Comparison of fertility outcomes between oil-based and water-based contrast media during hysterosalpingography: A meta-analysis

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Abstract. Water-based and oil-based contrast media are both widely used in clinical practice for patients receiving hysterosalpingography (HSG). However, minor controversy exists about whether the oil-based contrast medium has a superior fertility-enhancing effect during HSG. The present meta-analysis intended to comprehensively compare the fertility outcomes of patients receiving either an oil-based or a water-based contrast medium during HSG. Web of Science, PubMed, Excerpta Medica Database, Cochrane, China National Knowledge Infrastructure, Wanfang Data and China Science and Technology Journal Database were examined for literature comparing the fertility enhancement between oil-based and water-based contrast media during HSG up to November 10, 2022 and there was no cut off for studies published earlier than any given year. Data for clinical pregnancy, ongoing pregnancy, live birth, miscarriage and ectopic pregnancy were extracted and analyzed. A total of 11 studies with 2,462 patients receiving oil-based contrast medium and 2,830 patients receiving water-based contrast medium during HSG were included. Relative risks (RRs) and 95% confidence intervals (CIs) were presented for outcome assessment, and the random effects model was utilized for all analyses. Publication bias was analyzed using Egger's and Begg's tests. The results indicated that the rate of clinical pregnancy was increased using oil-based contrast medium compared with water-based contrast medium [relative risk (RR) (95% CI), 1.29 (1.07, 1.54); P=0.006]. In addition, the rate of ongoing pregnancy [RR (95% CI), 1.39 (1.22, 1.59); P<0.001] and live birth [RR (95% CI), 1.41 (1.07, 1.87); P=0.016] were also increased using oil-based contrast medium compared with water-based contrast medium. However, miscarriage [RR (95% CI), 1.06 (0.61, 1.86); P=0.833] and ectopic pregnancy [RR (95% CI), 0.66 (0.18, 2.36); P=0.518] were not affected by using oil-based or water-based contrast medium. Begg's test and Egger's test suggested that no publication bias of clinical pregnancy, ongoing pregnancy, live birth, miscarriage and ectopic pregnancy existed (all P>0.05), which indicated the stability of the present meta-analysis. In conclusion, the oil-based contrast medium enhances fertility outcomes compared with the water-based contrast medium in patients receiving HSG.

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Introduction

Infertility is estimated to affect ~186 million individuals worldwide with a prevalence of 9-13% among women, which results in various social, psychological and economic issues (1-4). In general, numerous factors are responsible for female infertility, and fallopian tube obstruction is an important cause, accounting for ~35% of anatomical factor-induced infertility (5,6). Hysterosalpingography (HSG) is a common and valuable X-ray test for the uterus and fallopian tubes that assists in checking the patency of the fallopian tubes, the site of obstruction and the morphology of the uterine cavity (7,8). Beyond the diagnostic value, HSG also has a potential therapeutic implication for infertile female patients, since contrast medium is injected to flush the uterus and fallopian tubes of the patient, which improves the tubal patency and is beneficial for pregnancy (9,10).

Oil-based and water-based contrast media are two options for HSG. The oil-based contrast medium has a high viscosity, which enhances the flushing and dilation of the fallopian tubes, while the water-based contrast medium has a low viscosity and is absorbed quickly with a short stay in the pelvic cavity, which places a minimal influence on the patients (11). A number of previous studies have explored the effect of these two contrast media during HSG on improving fertility, and hypothesized that an oil-based contrast medium may be superior to a water-based contrast medium; however, the improved fertility-enhancing effect of oil-based contrast medium has not been widely accepted yet (9,12-24). For example, one randomized controlled trial (RCT), including patients with primary and secondary infertility, has highlighted that the oil-based contrast medium for HSG increases the ongoing pregnancy rate, number of clinical pregnancies and number of live births, as well as reduces the time to pregnancy compared with the water-based contrast medium (23).

Another non-RCT study has indicated that the pregnancy rate is increased using the water-based contrast medium compared with the oil-based contrast medium in patients receiving HSG (22); however, this opposing finding may be due to the study having only enrolled patients with secondary infertility. Another study reported that the cumulative pregnancy rate is not influenced by using oil-based or water-based contrast medium in patients receiving HSG with primary or secondary infertility (19). A few previous meta-analyses have explored the optimal contrast medium for improving pregnancy in patients receiving HSG (25,26). However, these two meta-analyses used only RCTs and omitted the influence of non-RCTs. Additionally, some updated clinical studies regarding the fertility-enhancing effect in patients receiving HSG should be taken into account (23,24). Apart from the aforementioned study, a recently published meta-analysis also concluded that an oil-based contrast medium exhibits an improved fertility-enhancing effect compared with a water-based contrast medium in patients receiving HSG (27). However, all studies used in this meta-analysis were RCTs, thereby not taking into account the effect of non-RCTs. In addition, whether the fertility-enhancing effect of oil-based and water-based contrast media would be affected by the follow-up duration was not reported. Furthermore, only 4,739 patients were included in this meta-analysis, and a large-scale meta-analysis is required to improve the statistical power (27).

Therefore, the present meta-analysis comprehensively screened both RCTs and non-RCTs and slightly increased the number of patients with the aim of comparing the fertility-enhancing effect between the oil-based and water-based contrast media in patients receiving HSG.

