Ethiodized poppyseed oil-based contrast medium is superior to water-based contrast medium during hysterosalpingography regarding image quality improvement and fertility enhancement: A multicentric, randomized and controlled trial

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Summary

Background The efficacy of ethiodized poppyseed oil in hysterosalpingography (HSG) image quality and fertility enhancement has been revealed, but whether this HSG modality has similar effects in the Chinese population is still unclear.

Methods Between July 18, 2017, and December 29, 2019, this multicentric, randomized, two-arm, clinical trial was performed involving 15 medical centers. Infertile women meeting HSG indications were randomly assigned to an oil group and a water group. The coprimary outcome included HSG image quality during HSG and fertility-enhancing effects of HSG. This study was registered on ClinicalTrials.gov (NCT03370575).

Findings A total of 1026 subjects were randomly assigned to an oil group (N = 508) and a water group (N = 518). HSG image quality revealed that the oil group had outstanding visualization (all $P < 0.001$); total image quality scores for uterus opacification or uterine outline (2.9 ± 0.4 vs. 2.7 ± 0.5), fallopian tube outline (2.3 ± 0.8 vs. 1.7 ± 0.7), fimbrial rugae (1.7 ± 1.0 vs. 1.3 ± 0.8), fallopian tube spillage (2.1 ± 0.9 vs. 1.6 ± 0.8), peritoneal distribution (2.6 ± 0.9 vs. 2.1 ± 1.0) and diagnostic quality (11.6 ± 3.4 vs. 9.5 ± 3.1) (all $P < 0.001$) were higher in the oil group than in the water group. Regarding fertility-enhancing evaluation, the oil group showed an increased cumulative on-going pregnancy rate, on-going pregnancy within 6 months (29.1% vs. 20.1%), clinical pregnancy (39.5% vs. 29.1%) and live birth ≥ 24 weeks of gestation (36.1% vs. 27.7%) but a shorter time to pregnancy than the water group (all $P < 0.01$). Concerning adverse events, the oil group showed a lower occurrence rate of abdominal pain and vaginal bleeding after HSG (both $P < 0.01$).

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Interpretation Ethiodized poppyseed oil-based contrast is superior to water-based contrast during HSG in terms of image quality improvement and fertility enhancement. This study indicates the priority of the application of ethiodized poppyseed oil-based contrast during the HSG procedure in infertile patients.

Funding No funding was received.

Keywords: Hysterosalpingography; Ethiodized poppyseed oil-based contrast medium; Image quality; Fertility enhancement; Safety

Research in context

Evidence before this study

PubMed database was used for searching the evidence before undertaking this study. The articles mainly including the effect of oil-based contrast during hysterosalpingography on the image quality and pregnancy outcome in infertility patients were of great interest. To appraise the current evidence, we searched PubMed to identify articles published before September 2021. The search terms 'ethiodized poppyseed oil', 'oil-based', 'hysterosalpingography', 'HSG' and 'infertility' were used to select the manuscripts. We were unable to identify any studies about the efficacy of ethiodized poppyseed oil on HSG image quality and fertility-enhancement especially from multicentric study and focusing on Chinese population.

Added value of this study

The present study adds value to the present literature due to that: 1. It's a multicentric, randomized, controlled trial which provides high-quality evidence about the efficacy and safety of HSG with ethiodized poppyseed oil-based contrast medium on image quality and fertility-enhancing effects; 2. It also focuses on the Chinese population, which has not been reported before; 3. The existing data only focus on either the image quality or fertility-enhancing effects with oil-based contrast medium during the HSG, while in this study, we report these two aspects at the same time. This study found that oil group showed outstanding visualization; Meanwhile, oil group showed increased cumulative on-going pregnancy rate, on-going pregnancy within 6 months, clinical pregnancy and live birth ≥24 weeks of gestation, but shorter pregnancy duration compared to water group. In addition, oil group also showed decreased abdominal pain and colporrhagia after HSG.

Implications of all the available evidence

The study provides an optional contrast medium during the HSG process which discloses not only a better visualization but also a better pregnancy outcome in Chinese population. The application of ethiodized poppyseed oil-based contrast medium during HSG might improve fertility circumstance in Chinese patients with infertility.

Introduction

Infertility, referring to the failure to conceive after at least 12 months of regular unprotected sexual intercourse, presents with a 9–18% prevalence in the general population,[1–3] which is considered an urgent issue resulting in various social, economic, and psychological problems in China. Hysterosalpingography (HSG) is a valuable radiologic procedure that mainly consists of the injection of a contrast agent into the patient's uterus and fallopian tubes to discover the leading cause of infertility by screening for possible uterine cavity lesions, congenital malformations and fallopian tube stricture and obstruction, even though there is an unneglectable false-positive rate of approximately 20%.[4,5] Currently, HSG has been reported to be the most effective diagnostic method for infertility due to its reliability, availability, simplicity, and cost-effectiveness.[4,6] More importantly, HSG has therapeutic effects on infertility to some extent, including the treatment of proximal obstruction via tubal flushing.[6–9]

Despite its effect on increasing fertility, the efficacy of HSG is still influenced by the selection of contrast agents. From accumulating data, an oil-based contrast agent has a better effect of enhancing the fertility rate post-HSG compared to a water-soluble agent or no intervention.[10–12] For instance, a multicenter, randomized trial of 27 hospitals in the Netherlands revealed that an ethiodized poppyseed oil agent is correlated with elevated ongoing pregnancy and live births compared to water agents after HSG.[12]

In addition, the image quality is directly related to an accurate diagnosis. Therefore, the image quality is also of great concern. Based on the published literature, an oil-based contrast agent discloses better image quality than a water-soluble agent.[10,11] For example, a previous study illustrated that the HSG image of an oil-soluble contrast medium (OSCM) has a distinctive appearance that is sharper and more contrasting than that of a water-soluble contrast medium (WSCM).[10] In addition, a recent single-center prospective cohort study revealed that ethiodized poppyseed oil yields a better image quality than ioversol as a contrast agent in HSG.[11]

Although the efficacy of ethiodized poppyseed oil with respect to HSG image quality and fertility

enhancement has been revealed, most of the preceding data are from monocentric studies that do not focus on the Chinese population.[11] Therefore, we conducted this multicentric, randomized, controlled trial and enrolled 1026 infertile Chinese patients from 15 medical centers, aiming to explore the efficacy and safety of HSG with ethiodized poppyseed oil-based contrast medium regarding image quality and fertility-enhancing effects.

