyperstimulation, and 2 (1.2%) were conceived after embryo transfer following IVF or ICSI.

A total of 214 of 552 women in the oil group (38.8%) versus 155 of 552 women in the water group (28.1%) had a live birth (rate ratio, 1.38;
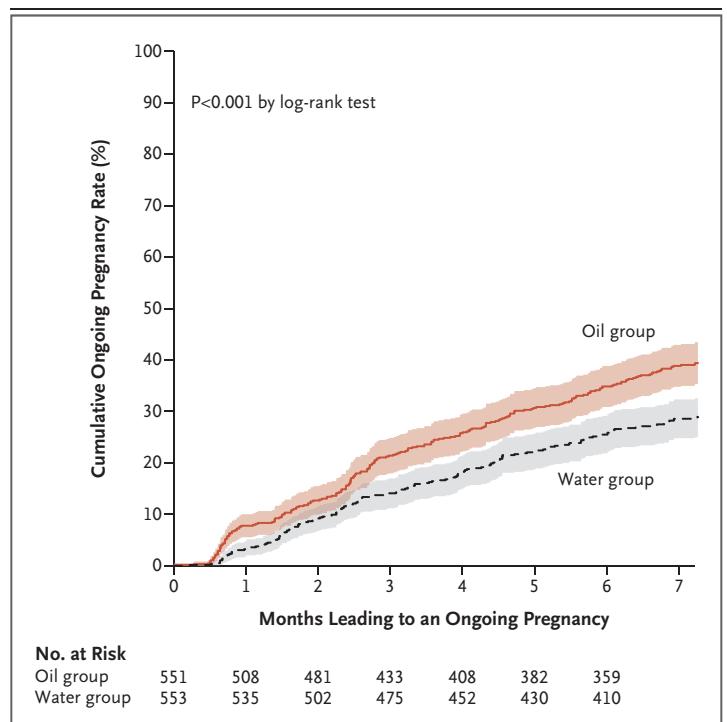
**Figure 2. Ongoing Pregnancy in Women Who Had Undergone Hysterosalpingography with Oil-Based or Water-Based Contrast Medium.**

Data on four participants (three in the oil group and one in the water group) were not included because information on the first day of the last menstrual period before an ongoing pregnancy was missing for these participants. The shaded areas indicate 95% confidence intervals.

| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Oil group | 551 | 508 | 481 | 433 | 408 | 382 | 359 |
| Water group | 553 | 535 | 502 | 475 | 452 | 430 | 410 |

95% CI, 1.17 to 1.64; P<0.001). The other secondary outcomes are listed in Table 3. A post hoc analysis excluding the 71 women who in retrospect did not meet inclusion criteria yielded results that were similar to those in the intention-to-treat analysis for ongoing pregnancy at 6 months (rate ratio, 1.39; 95% CI, 1.17 to 1.65).

A total of 3 of 554 women (0.5%) randomly assigned to oil contrast and 4 of 554 women (0.7%) randomly assigned to water contrast had an adverse event during the trial period (Table S4 in the Supplementary Appendix). In the oil group, 2 women who had an ectopic pregnancy underwent a laparoscopic unilateral salpingectomy. One woman had a molar pregnancy and underwent a vacuum curettage. In the water group, 2 women had an ectopic pregnancy and underwent a laparoscopic unilateral salpingectomy. One woman had a nosebleed after a Puregon injection during intrauterine insemination. In another woman, contrast material was seen in the urinary bladder during hysterosalpingography, and this material disappeared spontaneously. Three women (1.4%), all in the oil group, delivered a child with a congenital anomaly (Table S4 in the Supplementary Appendix).

## DISCUSSION

In this multicenter, randomized trial, we found that the rate of ongoing pregnancy within 6 months after randomization was significantly higher among infertile women who underwent hysterosalpingography with oil contrast than among women who underwent this procedure with the use of water contrast. The subsequent live-birth rate was also significantly higher among women who underwent hysterosalpingography with oil contrast.

Our trial has some limitations. The trial was not conducted in a blinded manner, since the doctor who administered contrast material also evaluated the patency of the fallopian tubes during the examination, and oil and water contrast provide different images on radiographs. However, our primary end point, ongoing pregnancy, was objective, and the number of women who underwent intrauterine insemination or IVF or ICSI was similar in the two groups, which makes it unlikely that a lack of blinding influenced our findings. Also, 38 women in the oil group and 33 women in the water group did not meet the inclusion criteria. However, the proportion of these women was similar in the two groups, and results were similar when we excluded these women. Our trial involved infertile women with a low risk of tubal disease. These women were younger than 39 years of age and did not have known endocrinologic diseases, and our findings should not be generalized to infertile women who do not share these features.

The results of previous studies directly comparing the therapeutic effect of oil-based contrast with water-based contrast during hysterosalpingography were conflicting,[8-12] with the largest and most robust trial[12] showing no effect, but these studies had methodologic limitations. Our trial was more than twice as large as the largest previous trial and had a very low rate of loss to follow-up (1%).