Materials and methods

Search strategy. The present meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines (28). Studies that assessed the fertility enhancement between oil-based and water-based contrast media during HSG were screened in Web of Science (WOS) (https://clarivate.com/products/webofscience/), PubMed (https://pubmed.ncbi.nlm.nih.gov/), Excerpta Medica Database (EMBASE) (https://elh.nhs.wales/databases/databases/embase-excerpta-medica1/),Cochrane (https://www.cochranelibrary.com/), China National Knowledge Infrastructure (CNKI) (https://en.cnki.com.cn/), Wanfang Data (https://www.wanfangdata.com.cn/index.html) and China Science and Technology Journal Database (CQVIP; http://csi1.cqvip.com/productor/pro_zk.shtml) up to November 10, 2022 and there was no cut off for studies published earlier than any given year. The following medical subject headings and keywords were used for study searching: 'Hysterosalpingography', 'HSG', 'hysterosalpingo contrast sonography', 'tubal patency test', 'laparoscopy', 'oil', 'ethiodol', 'lipiodol', 'poppy', 'water', 'iotrolan', 'iodipamide', 'iohexol', 'diatrizoate' and 'aqueous'. Additionally, the references of the included studies were also screened as aforementioned.

Study selection. Two researchers worked independently to complete the study screening. First, the studies were screened based on a previously designed information extraction form (25). Second, the title and the abstract were evaluated according to the inclusion and exclusion criteria described later. Third, the studies considered acceptable for inclusion were downloaded, and the full texts were read. Next, the data of the included studies were extracted, and their references were also examined as aforementioned. A cross-discussion or consultation with a 3rd investigator was held if there was a disagreement.

The inclusion criteria were as follows: i) RCT or non-RCT study (such as a cohort study or case-control study); ii) patients ≥18 years old; iii) patients underwent HSG with oil-based or water-based contrast medium; and iv) studies had ≥1 outcome concerned (including clinical pregnancy, ongoing pregnancy, live birth, miscarriage, or ectopic pregnancy) in the present study. The exclusion criteria were as follows: i) Other study types (such as a systematic review or meta-analysis); ii) duplicated study; and iii) incomplete or inconsistent data.

Data extraction. Two researchers worked independently to complete the data extraction. The extracted data contained the names of the authors, publication year, study type, study location, sample size, follow-up duration, method of tube flushing, contrast medium and outcome (clinical pregnancy, ongoing pregnancy, live birth, miscarriage or ectopic pregnancy). A cross-discussion or consultation with a 3rd investigator was held if there was a disagreement.

Quality assessment. The bias risk of RCTs was evaluated using the Cochrane Collaboration risk of bias tool, and involved selection, performance, detection, attrition and reporting bias amongst others (29). The bias risk of non-RCTs was evaluated using the Newcastle-Ottawa Scale criteria, and involved selection, comparability and outcome. A total score <4 was considered as high risk of bias; the total score ranging 4-6 was considered as moderate risk of bias; the total score ranging from 7-9 was considered as low risk of bias (30).

Statistical analysis. Stata software (version 14.0; StataCorp LP) was used for statistical analysis. Relative risks (RRs) and 95% confidence intervals (CIs) were presented for outcome assessment. Since none of the studies selected for this analysis have any relation with each other, the random effects model was utilized for all analyses regardless of the I^2 value or P-value. It should be mentioned that $I^2 \leq 50.0\%$ and $P \geq 0.10$ referred to low heterogeneity. $I^2 > 50\%$ and $P < 0.01$ referred to high heterogeneity. Publication bias was analyzed using Egger's and Begg's tests. Sensitivity analysis was carried out for the evaluation of data robustness and stability. Briefly, the RR and 95% CI calculations were performed again after sequentially omitting each study, then the results were compared with the previous data analysis and no statistically significant changes were considered to indicate low sensitivity to any study omission and robust results. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Study screening procedure. Initially, 258 records were identified through database screening, including 109 records from WOS, 74 records from PubMed, 52 records from EMBASE, 14 records from Cochrane, 3 records from CNKI, 2 records from

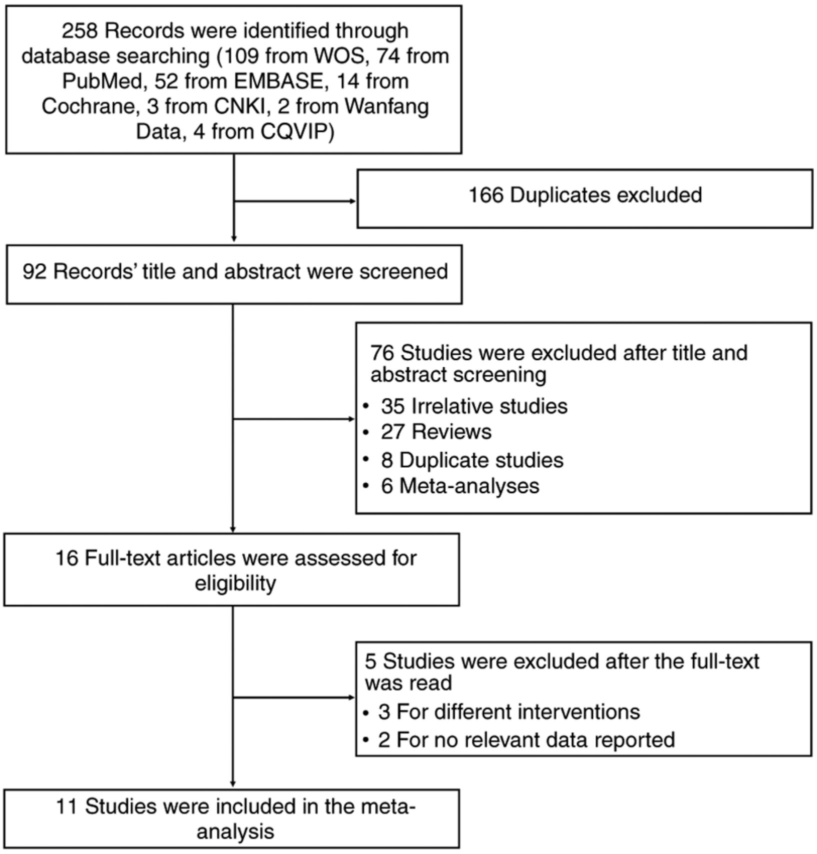

Figure 1. Study flow chart. A total of 258 records were identified through database searching, including 109 from WOS, 74 from PubMed, 52 from EMBASE, 14 from Cochrane, 3 from CNKI, 2 from Wanfang Data, and 4 from CQVIP. After that, 166 duplicates were excluded. The title and abstract of 92 records were screened, and 76 studies were further excluded, including 35 irrelevant studies, 27 reviews, 8 duplicate studies and 6 meta-analyses. Subsequently, 16 full-text articles were assessed for eligibility, and 5 studies were excluded after full-text was read, including 3 for different interventions and 2 for no relevant data reported. Ultimately, 11 studies were included in the meta-analysis. CNKI, China National Knowledge Infrastructure; CQVIP, China Science and Technology Journal Database; EMBASE, Excerpta Medica Database; WOS, Web of Science.