Methods

Study design

This was a multicentric, randomized, two-arm, clinical trial conducted in Guangdong, Gansu, Hubei, Hebei, Liaoning, Beijing, Guangxi, Jiangsu, Sichuan, Henan and Shanghai, China, in which 15 medical centers participated (as listed in Supplementary Table 1). During the period between July 18, 2017, and December 29, 2019, subjects meeting the HSG indications were enrolled and randomly and evenly assigned to one of the two treatment groups: the oil group (use of the ethiodized poppyseed oil contrast medium during HSG) and the water group (use of the water-based contrast medium during HSG). Assessments in the study were performed in two stages: stage 1 included an assessment of HSG image quality and the adverse events that occurred during the HSG procedure; stage 2 included an assessment of fertility-enhancing effects and the adverse events that occurred during the follow-up. This study was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center with approval number 2017,102708. Furthermore, this study was registered on ClinicalTrials.gov with registration number of NCT03370575. Moreover, the detailed study protocol can be viewed at the website https://clinicaltrials.gov/ct2/show/NCT03370575?term=NCT03370575&draw=2&rank=1. Before the HSG examination, the examinators were responsible for informing the patients about the study details. Then, all participants signed informed consent forms.

Participant enrollment

The inclusion criteria were as follows: (i) females aged 21–39 years; (ii) with more than 12 months of trying to conceive; (iii) with a spontaneous menstrual cycle; (iv) meeting the indications for HSG; and (v) able to understand the study contents and volunteer to sign the informed consent form. The exclusion criteria included (i) known endocrine disorders (such as polycystic ovary syndrome, diabetes, hyperthyroidism and hyperprolactinemia); (ii) less than 8 menstrual cycles per year; (iii) high risk of fallopian tube disease (e.g., history of pelvic inflammatory disease, previous chlamydia infection or known endometritis); (iv) vaginitis, active acute or subacute pelvic inflammatory disease, uterine or fallopian tube tuberculosis; (v) uterine or cervical bleeding; (vi) cessation of menstruation that could not rule out pregnancy; (vii) severe cardiopulmonary disease; (viii) body temperature higher than 37.5 ℃ within 3 days before HSG; (ix) total motile sperm counts of male partners at less than 1 million/mL; and (x) comorbidity or social circumstances that may cause subjects to fail to follow the study plan or even endanger patient safety.

Randomized grouping

The block randomization method was applied to generate the random assignment number using SAS 9.0 (SAS Institute, Inc., Cary, North Carolina, USA), which was performed by a statistical analyst. The random assignment number and grouping information were made into scratch cards, which were handled by the statistical analyst from the major research center. At each center, each eligible patient was assigned a scratch card in the order of clinic visits. After that, the patient was allocated to the oil group or water group according to the grouping information on the scratch card and received corresponding treatment.

HSG procedures

In both groups, the HSG procedures were performed uniformly except for the contrast medium used. In the oil group, ethiodized poppyseed oil (Jiangsu Hengrui Medicine Co., Ltd., Lianyungang, Jiangsu Province, China) was used as the contrast medium in the HSG. In the water group, Iohexol 300 (General Electric Pharmaceutical (Shanghai) Co., Ltd, Shanghai, China), Iopromide 300 (Bayer Healthcare Co., Ltd (Beijing), Beijing, China) or Ioverol 320 (Jiangsu Hengrui Medicine Co., Ltd., Lianyungang, Jiangsu Province, China) was used as the contrast medium in the HSG. In detail, the HSG procedure was performed as follows: a balloon catheter was inserted into the cervix via the vagina and fixed through the cervix. Then, the prewarmed ethiodized poppyseed oil contrast for the oil group or the prewarmed nonionic monomer contrast for the water group was slowly injected until the uterine cavity was fully filled or the contrast entered the pelvic cavity. At the same time, the process of the contrast entering the uterine cavity and fallopian tube was dynamically observed on the TV screen, and the appropriate images were photographed (a total of 3~4 pictures were taken at the following time-points: 1. Before injection of the contrast into the cavity; 2. When the contrast was filling the cavity and tubes; 3. When the contrast overflowed from the tubes; 4. Twenty minutes after HSG using the water-soluble agent and 24 h after HSG using the oil-based agent).

During the injection, the pressure was controlled in an appropriate range, which was controlled depending on the experience of the clinicians. Once intravasation

or interstitial reflux occurred, the injection of the contrast agent was stopped immediately, and the patients were asked to sit up in the bed, get out of bed and walk, and receive oxygen inhalation.

Outcome assessment

The coprimary outcome assessment included assessment of the quality of the HSG images and the fertility-enhancing effects of HSG. The quality of the HSG image was evaluated by an independent third-party radiologist (Deputy Chief Physician, Department of Radiology, Wuhan Third Hospital, Hubei Province, China) who had at least ten years of experience in radiological image assessment. The third-party radiologist was blinded to the study design, the patient information, and the contrast medium. According to the European guidelines on quality criteria for diagnostic radiographic images,[13] the assessment of HSG image quality focused on the following five dimensions: (a) uterus opacification or uterine outline; (b) fallopian tube outline; (c) fimbrial rugae; (d) fallopian tube spillage; and (e) peritoneal distribution. Each dimension was scored from 0 to 3, as follows[11,14]: (i) 0 indicated "weakly visualized and not diagnostic" (WVND); (ii) 1 indicated "weakly visualized but diagnostic" (WVD); (iii) 2 indicated "good demonstration and diagnostic" (GDD); and (iv) 3 indicated "outstanding visualization" (OV). The total image quality score was the sum of five-dimensional scores, ranging from 0 to 15, and a higher total score indicated higher image quality.

