Effectiveness on fertility outcome of tubal flushing with different contrast media: systematic review and network meta-analysis

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KEYWORDS: contrast media; Fallopian tube patency test; HSG; HyCoSy; hysterosalpingography; infertility; laparoscopy; systematic review; tubal flushing

ABSTRACT

Objectives To compare, in women with infertility, the effectiveness and safety of tubal flushing using oil-based contrast medium, water-based contrast medium or their combination, and no tubal flushing, and to evaluate the effectiveness of tubal flushing on fertility outcome over time.

Methods We performed a systematic review and network meta-analysis, searching the electronic databases MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials, and trial registries, up to 25 September 2018. We included randomized controlled trials (RCTs) comparing the following interventions with each other or with no intervention in women with infertility: tubal flushing using water-based contrast medium, tubal flushing using oil-based contrast medium or additional tubal flushing with oil-based medium following diagnostic tubal flushing with water-based medium. The outcomes included clinical pregnancy, live birth, ongoing pregnancy, miscarriage, ectopic pregnancy and adverse events.

Results Of the 283 studies identified through the search, 14 RCTs reporting on 3852 women with infertility were included. Network meta-analysis showed that tubal flushing using oil-based contrast medium was associated with higher odds of clinical pregnancy within 6 months after randomization and more subsequent live births compared with tubal flushing using water-based medium (odds ratio (OR), 1.67 (95% CI, 1.38–2.03), moderate certainty of evidence; and OR, 2.18 (95% CI, 1.30–3.65), low certainty of evidence, respectively) and compared with no intervention (OR, 2.28 (95% CI, 1.50–3.47), moderate certainty of evidence; and OR, 2.85 (95% CI, 1.41–5.74), low certainty of evidence, respectively). These results agreed with those of the pairwise meta-analysis. For clinical pregnancy within 6 months, there was insufficient evidence of a difference between tubal flushing with water-based contrast medium and no intervention (OR, 1.36 (95% CI, 0.91–2.04), low certainty of evidence). For fertility outcomes after 6 months, there was insufficient evidence of a difference in any comparison (low to very low certainty of evidence). Compared with tubal flushing using water-based contrast medium, the use of oil-based contrast medium was associated with higher odds of asymptomatic intravasation (OR, 5.06 (95% CI, 2.29–11.18), moderate certainty of evidence).

Conclusions In women with infertility undergoing fertility workup, tubal flushing using oil-based contrast medium probably increases clinical pregnancy rates within 6 months after randomization and may increase subsequent live-birth rates, compared with tubal flushing using water-based contrast medium and compared with no intervention. Evidence on fertility outcomes beyond 6 months is inadequate to draw firm conclusions. Copyright © 2019 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

Tubal flushing was initially introduced in reproductive medicine as a diagnostic test to evaluate tubal patency. It constitutes an essential part of the fertility workup...
and is recommended in clinical guidelines\textsuperscript{1,2}. Tubal flushing has been used in several different techniques to visualize tubal patency, including hysterosalpingography (HSG), hysterosalpingo-contrast sonography (HyCoSy), hysterosalpingo-foam sonography (HyFoSy) and laparoscopy with dye testing. Water-based contrast media are widely used in all these procedures while oil-based contrast media are used mainly in HSG.

A debate about the therapeutic effects of tubal flushing started over six decades ago\textsuperscript{3,4}. Several potential mechanisms have been proposed to explain such therapeutic effects, including mechanical flushing out of the debris or mucus plugs in the Fallopian tubes\textsuperscript{5}, enhancement of ciliary activity\textsuperscript{6} and immunobiological actions on the endometrium or peritoneum\textsuperscript{7–11}.

In order to evaluate the effect of tubal flushing on fertility outcomes, a number of studies have compared tubal flushing using different contrast media, alone or in combination, with each other or with no treatment. However, no large randomized controlled trial (RCT) has compared all these different interventions, therefore a network meta-analysis incorporating both direct and indirect evidence is required to determine the most effective contrast medium in imaging techniques. Moreover, considering the mechanisms proposed so far to explain the beneficial effects of tubal flushing, it is likely that its effectiveness may not remain the same over time, and therefore it is also important to assess the trend of fertility outcomes with different contrast media over time.