Wanfang Data and 4 records from CQVIP. Subsequently, 166 duplicates were excluded, and the remaining 92 records were screened by title and abstract. Subsequently, 76 records were excluded, including 35 irrelevant studies, 27 reviews, 8 duplicated studies and 6 meta-analyses. The remaining 16 full-text articles were then assessed for eligibility, during which 5 records were further excluded after the full-text was read, including 3 records for different interventions and 2 records for lacking relevant data. Finally, 11 studies were selected to be included in the present meta-analysis (Fig. 1).

Features of the included studies. The screened studies included eight RCTs (14-19,21,23) and three non-RCTs (20,22,24). Regarding the locations of the studies, the eight RCTs were conducted in USA, The Netherlands, Denmark and China, whereas the three non-RCTs were all conducted in China. The publication year of the selected studies ranged from 1986 to 2022; specifically, four studies were published before 2000, including Alper *et al* (14), de Boer *et al* (15), Rasmussen *et al* (16) and Lindequist *et al* (17); three studies were published between 2000 and 2010, including Spring *et al* (18), Steiner *et al* (19) and Qiu (20); and four studies were published after 2010, including Dreyer *et al* (21), Wang *et al* (22), Zhang *et al* (23) and Lu *et al* (24). A total of 5,292 patients were included in the present study, including 2,462 patients receiving oil-based contrast medium and 2,830 patients receiving water-based contrast medium during HSG. The majority of the studies included patients with primary and patients with secondary infertility; however, this information was unclear in two of the studies, and one study included only patients with secondary infertility. Regarding endometriosis, six studies did not report this information and three studies excluded patients with endometriosis; however, 24.8 and 18.6% of patients had a history of endometriosis in the other two studies. The specific features of the included studies are listed in Table I.

Quality assessments. Regarding selection bias, 5 RCTs were ranked as low risk of random sequence generation; thus, 62.5% (5/8) of the RCTs presented sufficient methods of random sequence generation. Meanwhile, 1 RCT was ranked as low risk of allocation concealment; thus,12.5% (1/8) of the studies disclosed adequate methods of allocation concealment. Since blind trials were impossible owing to the nature of the interventions, the risk of performance bias was scored as unclear. Considering that the fertility outcome was objective, a non-blinded design would not influence the outcome assessment; thus, the risk of detection bias was low in all studies. There were three RCTs at high risk of allocation concealment (19), incomplete outcome data (14) and other sources of bias (18) (Table II). In the three non-RCTs, the total

Table I. Details of the included studies.

First author, year	Study type	Study location	Sample size, n		Follow-up duration, months	Method of tubal flushing	Contrast medium		Type of patient		Outcome	(Refs.)
			Oil	Water			Oil	Water	Primary or secondary infertility	Endometriosis		
Alper *et al*, 1986	RCT	USA	58	73	6	HSG	Lipiodol	Reno-M-60	Unclear	Unclear	Clinical pregnancy	(14)
de Boer *et al*, 1988	RCT	The Netherlands	87	88	6	HSG	Ethiodol	Lopamidol	Both types	Unclear	Clinical pregnancy	(15)
Rasmussen *et al*, 1991	RCT	Denmark	98	300	10	HSG	Lipiodol	Iohexol, ioxaglate or diatrizoate	Both types	Unclear	Clinical pregnancy and live birth	(16)
Lindequist *et al*, 1994	RCT	Denmark	121	121	9	HSG	Lipiodol	Iotrolan	Both types	Unclear	Clinical pregnancy	(17)
Spring *et al*, 2000	RCT	USA	273	260	12	HSG	Ethiodol	Sinografin	Both types	Unclear	Clinical pregnancy, live birth, miscarriage and ectopic pregnancy	(18)
Steiner *et al*, 2003	RCT	USA	28	25	18	HSG	Ethiodol	Sinografin	Both types	A total of 24.8% of patients had a history of endometriosis	Clinical pregnancy	(19)
Qiu, 2005	Non-RCT	China	132	283	6	HSG	Iodinate oil	Iohexol	Unclear	Unclear	Clinical pregnancy	(20)
Dreyer *et al*, 2017	RCT	The Netherlands	557	562	6	HSG	Lipiodol	Telebrix Hystero	Both types	Excluded patients with endometriosis	Clinical pregnancy, ongoing pregnancy, live birth, miscarriage and ectopic pregnancy	(21)
Wang *et al*, 2021	Non-RCT	China	100	100	6	HSG	Iodinate oil	Iohexol	Secondary infertility	Excluded patients with endometriosis	Clinical pregnancy	(22)
Zhang *et al*, 2022	RCT	China	508	518	6	HSG	Ethiodized poppyseed oil	Iohexol (300 mg/ml), iopromide (300 mg/ml) or ioversol (320 mg/ml)	Both types	Excluded patients with endometriosis	Clinical pregnancy, ongoing pregnancy, live birth and miscarriage	(23)
Lu *et al*, 2022	Non-RCT	China	500	500	36	HSG	Ethiodized poppy seed oil	Ioversol	Both types	A total of 18.6% of patients had a history of endometriosis	Clinical pregnancy	(24)

HSG, hysterosalpingography; RCT, randomized controlled trial.