In terms of the fertility-enhancing effects of HSG, all patients were followed up at month 2 (M2) after HSG, and follow-up was conducted every 3 months through telephone until the endpoint of the follow-up (including the end of the study, live birth, miscarriage, or patient death). The final follow-up date was December 24, 2020. The assessment of fertility-enhancing effects included (a) ongoing pregnancy, which was defined as a positive fetal heartbeat on ultrasonographic examination after 12 weeks of gestation, from the first day of the last menstrual cycle of pregnancy within 6 months after HSG[12]; (b) clinical pregnancy, which was defined as a gestational sac detected by ultrasonography; (c) live birth, which was defined as a live birth after 24 weeks of gestation; (d) miscarriage, which was defined as the absence of a fetal heartbeat on ultrasonography or spontaneous loss of pregnancy before 12 weeks of gestation; (e) twin live birth ≥ 24 weeks of gestation; and (f) time to pregnancy, which was calculated from the first day of the last menstrual period plus 4 weeks minus the day of HSG. In addition, the pain during the HSG was scored using a 10 cm Analog Visual Scale (VAS). A higher score was associated with more severe pain. In detail, the patients assessed their VAS by themselves after the HSG examination based on their subjective sensation.

The second outcome was safety. For safety assessment, adverse events, including allergy, intravasation, interstitial reflux during the HSG and abdominal pain, vaginal bleeding, allergy, and fever after HSG, were documented within seven days after HSG. In addition, adverse events that occurred within two months after HSG were also recorded at M2 during the follow-up. Interstitial reflux is an adverse event that especially occurs in infertility patients with interstitial fallopian tube obstruction during HSG ("interstitial fallopian tube" means that a narrow and short part of the fallopian tube runs into the inner wall of the uterus, with an approximate length of 1 cm). The interstitial reflux manifested as contrast refluxing back to the uterus at the interstitial site of the fallopian tube when injecting the contrast to the fallopian tube.

Statistical analysis

The minimum sample size estimation was based on the quality of the HSG image and the ongoing pregnancy. According to a previous study comparing the HSG image quality of the oil-based contrast medium with the water-based contrast medium,[15] the rate of the OV image in the oil group and the water group was 89% vs. 55%, respectively. With a power of 85% and alpha of 0.05, the calculated total sample size was $N = 60$ (30 cases in each group). In the H2Oil trial,[12] the reported ongoing pregnancy rates in the oil group and the water group were 39.7% and 29.1%, respectively. With a power of 85% and alpha of 0.05, the calculated total sample size was $N = 720$ (360 cases in each group). Based on the above two estimated results, the minimum sample size was 720; meanwhile, taking a dropout rate of 20% into consideration, the final minimum sample size was 900.

Qualitative data are described as numbers with percentages, which were analyzed using the chi-square test or Fisher's exact test between two groups as appropriate. The risk ratio and 95% confidence interval (CI) were univariate results of a two-sided test. Normality of quantitative data was determined by the Kolmogorov–Smirnov test. Quantitative data are described as the mean with standard deviation (SD) and median with range, which were analyzed by the independent *t*-test or Wilcoxon rank sum test between two groups as appropriate. The Cochran–Mantel–Haenszel chi-squared test with adjustment for central effects was used for the comparison between groups. A Kaplan–Meier curve was applied to illustrate the cumulative ongoing pregnancy rate within 6 months, which was analyzed by the log-rank test. SAS 9.0 (SAS Institute, Inc., Cary, North Carolina, USA) was employed for statistical analysis. Statistical significance was concluded if there was a two-sided P value less than 0.05 in the corresponding analysis. The analysis of this study was based on the intention-to-treat population.

Role of the funding source

No funding was received. Data collection was performed by JZ, WSL, YTW, KSC, GFZ, WZY, HCC, WJX, JXM, WHQ, YZ, WQW, HCW, ZJD, YLW, YC, NG and YCT. Data analysis was completed by JZ, WSL, YTW, KSC, GFZ, WZY, HCC and WJX. JXM, WHQ, YZ, WQW, HCW, ZJD were responsible for data verification. Data interpretation was performed by JZ, WSL, YTW and KSC. All authors approved the final version of the manuscript. JZ is responsible for submitting the manuscript and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved.

Results

Trial participants

A total of 1026 subjects meeting HSG indications from 15 medical centers were enrolled. There were 1072 patients assessed for eligibility, among which 46 patients were excluded (including 27 patients who did not meet the inclusion criteria and 19 patients who declined to participate), and the remaining 1026 patients were randomly assigned to the oil group (N = 508) and the water group (N = 518). The detailed enrollment procedures are shown in **Supplementary Table 2**. In the oil group, 491 patients were available for the evaluation of the diagnostic performance and image quality, and after 18 patients were lost to follow-up, the remaining 473 patients were eligible for the fertility-enhancing assessment. In the water group, 491 patients were available for the assessment of the diagnostic performance and image quality, and after 12 patients were lost to follow-up, the remaining 479 patients were available for the fertility-enhancing assessment (Figure 1).

The mean and median ages of all patients were 30.6 ± 3.7 years and 30.0 (range: from 21 to 39) years, respectively. In the oil group, the mean and median ages of the patients were 30.5 ± 3.7 years and 30.0 (range: from 21 to 39) years, respectively, while in the water group, those ages were 30.8 ± 3.6 years and 31.0 (range: from 21 to 39) years, respectively. Detailed information on the other sociodemographic characteristics, sexual history, obstetric history, gynecological history and medical history is shown in Table 1.

Outcomes

The mean and median dosages of the contrast medium in the oil group were lower than those in the water group (P < 0.001), whereas the number of images taken in the oil group was higher than that in the water group (P = 0.030) (Table 2).

For the five dimensions of uterus opacification or uterine outline (436 (88.8%) vs. 342 (69.7%), P < 0.001), fallopian tube outline (231 (47.0%) vs. 59 (12.0%), P < 0.001), fimbrial rugae (135 (27.5%) vs. 26 (5.3%), P < 0.001), fallopian tube spillage (171 (34.8%) vs. 50 (10.2%), P < 0.001) and peritoneal distribution (408 (83.1%) vs. 202 (41.1%), P < 0.001), a higher percentage of patients in the oil group showed OV compared to the water group (Table 3). The total scores for image quality of uterus opacification or uterine outline (2.9 ± 0.4 vs. 2.7 ± 0.5; P < 0.001), fallopian tube outline (2.3 ± 0.8 vs. 1.7 ± 0.7; P < 0.001), fimbrial rugae (1.7 ± 1.0 vs. 1.3 ± 0.8; P < 0.001), fallopian tube spillage (2.1 ± 0.9 vs. 1.6 ± 0.8; P < 0.001) and peritoneal distribution (2.6 ± 0.9 vs. 2.1 ± 1.0; P < 0.001) were higher in the oil group than in the water group. In terms of the diagnostic quality (11.6 ± 3.4 vs. 9.5 ± 3.1; P < 0.001), the image quality score was also increased in the oil group compared with the water group (Figure 2).