The underlying mechanisms by which oil contrast might enhance fertility are unclear. Some studies suggest that tubal-patency testing with an oily medium will flush debris and dislodge mucus plugs from undamaged tubes. Two previous trials involving women with normal fallopian tubes showed significantly higher pregnancy rates after tubal flushing with oil contrast than with no tubal-patency testing.[4,6] Also, the oil contrast might have an effect on peritoneal macrophage activity and on endometrial receptivity, thereby enhancing fertility by an implantation-mediated mechanism.[16,17] Since we observed an effect that continued to persist over multiple menstrual cycles, we consider a direct endometrial effect unlikely.

Tubal flushing with hysterosalpingography during a fertility workup is minimally invasive and inexpensive, as compared with IVF. The 10-percentage-point increase in the clinical pregnancy rate after the use of oil contrast corresponds with a number needed to treat of 10. Data from a formal cost-effectiveness analysis of the potential cost advantage are lacking.

The safety of the use of oil contrast must be considered. There is a theoretical risk of intravasation of the oil contrast with a subsequent allergic reaction or fat embolism. A case report has described intravasation of oil contrast with a subsequent fat embolism, which resolved with supportive measures.[18] However, this is a rare complication; no cases were observed in our

trial nor in other trials involving hysterosalpingography with oil contrast.[19] In our trial, three infants in the oil group and none in the water group had congenital abnormalities. This finding is probably due to chance; the frequency of congenital anomalies with oil contrast was not greater than rates reported in the general population, and we are unaware of other data suggesting an increased risk of congenital anomalies with oil contrast.

New techniques for outpatient tubal testing have been introduced, including hysterosalpingofoam sonography.[20,21] Data to assess the effects of the use of oil contrast for ultrasonography-based tubal tests or tubal flushing with oil contrast after ultrasonographic examination on rates of pregnancy and live births are lacking.

## APPENDIX

The authors' affiliations are as follows: the Department of Reproductive Medicine (K.D., J.R., V.M., P.G.A.H.) and the Department of Epidemiology and Biostatistics (J.W.R.T.), VU University Medical Center, the Center for Reproductive Medicine, Department of Obstetrics and Gynecology, Academic Medical Center (M.G.), the Department of Obstetrics and Gynecology, Onze Lieve Vrouwe Gasthuis (H.R.V.), and the Department of Obstetrics and Gynecology, Slotervaart Medical Center (A.E.J.D.), Amsterdam, and the Department of Obstetrics and Gynecology, TweeSteden Hospital (I.A.J.R.), and the Department of Obstetrics and Gynecology, Sint Elisabeth Hospital (J.M.J.S.), Tilburg, the Department of Reproductive Medicine and Gynecology, University of Groningen, University Medical Center Groningen, Groningen (A.H.), the Department of Obstetrics and Gynecology, VieCuri Medical Center, Venlo (P.B.), the Department of Obstetrics and Gynecology, Rijnstate Hospital, Arnhem (A.W.N.), the Department of Obstetrics and Gynecology, Albert Schweitzer Hospital, Dordrecht (H.G.M.R.-L.), the Department of Obstetrics and Gynecology, Bravis Hospital, Roosendaal (C.C.M.T.), the Department of Obstetrics and Gynecology, Röpcke-Zweers Hospital, Hardenberg (M.K.), the Department of Obstetrics and Gynecology, Zaans Medical Center, Zaandam (A.B.H.), the Department of Obstetrics and Gynecology, Elkerliek Hospital, Helmond (A.P.G.), the Department of Reproductive Medicine, Maastricht University Medical Center, Maastricht (R.G.), the Department of Obstetrics and Gynecology, Canisius–Wilhelmina Hospital, Nijmegen (C.F.H.), the Department of Obstetrics and Gynecology, Wilhelmina Hospital, Assen (A.V.S.), the Department of Obstetrics and Gynecology, Jeroen Bosch Hospital, Den Bosch (J.-P.B.), the Department of Obstetrics and Gynecology, Westfriesgasthuis, Hoorn (J.A.M.B.), the Department of Obstetrics and Gynecology, Hospital Gelderse Vallei, Ede (E.S.), the Department of Obstetrics and Gynecology, Amstelland Hospital, Amstelveen (A.M.), the Department of Obstetrics and Gynecology, Scheper Hospital, Emmen (M.J.P.), the Department of Obstetrics and Gynecology, Gelre Hospital, Apeldoorn (M.A.F.T.), the Department of Obstetrics and Gynecology, Sint Franciscus Hospital, Rotterdam (M.H.A.H.), the Department of Obstetrics and Gynecology, Diaconessenhuis (G.A.U.), and the Department of Medical Statistics and Bioinformatics, Leiden University Medical Center (N.G.), Leiden, and the Department of Obstetrics and Gynecology, Tergooi Hospital, Blaricum (C.H.K.) — all in the Netherlands; and the School of Medicine, Robinson Research Institute, University of Adelaide, and the South Australian Health and Medical Research Institute, Adelaide, SA, Australia (B.W.J.M.).