Table II. Assessment of the risk of bias among the eight randomized controlled trials.

First author, year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other sources of bias (other bias)	(Refs.)
Alper *et al*, 1986	Low risk	Unclear	Unclear	Low risk	High risk	Unclear	Unclear	(14)
de Boer *et al*, 1988	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk	(15)
Rasmussen *et al*, 1991	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear	Unclear	(16)
Lindequist *et al*, 1994	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear	Low risk	(17)
Spring *et al*, 2000	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	High risk	(18)
Steiner *et al*, 2003	Low risk	High risk	Unclear	Low risk	Low risk	Unclear	Low risk	(19)
Dreyer *et al*, 2017	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	(21)
Zhang *et al*, 2022	Low risk	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk	(23)

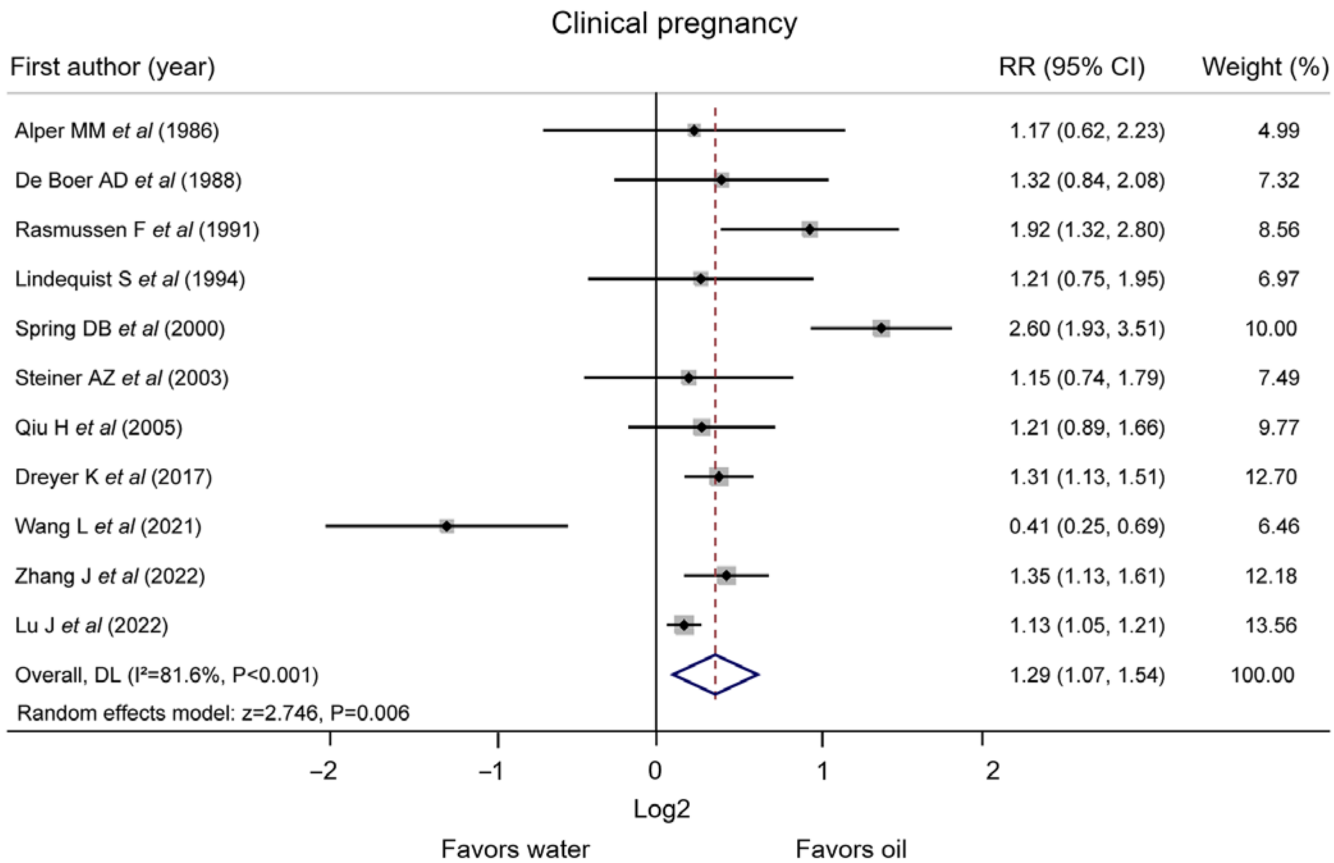

Figure 2. Forest plot of the comparison of clinical pregnancy between oil-based and water-based contrast media. RR, relative risk; DL, DerSimonian-Laird.

score of the assessment of the risk of bias ranged from 7 to 9, which indicated a low risk of bias (Table III). Briefly, Qiu (20) lacked a definition for the controls and an adequate follow-up, resulting in a total score of 7. Wang *et al* (22) had a score of 1 for the risk of comparability owing to a lack of control for confounders, resulting in a total score of 8. Lu *et al* (24) had reduced bias compared with other two non-RCTs with a total score of 9.

Clinical pregnancy. All 11 studies reported clinical pregnancy. The pooled analysis revealed that the oil-based contrast medium increased the rate of clinical pregnancy compared with the water-based contrast medium [RR (95% CI), 1.29 (1.07, 1.54); P=0.006]. Heterogeneity existed among the studies (I^2=81.6%; P<0.001; Fig. 2).

Subgroup analyses were carried out based on the study type. The pooled analysis of the eight RCTs revealed that the rate of clinical pregnancy was increased following the use of oil-based contrast medium compared with water-based contrast medium during HSG [RR (95% CI), 1.48 (1.22, 1.80); P<0.001]; heterogeneity existed among these studies (I^2=67.5%;

Table III. Assessment of the risk of bias among the three non-randomized controlled trials.