In addition, the cumulative ongoing pregnancy rate in the oil group was higher than that in the water group (Figure 3). In addition, the oil group exhibited higher rates of ongoing pregnancy within 6 months (136 (29.1%) vs. 96 (20.1%), risk ratio (RR): 1.44, (95% CI: 1.15–1.81), P = 0.001), clinical pregnancy (185 (39.5%) vs. 139 (29.1%), RR: 1.36 (95% CI: 1.13–1.62), P < 0.001), and live birth ≥ 24 weeks of gestation (169 (36.1%) vs. 132 (27.7%), RR: 1.3 (95% CI: 1.08–1.58), P = 0.006) than the water group. Additionally, the time to pregnancy in the oil group was shorter than that in the water group (41.7 ± 18.5 vs. 46.1 ± 16.8, P < 0.001) (Table 4). In terms of other fertility-enhancing treatments, it was found that the proportion of patients who received fertility-enhancing treatments after HSG (18 (3.8%) vs. 17 (3.5%)), planned to undergo hysteroscopy (7 (1.5%) vs. 3 (0.6%)), planned to receive assisted reproduction (11 (2.3%) vs. 5 (1.0%)), underwent specific protocols for assisted reproduction (artificial insemination: 5 (45.5%) vs. 3 (60.0%); *in vitro* fertilization-embryo transfer: 5 (45.5%) vs. 2 (40.0%); unknown: 1 (9.0%) vs. 0 (0.0%)), received collaborative treatments (ovulation stimulation: 10 (2.1%) vs. 11 (2.3%); traditional Chinese medicine: 65 (13.8%) vs. 53 (11.0%); others: 0 (0.0%) vs. 2 (0.4%)) and received mild ovarian hyperstimulation (1 (0.2%) vs. 2 (0.4%)) did not differ between the oil group and the water group (All P > 0.05) (**Supplementary Table 3**). In addition, the oil group showed a decreased VAS pain score (1.8 ± 1.5 vs. 2.3 ± 1.6, P < 0.001) compared with that of the water group.

During HSG, the oil group presented no difference in allergies, intravasation (11 (2.2%) vs. 7 (1.4%), P = 0.341) or interstitial reflux (5 (0.1%) vs. 1 (0.2%), P = 0.123) compared with the water group (Table 5). After HSG, the oil group revealed a decreased occurrence of abdominal pain (180 (36.7%) vs. 225 (45.8%), P = 0.004) and vaginal bleeding (170 (34.6%) vs. 217 (44.2%), P = 0.003) but presented no difference in allergies or fever (2 (0.4%) vs. 0 (0.0%), P = 0.249) compared to the water group (Table 5).

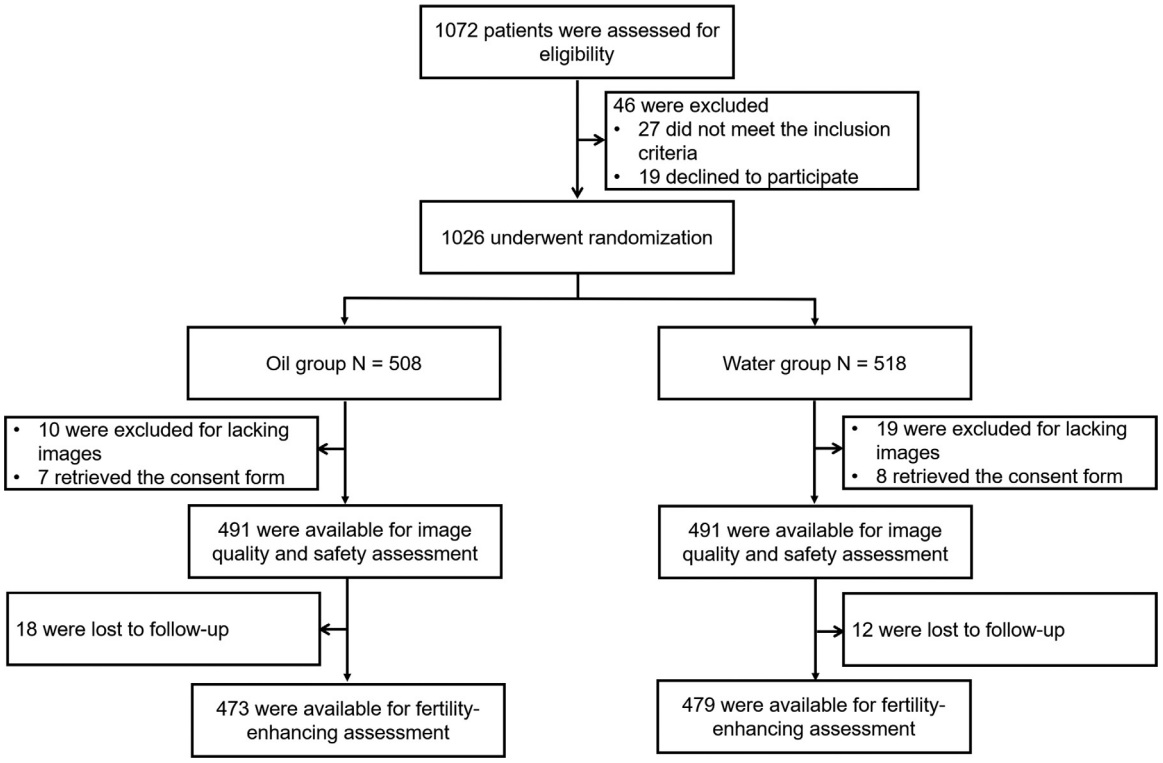

Figure 1. Study flow.