## REFERENCES

**1.** Thoma ME, McLain AC, Louis JF, et al. Prevalence of infertility in the United States as estimated by the current duration approach and a traditional constructed approach. Fertil Steril 2013;99(5):1324-1331.e1.
**2.** Cundiff G, Carr BR, Marshburn PB. Infertile couples with a normal hysterosalpingogram: reproductive outcome and its relationship to clinical and laparoscopic findings. J Reprod Med 1995;40: 19-24.
**3.** Weir WC, Weir DR. Therapeutic value of salpingograms in infertility. Fertil Steril 1951;2:514-22.
**4.** Johnson NP, Farquhar CM, Hadden WE, Suckling J, Yu Y, Sadler L. The FLUSH trial — flushing with lipiodol for unexplained (and endometriosis-related) subfertility by hysterosalpingography: a randomized trial. Hum Reprod 2004;19: 2043-51.

**5.** Nugent D, Watson AJ, Killick SR, Balen AH, Rutherford AJ. A randomized controlled trial of tubal flushing with lipiodol for unexplained infertility. Fertil Steril 2002;77:173-5.
**6.** Ogata R, Nakamura G, Uchiumi Y, et al. Therapeutic efficacy of hysterosalpingography (HSG) in infertility: a prospective, randomized, clinical study. Jap J Fertil Steril 1993;38:91-4.
**7.** Mohiyiddeen L, Hardiman A, Fitzgerald C, et al. Tubal flushing for subfertility. Cochrane Database Syst Rev 2015; 5:CD003718.
**8.** Alper MM, Garner PR, Spence JE, Quarrington AM. Pregnancy rates after hysterosalpingography with oil- and water-soluble contrast media. Obstet Gynecol 1986;68:6-9.
**9.** de Boer AD, Vemer HM, Willemsen WN, Sanders FB. Oil or aqueous contrast media for hysterosalpingography: a pro-

spective, randomized, clinical study. Eur J Obstet Gynecol Reprod Biol 1988;28:65-8.
**10.** Lindequist S, Rasmussen F, Larsen C. Use of iotrolan versus ethiodized poppy-seed oil in hysterosalpingography. Radiology 1994;191:513-7.
**11.** Rasmussen F, Lindequist S, Larsen C, Justesen P. Therapeutic effect of hysterosalpingography: oil- versus water-soluble contrast media — a randomized prospective study. Radiology 1991;179:75-8.
**12.** Spring DB, Barkan HE, Pruyn SC. Potential therapeutic effects of contrast materials in hysterosalpingography: a prospective randomized clinical trial. Radiology 2000;214:53-7.
**13.** National guideline for the fertility workup: Dutch guidelines for obstetrics and gynaecology. Utrecht, the Netherlands: Dutch Society of Obstetrics and Gynaecology, 2004 (http://www.med-info.nl/Richtlijnen/ Gynecologie/Voortplantingsgeneeskunde/

Orienterend%20Fertiliteitsonderzoek%20 (OFO).pdf).

**14.** 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;19:2019-26.

**15.** van der Steeg JW, Steures P, Eijkemans MJ, et al. Pregnancy is predictable: a large-scale prospective external validation of the prediction of spontaneous pregnancy in subfertile couples. Hum Reprod 2007;22:536-42.

**16.** Johnson JV, Montoya IA, Olive DL. Ethiodol oil contrast medium inhibits macrophage phagocytosis and adherence by altering membrane electronegativity and microviscosity. Fertil Steril 1992;58:511-7.

**17.** Johnson NP. Review of lipiodol treatment for infertility — an innovative treatment for endometriosis-related infertility? Aust N Z J Obstet Gynaecol 2014;54:9-12.

**18.** Uzun O, Findik S, Danaci M, Katar D, Erkan L. Pulmonary and cerebral oil embolism after hysterosalpingography with oil soluble contrast medium. Respirology 2004;9:134-6.

**19.** Court KA, Dare AJ, Weston-Webb M, Hadden WE, Sim RG, Johnson NP. Establishment of lipiodol as a fertility treatment — prospective study of the complete innovative treatment data set. Aust N Z J Obstet Gynaecol 2014;54:13-9.

**20.** Dijkman AB, Mol BW, van der Veen F, Bossuyt PM, Hogerzeil HV. Can hysterosalpingocontrast-sonography replace hysterosalpingography in the assessment of tubal subfertility? Eur J Radiol 2000;35:44-8.

**21.** Emanuel MH, van Vliet M, Weber M, Exalto N. First experiences with hysterosalpingo-foam sonography (HyFoSy) for office tubal patency testing. Hum Reprod 2012;27:114-7.

*Copyright © 2017 Massachusetts Medical Society.*