	Selection				Comparability	Outcome				
First author, year	Adequate definition of cases	Representativeness of the cases	Selection of controls	Definition of controls	Cohorts on the basis of the design or analysis controlled for confounders	Assessment of outcome	Was follow-up long enough	Adequacy of follow-up	Total score[a]	(Refs.)
Qiu, 2005	1	1	1	0	2	1	1	0	7	(20)
Wang *et al*, 2021	1	1	1	1	1	1	1	1	8	(22)
Lu *et al*, 2022	1	1	1	1	2	1	1	1	9	(24)

[a]The highest score on the Newcastle-Ottawa scale is 9 points.

P=0.003) (Fig. 3A). Pooled analysis of the three non-RCTs suggested that the rate of clinical pregnancy was not different between patients receiving oil-based contrast medium and patients receiving water-based contrast medium for HSG [RR (95% CI), 0.89 (0.57, 1.38); P=0.594]; there was heterogeneity among these studies (I^2=86.5%; P=0.001) (Fig. 3B). The pooled analysis of six studies with a follow-up duration ≤6 months revealed that the rate of clinical pregnancy was not affected by using oil-based or water-based contrast medium [RR (95% CI), 1.12 (0.88, 1.42); P=0.345]; heterogeneity existed among these studies (I^2=73.8%; P=0.002) (Fig. 3C). Pooled analysis of five studies with a follow-up duration >6 months indicated that the rate of clinical pregnancy was increased using oil-based contrast medium compared with water-based contrast medium during HSG [RR (95% CI), 1.51 (1.03, 2.22); P=0.034]; heterogeneity existed among the studies (I^2=88.5%; P<0.001) (Fig. 3D).

Ongoing pregnancy and live birth. There were two studies that reported ongoing pregnancy. The pooled analysis suggested that the rate of ongoing pregnancy was enhanced by the oil-based contrast medium compared with the water-based contrast medium during HSG [RR (95% CI), 1.39 (1.22, 1.59); P<0.001]; heterogeneity did not exist between the two studies (I^2=0.0%; P=0.735) (Fig. 4A). In addition, four studies reported live birth, and the pooled analysis indicated that the rate of live birth was increased using oil-based contrast medium compared with water-based contrast medium [RR (95% CI), 1.41 (1.07, 1.87); P=0.016]; there was heterogeneity among the studies (I^2=79.4%; P=0.002; Fig. 4B).

Miscarriage and ectopic pregnancy. There were three studies that reported miscarriage; however, the pooled analysis revealed that the rate of miscarriage was not affected by using oil-based or water-based contrast medium [RR (95% CI), 1.06 (0.61, 1.86); P=0.833]; there was no heterogeneity among the studies (I^2=58.1%; P=0.092) (Fig. 5A). Furthermore, two studies reported ectopic pregnancy. The pooled analysis revealed that the rate of ectopic pregnancy was not affected by using oil-based or water-based contrast medium [RR (95% CI), 0.66 (0.18, 2.36); P=0.518]; there was no heterogeneity between the two studies (I^2=0.0%; P=0.569) (Fig. 5B).

Publication bias and sensitivity analysis. Begg's and Egger's tests were carried out to estimate the potential publication bias, and the results suggested that no publication bias for clinical pregnancy, ongoing pregnancy, live birth, miscarriage and ectopic pregnancy existed (all P>0.05) (Table IV). In addition, sensitivity analysis was conducted, and it was demonstrated that omitting Dreyer *et al* (21) or Zhang *et al* (23) would affect the RR of the rate of live birth. Furthermore, the RR of clinical pregnancy, ongoing pregnancy, miscarriage and ectopic pregnancy did not change by omitting any single study, which indicated the stability of the present meta-analysis (Table V).

Discussion

The oil-based contrast medium has the benefit of increasing the rate of clinical pregnancy in patients receiving HSG; however, it has not been widely accepted and incorporated into clinical practice (14-24). For example, a previous study demonstrated