Participants were randomized assigned to oil group and water group. Patients who lost to follow-up and lacking image were excluded from the image quality and safety assessment; patients who retrieved the consent form were also excluded from the fertility-enhancing assessment. HSG: hysterosalpingography.

Discussion

In this multicentric, randomized, controlled trial that focused on the Chinese population, we discovered that the ethiodized poppyseed oil-based contrast medium had a more obvious efficacy on image quality than the water-based contrast medium during HSG. In addition, the fertility-enhancing effects of the ethiodized poppyseed oil-based contrast medium were superior to those of the water-based contrast medium. Furthermore, the ethiodized poppyseed oil-based contrast medium showed a decreased pain VAS score compared to that with the water-based contrast medium.

There were still several limitations in the present study. First, although this was a multicentric, randomized, controlled trial enrolling 1026 infertile Chinese patients from 15 medical centers, a larger sample size might be more convincing. Second, even though the fertility enhancement mechanism of the oil-based contrast medium has been reported in a few studies, its in-depth mechanism has not been systematically and comprehensively determined and needs to be explored in further research. Third, the randomization method of "scratch cards" was relatively simple. It did not achieve center randomization by using a computerized system, which might have caused selection bias. Fourth, even though this study enrolled Chinese patients from all parts of the country, it could not be representative of the wider population, such as infertile patients from Europe or the US. Fifth, all patients were asked to prepare for pregnancy for 1 year instead of receiving hysteroscopic surgery or tubal surgery after HSG examination; therefore, the effect of image quality on the subsequent choice of hysteroscopic surgery or tubal surgery was hard to determine, which might be explored in future studies. Sixth, the quality of images was assessed by only one radiologist; therefore, this might reduce the reliability of the study findings. Seventh, the exact pressure of injection of contrast was not determined by clinicians using a pressure monitor but was only controlled depending on the clinicians' experience; thus, this issue should be determined in future studies.

The quality of images after HSG is important for clinicians to make a diagnosis and influences the choice of subsequent treatments.[10,11] Therefore, it is necessary to conduct a trial to compare the image quality between oil-based contrast medium and water-based contrast medium. In the current study, we found that the image quality of the ethiodized poppyseed oil-based contrast medium exceeded that of the water-based contrast medium during HSG in five dimensions, which was in

Items	Oil group, (*N* = 491)	Water group, (*N* = 491)	Total (*N* = 982)
Sociodemographic characteristics			
Age (years)			
Mean±SD	30.5 ± 3.7	30.8 ± 3.6	30.6 ± 3.7
Median (range)	30.0 (21, 39)	31.0 (21, 39)	30.0 (21, 39)
Height (cm)			
Mean±SD	161.2 ± 5.1	161.2 ± 4.9	161.2 ± 5.0
Median (range)	160.0 (146, 179)	160.0 (145, 175)	160.0 (145, 179)
Weight (kg)			
Mean±SD	56.9 ± 10.6	57.1 ± 9.9	57.0 ± 10.3
Median (range)	55.0 (37, 130)	55.0 (36, 110)	55.0 (36, 130)
Smoker, No. (%)	4 (0.8)	6 (1.2)	10 (1.0)
Drinker, No. (%)	3 (0.6)	3 (0.6)	6 (0.6)
Obstetric history			
Previous duration of infertility (days)			
Mean±SD	612.0 ± 399.7	607.2 ± 598.1	609.6 ± 508.3
Median (range)	480.0 (360, 3600)	435.0 (360, 10950)	450.0 (360, 10950)
Total number of previous pregnancies resulting in live births, No. (%)			
0	422 (85.9)	396 (80.7)	818 (83.3)
1	65 (13.2)	90 (18.3)	155 (15.8)
2	3 (0.6)	4 (0.8)	7 (0.7)
≥3	1 (0.2)	1 (0.2)	2 (0.2)
Miscarriage times, No. (%)			
None	313 (63.7)	312 (63.5)	625 (63.6)
Once	119 (24.2)	109 (22.2)	228 (23.2)
Twice	39 (7.9)	48 (9.8)	87 (8.9)
Three times and above	20 (4.1)	22 (4.5)	42 (4.3)
Gynecological history			
Duration of infertility (days)			
Mean±SD	629.5 ± 464.7	611.2 ± 477.9	620.4 ± 471.2
Median (range)	480.0 (360, 5840)	450.0 (360, 6570)	480.0 (360, 6570)
Current menstrual cycle (days)			
Mean±SD	30.3 ± 4.2	29.9 ± 3.6	30.1 ± 3.9
Median (range)	30.0 (4, 72)	30.0 (5, 45)	30.0 (4, 72)

***Table 1*: Characteristics of the patients.**
SD, standard deviation.

line with previous data.[11] Moreover, the excellent visualization quantity distribution of the ethiodized poppyseed oil-based contrast medium was also superior to that of the water-based contrast medium. These results suggested a more obvious efficacy on the image quality of the ethiodized poppyseed oil-based contrast medium compared to the water-based contrast medium during HSG. The possible explanations were that (1) the ethiodized poppyseed oil-based contrast medium was characterized by strong viscosity, and its duration from contrast agent injection to the initiation of photography was usually 24 h (but just 20 min for the water-based contrast medium), which could provide much more time to take pictures, thereby to some extent improving the HSG image quality.[11] (2) The ethiodized poppyseed oil-based contrast medium had more apparent effects on removing or flushing the residual mucus plug remaining in the fallopian tubes compared to the water-based contrast medium during HSG, which was helpful to make a clearer HSG image.[12,16] (3) The ethiodized poppyseed oil-based contrast medium flowed more slowly and extensively to fill out the contours of the uterine cavity and tubes, thereby making the images clearer and sharper.[10] (4) The water-based contrast medium was easy to mix with the water-soluble mucus plug, resulting in poor HSG image quality.[16] Another finding should be pointed out: although there was a difference in image quality, the type of contrast did not have an impact on treatment modality. This finding could be explained as follows: the number of patients who received fertility-enhancing treatments after HSG was small, which caused low statistical power; therefore, the treatment modality was not different between these two groups.