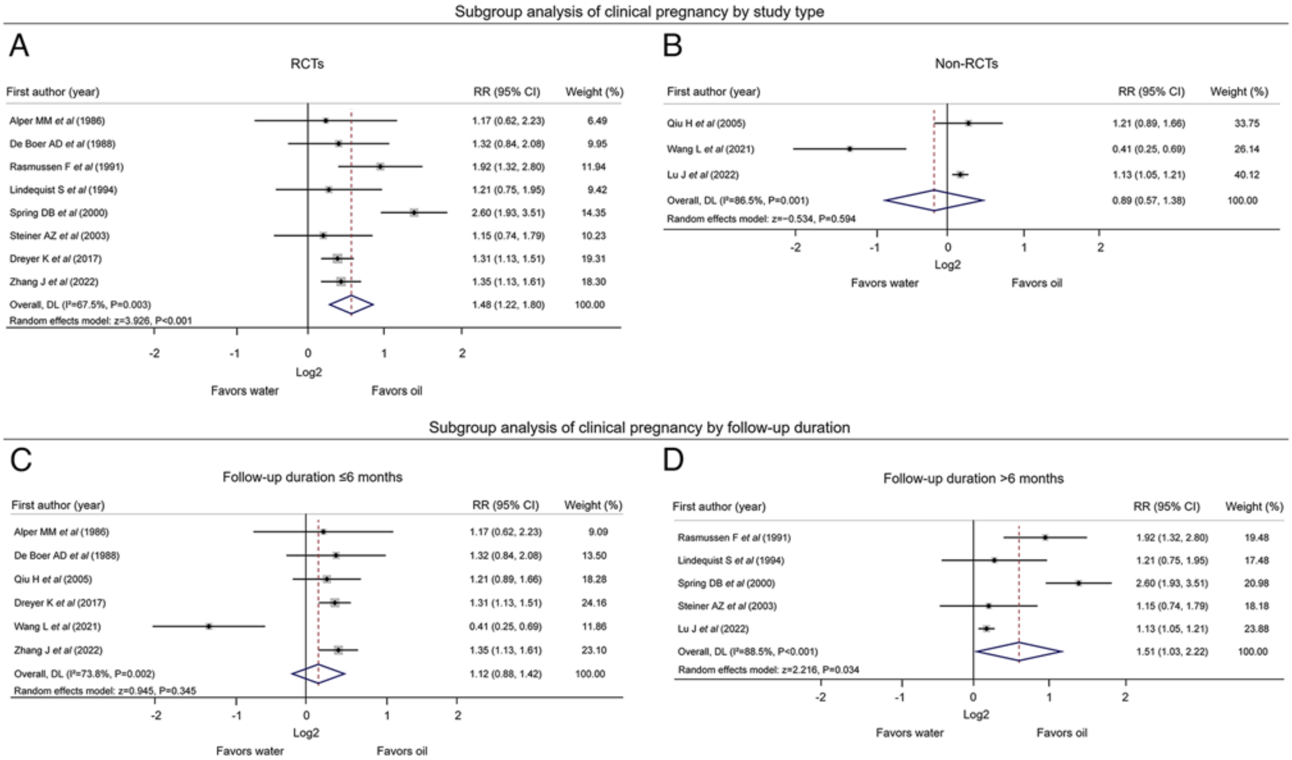

Figure 3. Forest plot of subgroup analysis for clinical pregnancy based on study type and follow-up duration. (A) Pooled analysis of RCTs, (B) non-RCTs, (C) studies with follow-up duration ≤6 months and (D) studies with follow-up duration >6 months. RCT, randomized controlled trial; RR, risk ratio.

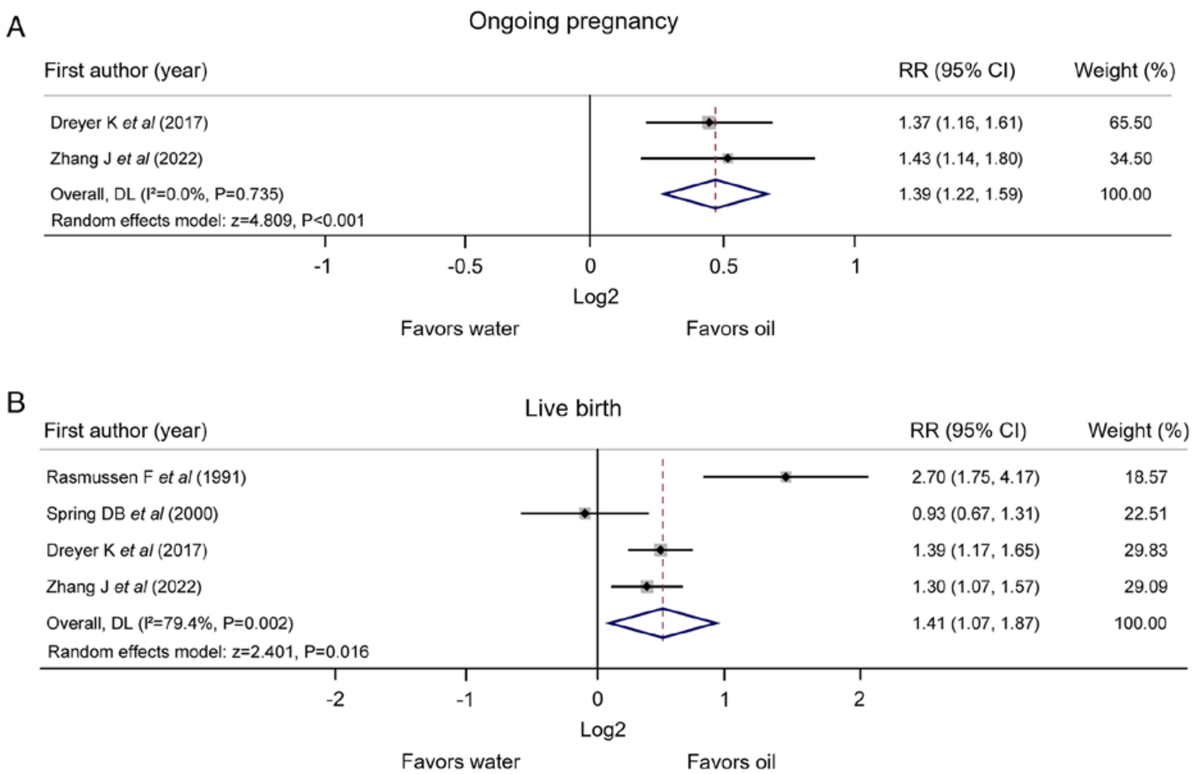

Figure 4. Forest plot of the comparison of live birth and ongoing pregnancy between oil-based and water-based contrast media. Pooled analysis of (A) ongoing pregnancy and (B) live birth. RR, relative risk; DL, DerSimonian-Laird.

that the clinical pregnancy rate was unchanged between patients receiving oil-based and water-based contrast media for HSG (14); however, this study did not indicate the infertility status (primary or secondary) of the patients. Another study reported that the use of oil-based contrast medium enhances clinical pregnancy compared with the water-based contrast medium during HSG

Table IV. Publication bias.