Items	Oil group (*N* = 491)	Water group (*N* = 491)	Total (*N* = 982)	*P* value
Contrast medium, No. (%)				–
Ethiodized poppyseed oil	489 (99.6)	1 (0.2)	490 (49.9)	
Ioverol 320	2 (0.4)	334 (68.0)	336 (34.2)	
Iohexol 300	0 (0.0)	23 (4.7)	23 (2.3)	
Iopromide 300	0 (0.0)	133 (27.1)	133 (13.5)	
Dosage of contrast medium (mL)				<0.001
Mean±SD	8.4 ± 2.0	10.3 ± 4.7	9.4 ± 3.7	
Median (range)	9.0 (3, 20)	10.0 (4, 70)	10.0 (3, 70)	
Surgery duration (min)				0.407
Mean±SD	8.8 ± 6.6	8.4 ± 6.4	8.6 ± 6.5	
Median (range)	8.0 (1, 48)	7.0 (1, 50)	8.0 (1, 50)	
At least three images taken, No. (%)	491 (100.0)	491 (100.0)	982 (100.0)	–
Number of images taken				0.030
Mean±SD	4.8 ± 1.6	4.3 ± 1.5	4.5 ± 1.5	
Median (range)	6.0 (3, 9)	3.0 (3, 6)	4.0 (3, 9)	
Diagnostic results, No. (%)				–
Unobstructed uterus	490 (99.8)	489 (99.6)	979 (99.7)	
Uterine atresia	1 (0.2)	2 (0.4)	3 (0.3)	
Unobstructed bilateral fallopian tubes	357 (72.7)	322 (65.6)	679 (69.1)	
Obstruction of bilateral fallopian tubes	53 (10.8)	65 (13.2)	118 (12.0)	
Obstruction of a unilateral fallopian tube	81 (16.5)	103 (21.0)	184 (18.7)	

***Table 2*: HSG-related information and diagnostic results.**
HSG, hysterosalpingography; SD, standard deviation.

Items	Oil group, No. (%) *N* = 491	Water group, No. (%) *N* = 491	Total, No. (%) *N* = 982	*P* value
Uterus opacification or uterine outline				<0.001
Weakly visualized and not diagnostic	0 (0.0)	1 (0.2)	1 (0.1)	
Weakly visualized but diagnostic	6 (1.2)	8 (1.6)	14 (1.4)	
Good demonstration and diagnostic	49 (10.0)	140 (28.5)	189 (19.2)	
Outstanding visualization	436 (88.8)	342 (69.7)	778 (79.2)	
Fallopian tube outline				<0.001
Weakly visualized and not diagnostic	22 (4.5)	24 (4.9)	46 (4.7)	
Weakly visualized but diagnostic	51 (10.4)	140 (28.5)	191 (19.5)	
Good demonstration and diagnostic	187 (38.1)	268 (54.6)	455 (46.3)	
Outstanding visualization	231 (47.0)	59 (12.0)	290 (29.5)	
Fimbrial rugae				<0.001
Weakly visualized and not diagnostic	61 (12.4)	72 (14.7)	133 (13.5)	
Weakly visualized but diagnostic	148 (30.1)	212 (43.2)	360 (36.7)	
Good demonstration and diagnostic	147 (29.9)	181 (36.9)	328 (33.4)	
Outstanding visualization	135 (27.5)	26 (5.3)	161 (16.4)	
Fallopian tube spillage				<0.001
Weakly visualized and not diagnostic	50 (10.2)	64 (13.0)	114 (11.6)	
Weakly visualized but diagnostic	42 (8.6)	107 (21.8)	149 (15.2)	
Good demonstration and diagnostic	228 (46.4)	270 (55.0)	498 (50.7)	
Outstanding visualization	171 (34.8)	50 (10.2)	221 (22.5)	
Peritoneal distribution				<0.001
Weakly visualized and not diagnostic	49 (10.0)	60 (12.2)	109 (11.1)	
Weakly visualized but diagnostic	5 (1.0)	23 (4.7)	28 (2.9)	
Good demonstration and diagnostic	29 (5.9)	206 (42.0)	235 (23.9)	
Outstanding visualization	408 (83.1)	202 (41.1)	610 (62.1)	

***Table 3*: Qualitative results of HSG images.**
HSG, hysterosalpingography.

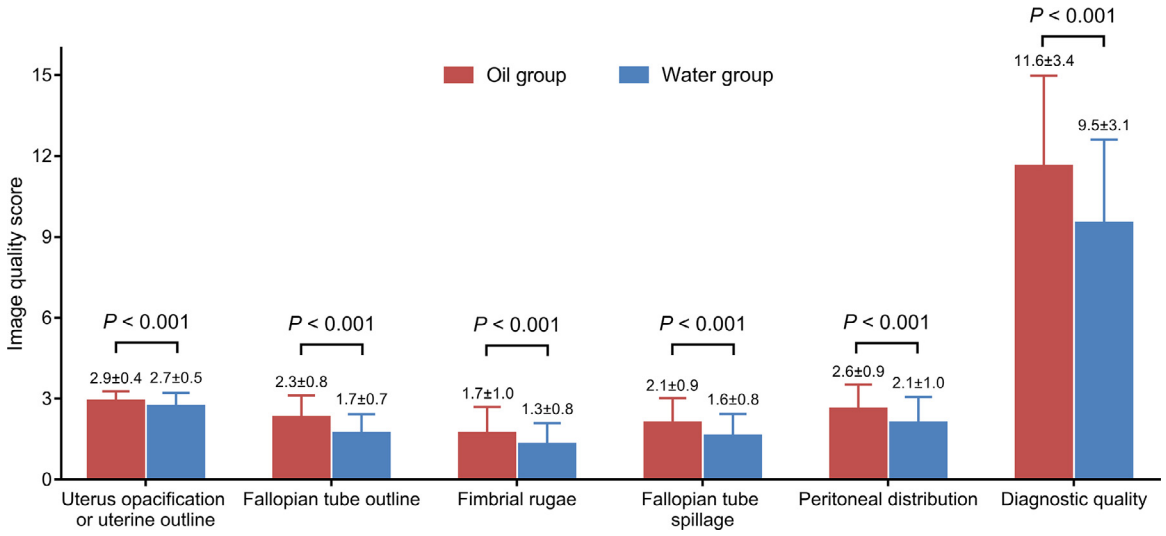

Figure 2. Comparison of image quality scores between the oil group and the water group.