Outcomes	Number of included studies	P-value (Begg's test)	P-value (Egger's test)
Clinical pregnancy	11	0.276	0.530
Ongoing pregnancy	2	1.000	1.000
Live birth	4	1.000	0.709
Miscarriage	3	1.000	0.381
Ectopic pregnancy	2	1.000	1.000

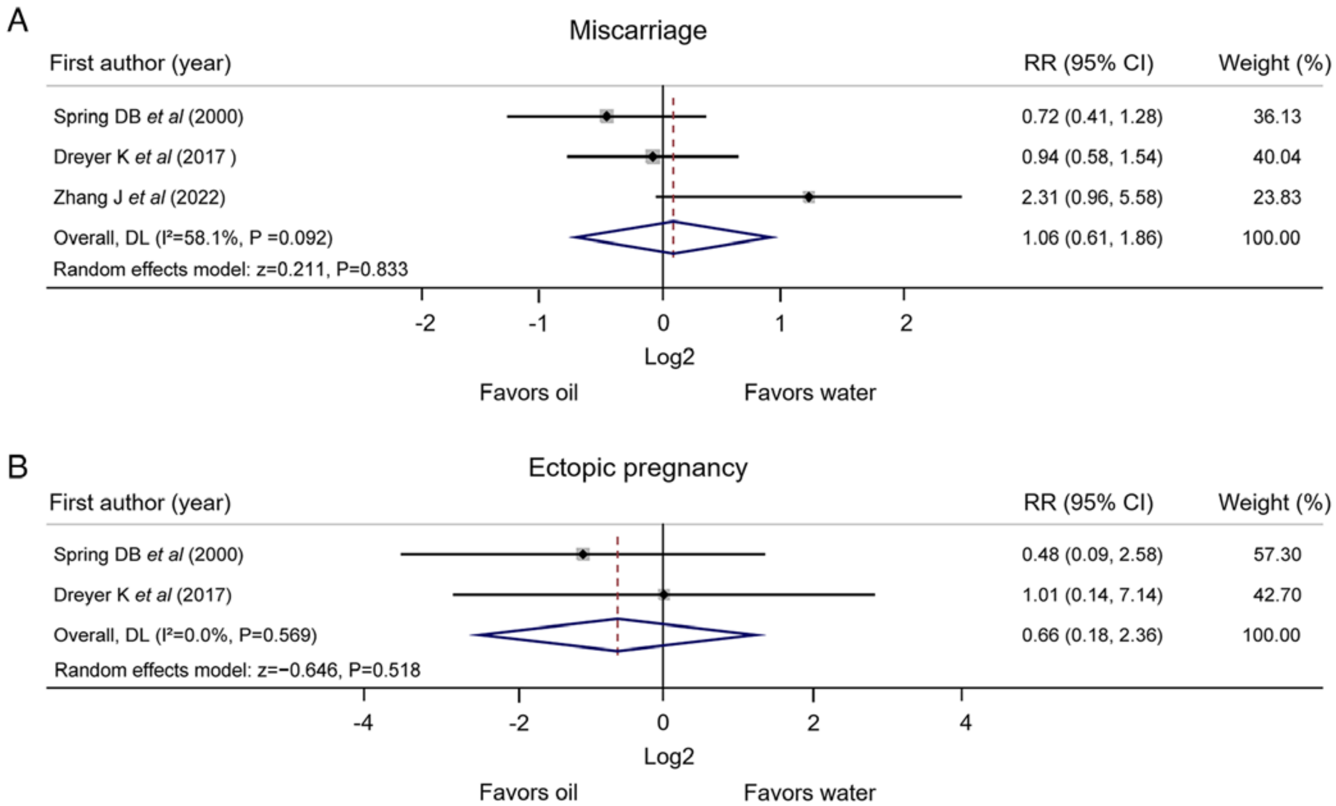

Figure 5. Forest plot of the comparison of miscarriage and ectopic pregnancy between oil-based and water-based contrast media. Pooled analysis of (A) miscarriage and (B) ectopic pregnancy. RR, relative risk; DL, DerSimonian-Laird.

in patients with primary infertility as well as in patients with secondary infertility (16). However, a recent study demonstrated that the water-based contrast medium improves the pregnancy rate compared with the oil-based contrast medium in patients with secondary infertility; this opposing finding may be attributable to the fact that all included patients had secondary infertility (22). The present meta-analysis reviewed 11 studies (including 8 RCTs and 3 non-RCTs), and revealed that the rate of clinical pregnancy was increased by using an oil-based contrast medium compared with a water-based contrast medium in patients receiving HSG; in addition, this finding was further confirmed in the subgroup analysis conducted in RCTs and studies with a follow-up duration >6 months. The potential reasons for this outcome could be as follows: i) The oil-based contrast medium regulates the dendritic cells and regulatory T cell profiles and it could be incorporated by dendritic cells, thus altering the immune environment in the peritoneal cavity, which further improves the fertility (31); ii) the slow absorption speed of the oil-based contrast medium enhances the suppression of macrophage phagocytosis and adherence, which further reduces sperm phagocytosis and increases clinical pregnancy (32); and iii) the oil-based contrast medium removes mucus plugs from the fallopian tubes, which improves tubal patency and is beneficial for clinical pregnancy (33-35). The oil-based contrast medium increased rate of clinical pregnancy compared with the water-based contrast medium in studies with a follow-up duration >6 months, which indicated that the pregnancy-enhancing effect of the oil-based contrast medium was improved over 6 months. Notably, heterogeneity in the rate of clinical pregnancy existed among the 11 studies analyzed. Although sensitivity analysis disclosed that no single study affected the pooled analysis of clinical pregnancy, further studies are required to verify these findings.

Apart from clinical pregnancy, the present meta-analysis also explored the efficacy of using an oil-based or a water-based contrast medium for improving ongoing pregnancy and live birth in patients receiving HSG. It was revealed that the rates

Table V. Sensitivity analysis for omitted studies.