The comparison between two groups was performed by independent *t*-test. Image quality scores for uterus opacification or uterine outline, fallopian tube outline, fimbrial rugae, fallopian tube spillage, peritoneal distribution, and diagnostic quality were higher in the oil group than in the water group.

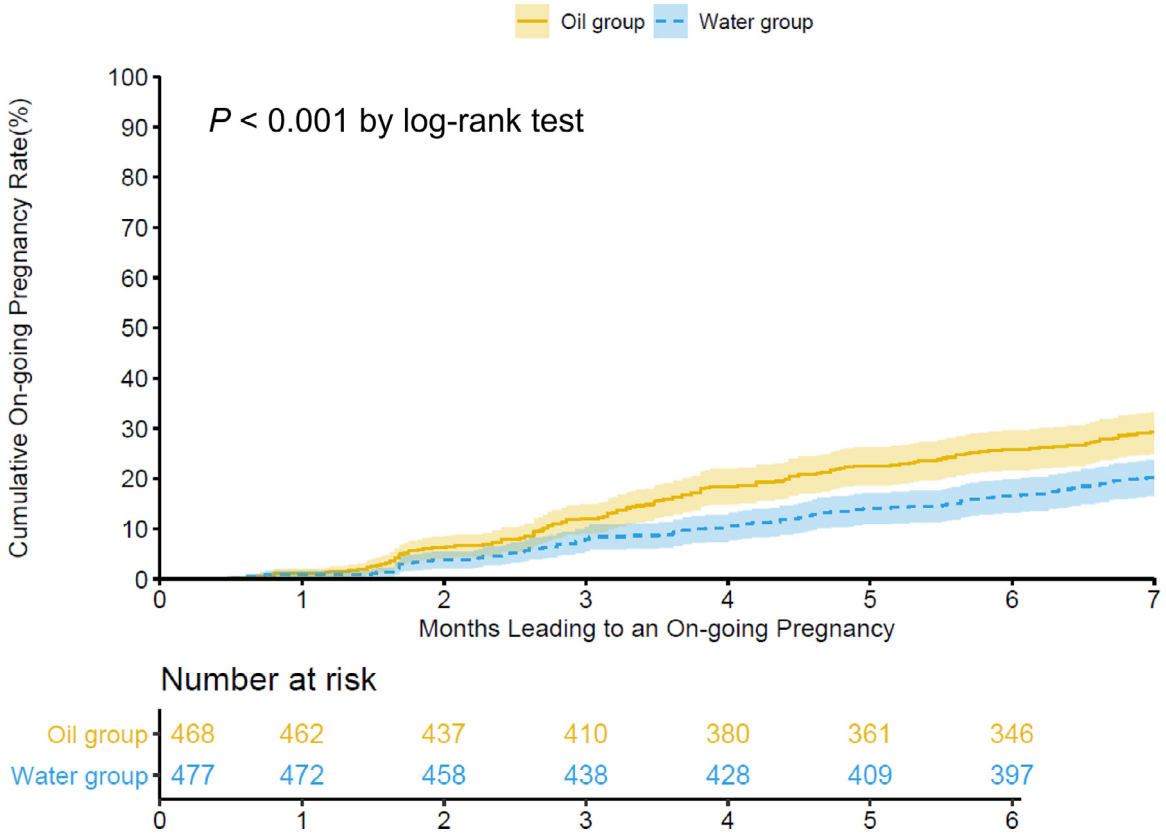

Figure 3. Comparison of fertility-enhancing evaluations between the oil group and the water group.

The comparison between two groups was performed by log-rank test. The oil group showed an increased cumulative on-going pregnancy rate than in the water group.

Items	Oil group (*N* = 473)	Water group (*N* = 479)	Risk Ratio (95% CI)	*P* value
Ongoing pregnancy within 6 months, No. (%)	136 (29.1)	96 (20.1)	1.44 (1.15−1.81)	0.001
Clinical pregnancy, No. (%)	185 (39.5)	139 (29.1)	1.36 (1.13−1.62)	<0.001
Miscarriage, No. (%)	16 (3.4)	7 (1.4)	2.33 (0.97−5.61)	0.059
Live birth ≥24 weeks of gestation, No. (%)	169 (36.1)	132 (27.7)	1.3 (1.08−1.58)	0.006
Twin live birth ≥24 weeks of gestation, No. (%)	4 (2.4)	4 (3.0)	0.78 (0.2−3.06)	0.734
Time to pregnancy (weeks)				<0.001
Mean±SD	41.7 ± 18.5	46.1 ± 16.8	–	
Median (range)	53.9 (1.7, 72.9)	54.4 (1.9, 103)	–	
Pain VAS score				<0.001
Mean±SD	1.8 ± 1.5	2.3 ± 1.6		
Median (range)	2.0 (0, 10)	2.0 (0, 11)		

***Table 4*: Fertility-enhancing evaluation.**
Note: Risk ratio and 95% CI were univariate results by two-sided test.
CI, confidence interval; SD, standard deviation.

Items	Oil group (*N* = 491)	Water group (*N* = 491)	Total (*N* = 982)	*P* value
Adverse events during HSG				
Allergy, No. (%)				–
Yes	0 (0.0)	0 (0.0)	0 (0.0)	
No	491 (100.0)	491 (100.0)	982 (100.0)	
Intravasation, No. (%)				0.341
Yes	11 (2.2)	7 (1.4)	18 (1.8)	
No	480 (97.8)	484 (98.6)	964 (98.2)	
Interstitial reflux, No. (%)				0.123
Yes	5 (0.1)	1 (0.2)	6 (0.6)	
No	482 (98.2)	488 (99.4)	970 (98.8)	
Unknown	4 (0.7)	2 (0.4)	6 (0.6)	
Adverse events after HSG				
Abdominal pain, No. (%)				0.004
Yes	180 (36.7)	225 (45.8)	405 (41.2)	
No	308 (62.7)	265 (54.0)	573 (58.4)	
Unknown	3 (0.6)	1 (0.2)	4 (0.4)	
Vaginal bleeding, No. (%)				0.003
Yes	170 (34.6)	217 (44.2)	387 (39.4)	
No	318 (64.8)	274 (55.8)	592 (60.3)	
Unknown	3 (0.6)	0 (0.0)	3 (0.3)	
Allergy, No. (%)				–
Yes	0 (0.0)	0 (0.0)	0 (0.0)	
No	488 (99.4)	491 (100.0)	979 (99.7)	
Unknown	3 (0.6)	0 (0.0)	3 (0.3)	
Fever, No. (%)				0.249
Yes	2 (0.4)[#]	0 (0.0)	2 (0.2)	
No	486 (99.0)	490 (99.8)	976 (99.4)	
Unknown	3 (0.6)	1 (0.2)	4 (0.4)	

***Table 5*: Adverse events during and after HSG.**
[#] The fever in these two patients resolved spontaneously. HSG, hysterosalpingography; VAS, visual analog scale; SD, standard deviation.