A, Clinical pregnancy

First author, year	Relative risk (95% CI)	(Refs.)
Alper *et al*, 1986	1.291 (1.071, 1.555)	(14)
de Boer *et al*, 1988	1.281 (1.060, 1.549)	(15)
Rasmussen *et al*, 1991	1.239 (1.032, 1.489)	(16)
Lindequist *et al*, 1994	1.290 (1.067, 1.559)	(17)
Spring *et al*, 2000	1.202 (1.037, 1.393)	(18)
Steiner *et al*, 2003	1.296 (1.071, 1.567)	(19)
Qiu, 2005	1.291 (1.062, 1.570)	(20)
Dreyer *et al*, 2017	1.274 (1.023, 1.586)	(21)
Wang *et al*, 2021	1.387 (1.183, 1.626)	(22)
Zhang *et al*, 2022	1.272 (1.034, 1.565)	(23)
Lu *et al*, 2022	1.299 (1.039, 1.624)	(24)
Combined	1.285 (1.075, 1.537)	

B, Ongoing pregnancy

First author, year	Relative risk (95% CI)	(Refs.)
Dreyer *et al*, 2017	1.435 (1.142, 1.803)	(21)
Zhang *et al*, 2022	1.366 (1.158, 1.613)	(23)
Combined	1.390 (1.215, 1.589)	

C, Live birth

First author, year	Relative risk (95% CI)	(Refs.)
Rasmussen *et al*, 1991	1.250 (1.039, 1.503)	(16)
Spring *et al*, 2000	1.576 (1.174, 2.115)	(18)
Dreyer *et al*, 2017	1.449 (0.893, 2.352)	(21)
Zhang *et al*, 2022	1.486 (0.928, 2.381)	(23)
Combined	1.410 (1.065, 1.867)	

D, Miscarriage

First author, year	Relative risk (95% CI)	(Refs.)
Spring *et al*, 2000	1.196 (0.784, 1.824)	(18)
Dreyer *et al*, 2017	1.064 (0.669, 1.690)	(21)
Zhang *et al*, 2022	0.844 (0.582, 1.225)	(23)
Combined	1.062 (0.607, 1.856)	

E, Ectopic pregnancy

First author, year	Relative risk (95% CI)	(Refs.)
Spring *et al*, 2000	1.009 (0.143, 7.138)	(18)
Dreyer *et al*, 2017	0.476 (0.088, 2.578)	(21)
Combined	0.656 (0.183, 2.356)	

of ongoing pregnancy and live birth were enhanced using an oil-based contrast medium compared with a water-based contrast medium in patients receiving HSG. It can be speculated that the oil-based contrast medium may be helpful for enhancing the receptivity of the endometrium, which is beneficial for embryo development and implantation (34,36,37), ultimately leading to the improvement of ongoing pregnancy and live birth. However, heterogeneity in live birth rates existed among the four studies analyzed, and sensitivity analysis indicated that after omitting Dreyer *et al* (21) or Zhang *et al* (23), the results of live birth would be affected. However, considering the number of studies that reported ongoing pregnancy and live birth were relatively few compared with the total number of studies analyzed, the reliability and generalization of these findings should be verified by further large-scale studies.

Miscarriage and ectopic pregnancy are two major concerns in pregnant patients, and these two issues may occur after HSG (18,21,23,38,39). The present study revealed that miscarriage and ectopic pregnancy did not differ after HSG with the oil-based or water-based contrast medium. The potential reason behind this may be that the major causes of miscarriage and ectopic pregnancy are chromosomal abnormalities, uterus abnormalities and hormonal problems, rather than the administration of contrast media (38,39). Thus, miscarriage and ectopic pregnancy were not affected by using oil-based or water-based contrast medium during HSG.

A recently published meta-analysis has demonstrated that using an oil-based contrast medium improves the pregnancy and live birth rates compared with a water-based contrast medium, whereas miscarriage and ectopic pregnancy are not affected by either an oil-based or a water-based contrast medium in patients receiving HSG (27). The present meta-analysis slightly increased the number of patients and screened both RCTs and non-RCTs, aiming to provide a comprehensive view of the fertility-enhancing effect of oil-based and water-based contrast media during HSG. In accordance with the aforementioned meta-analysis (27), it was also revealed in the present study that the fertility-enhancing effect was increased using an oil-based contrast medium compared with a water-based contrast medium during HSG, whereas miscarriage and ectopic pregnancy remained unchanged between the two contrast media. The present meta-analysis also revealed that in studies with a follow-up duration >6 months, the fertility-enhancing effect was increased using an oil-based contrast medium compared with a water-based contrast medium during HSG.

The majority of the studies used in the present meta-analysis did not include information on endometriosis. However, two of the studies reported 24.8% (19) and 18.6% (24) of patients with a history of endometriosis. In addition, three studies indicated that patients with fallopian tube disease, including endometriosis, were excluded (21-23). Furthermore, the majority of the studies contained patients with primary and secondary infertility (15-19,21,23,24); however, two studies did not clearly report whether the patients had primary or secondary infertility (14,20), and one study included only patients with secondary infertility (22). Although whether patients have primary or secondary infertility may unavoidably affect the results of the present meta-analysis, the majority of the included studies did not distinguish patients based on the type of infertility. Thus, the present study could not analyze the results based on whether the patients had primary or secondary infertility, and further studies that focus on the specific type of patients should be conducted.

A number of limitations of the present study should be noted: i) The number of studies that reported ongoing pregnancy and live birth was small, thus, more large-scale studies are required to validate these findings; ii) sensitivity analysis revealed that omitting Dreyer *et al* (21) or Zhang *et al* (23) would affect the pooled analysis finding of rates of live births; thus, more updated studies are required to validate this finding; iii) there were three studies at high risk of selection, attrition or other bias, which may interfere with the results; and iv) the findings of the present meta-analysis require further verification with real-world clinical-setting studies.

The present meta-analysis concluded that using an oil-based contrast medium increases the rates of clinical pregnancy, ongoing pregnancy and live birth compared with a water-based contrast medium in patients receiving HSG, indicating the oil-based contrast medium for HSG may exert a superior fertility-enhancing effect.

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Availability of data and materials

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

Authors' contributions

JL contributed to the study conception and design. JC and SL performed data acquisition, analysis and interpretation. JL and JC confirm the authenticity of all raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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