In addition, this study found that the dose of the water-based contrast agent was higher than that of the oil-soluble contrast agent. An explanation might be that iodized opium poppyseed ethyl oleate was the main component of the oil-soluble contrast agent, while amine or alcohol was the main component of the water-soluble contrast agent. Thus, the water-soluble contrast agent had significantly lower viscosity than the oil-soluble contrast agent and flowed faster. Therefore, more of the water-soluble contrast agent was needed to ensure adequate time to observe and take pictures. In addition, the packaging of the water-soluble contrast agent was 20 mL/vial, while that of the ethiodized poppyseed oil was 10 mL/vial. One vial of ethiodized poppyseed oil was sufficient for each patient, and 20 mL of ethiodized poppyseed oil was not utilized, for economic reasons.

The fertility efficacy of the use of oil contrast must be considered. In the present study, we also discovered that the ethiodized poppyseed oil-based contrast medium was correlated with an increased cumulative ongoing pregnancy rate, ongoing pregnancy within 6 months, clinical pregnancy and live birth ≥ 24 weeks of gestation, suggesting its increased fertility effects. These findings could be explained by the following: (1) Flushing with ethiodized poppyseed oil had been disclosed to have therapeutic effects on increasing the fertility rate and live birth rate in infertile women.[16] (2) Ethiodized poppyseed oil had the potential to decrease macrophage phagocytosis and adherence after exposure, further reducing sperm phagocytosis and increasing the fertility rate.[17,18] (3) The slow absorption of ethiodized poppyseed oil could also prolong the inhibition time of macrophage activity, which helped elevate the fertility rate to some extent.[17] (4) Ethiodized poppyseed oil was able to ameliorate the endometrial receptivity and promote the dislodgement of debris in the proximal part of the tubes.[8,9] Generally, the efficacy of the ethiodized poppyseed oil-based contrast medium in fertility was superior to that of the water-based contrast medium. In addition, another finding of this study is worth noting: we observed that the VAS score in our study was numerically lower than that in a previous study (H2Oil trial: 4.8 (3.0–6.4) in the oil group vs. 5.0 (3.0–6.7) in the water group).[12] The possible reason might be that the Chinese patients were more tolerant to the pain, which caused a numerically lower VAS score than those reported in the H2Oil trial. However, this hypothesis needs further exploration.

The fertility-enhancement effect in this study was in line with that of a previous multicenter, randomized trial in the Netherlands.[12] However, compared with that previous study, the efficacy of the ethiodized poppyseed oil-based contrast medium for increased fertility was still underestimated in this study due to the following three factors: (1) Participant's screening: none of the patients in this study had less than 12 months of infertility, while 28 patients had less than 12 months of infertility in that previous study.[12] (2) Primary outcome assessment: the starting point for calculation of the ongoing pregnancy rate was post-HSG in this study, while it was after randomization in that previous study, which might indicate the possibility of prediagnostic pregnancy.[12] (3) Scheme deviation: Two patients in the oil group underwent HSG with water-based contrast medium, and 1 patient in the water group underwent HSG with oil-based contrast medium in this study. (4) Number of HSG examinations: Some patients received two HSG examinations in the H2Oil study, but all patients received only one HSG examination in this study.

In terms of safety concerns, HSG is an important diagnostic method for distinguishing the openness of the uterus and uterine tubes, whereas many patients have feelings of discomfort, including lower abdominal pain during and after HSG.[19] The primary reasons were as follows: (1) The external pull and expansion produced by instruments (such as vaginal specula) stimulated the patient's visceral sensory nerves, thus causing pain.[20] (2) The intrauterine injection of contrast agents may promote the rapid release of local prostaglandin, causing abnormal uterine contraction and producing a pain response.[20] (3) The umbrella tip overflow of the contrast agent may cause peritoneal stimulation, subsequently producing pain.[20] In the current study, we found that the ethiodized poppyseed oil-based contrast medium resulted in a decreased VAS pain score during HSG and a lower occurrence rate of abdominal pain and vaginal bleeding after HSG, which might be because the peritoneal stimulation caused by the umbrella tip overflow of the ethiodized poppyseed oil-based contrast medium was gentle. However, the detailed mechanism of the effect of the ethiodized poppyseed oil-based contrast medium on decreasing pain during and after HSG still needs to be further explored.

In conclusion, ethiodized poppyseed oil-based contrast medium is superior to water-based contrast medium during HSG in terms of image quality improvement and fertility enhancement. This study indicates the priority of the application of ethiodized poppyseed oil-based contrast during the HSG procedure in infertile patients.

Contributors

JZ, WSL, YTW and KSC contributed equally to the design of the present study. Data collection was performed by JZ, WSL, YTW, KSC, GFZ, WZY, HCC, WJX, JXM, WHQ, YZ, WQW, HCW, ZJD, YLW, YC, NG and YCT. Data analysis was completed by JZ, WSL, YTW, KSC, GFZ, WZY, HCC and WJX. JXM, WHQ, YZ, WQW, HCW, ZJD were responsible for data verification. Data interpretation was performed by JZ, WSL, YTW and KSC. The first draft of the article was written by WSL, YTW, KSC, YLW, YC, NG and YCT, and then

JZ critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript. JZ is responsible for submitting the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved.

Data sharing statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of interests

All other authors declare no competing interests.

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Supplementary materials

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