Several meta-analyses on this topic have been published\textsuperscript{12–14}. These used only direct evidence in the evidence synthesis and some evaluated water \textit{vs} oil-based contrast in HSG only\textsuperscript{12,13}, but did not consider women who did not undergo tubal flushing or women with tubal flushing undergoing non-HSG techniques. Moreover, none of these meta-analyses considered fertility outcomes over time\textsuperscript{12–14}.

We conducted this systematic review and network meta-analysis to compare the effectiveness and safety of tubal flushing according to the use of oil-based \textit{vs} water-based contrast medium \textit{vs} their combination, or compared with no tubal flushing, in the outcome of women with infertility undergoing fertility workup. Our secondary objective was to evaluate the effectiveness of tubal flushing on fertility outcomes over time.

METHODS

The protocol of this systematic review was registered on PROSPERO (CRD42017059832). We reported the systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) extension statement for network meta-analysis\textsuperscript{15}.

Information sources and search strategy

We searched the electronic databases EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and MEDLINE, as well as the trial registers ClinicalTrials.gov, International Clinical Trials Registry Platform and Australian New Zealand Clinical Trials Registry, using combinations of relevant free words and/or index terms (Appendix S1). The last electronic database search was conducted on 25 September 2018. The reference lists of identified publications were searched manually to identify additional relevant papers.

Eligibility criteria

We intended to include studies in which the participants were women wishing to conceive. We included RCTs comparing at least two of the following treatment or control groups: (1) no tubal flushing; (2) tubal flushing with water-based contrast medium; (3) tubal flushing with oil-based contrast medium; or (4) an additional tubal flushing procedure with oil-based contrast medium after diagnostic tubal flushing with water-based contrast medium. Studies reporting on tubal flushing procedures using any imaging technique, including HSG, HyCoSy, HyFoSy or laparoscopy (or hydrolaparoscopy), were eligible for inclusion. Studies comparing different types of water-based, or different types of oil-based, contrast media were excluded. Quasi-RCTs were excluded. No language limitation was applied.

Outcomes

The outcomes included clinical pregnancy, live birth, ongoing pregnancy, miscarriage, ectopic pregnancy and adverse events. We intended to use outcomes at the longest time of follow-up in each study for the primary analysis. In order to show the trend over time, we also planned a subgroup analysis to evaluate clinical pregnancy at different follow-up timepoints (i.e. at 3, 6, 9, 12 and 18 months) after randomization, if data were available. All short-term outcomes related to tubal flushing, such as pelvic infection and intravasation, as well as long-term outcomes, such as birth defects, were reported on.

Study selection, data collection and quality assessment

Two reviewers (R.W. and N.v.W.) independently evaluated study eligibility, extracted the data and assessed the quality of the included studies. Disagreements were solved by consensus or by discussion with a third reviewer (B.W.M.).

A predesigned form was used to collect the following information: name of the first author, publication year, study population, participant characteristics, study funding, types of contrast medium evaluated, details of interventions and co-interventions, sample size and outcomes. If outcome data were reported in published figures, DigitizeIt version 2.2 software (I. Bormann, Braunschweig, Germany; https://www.digitizeit.de/) was used to reconstruct the data from the publications\textsuperscript{16}. Risk of bias within individual studies was assessed using the Cochrane Collaboration tool\textsuperscript{17}. The certainty of
evidence across the included studies was evaluated by considering study limitations (risk of bias), indirectness of evidence, inconsistency of results, imprecision of results and risk of publication bias, using Confidence in Network Meta-analysis (CINeMA)\textsuperscript{18}.

### Statistical analysis

We used network plots to show available head-to-head comparisons in included RCTs and a contribution matrix to illustrate the contribution of each head-to-head comparison to the overall body of evidence\textsuperscript{19,20}.

We then tested global inconsistency using the design-by-treatment interaction model\textsuperscript{21} and tested local inconsistency using inconsistency plots\textsuperscript{22}. When there was no significant inconsistency, we performed network meta-analyses within multivariate random-effects meta-analysis models\textsuperscript{23} as well as random-effects pairwise meta-analysis\textsuperscript{17}.

We used the surface under the cumulative ranking (SUCRA) to rank the treatments\textsuperscript{24}, and applied comparison-adjusted funnel plots to assess small-study effects\textsuperscript{19}. STATA version 15.0 (StataCorp., College Station, TX, USA) was used to perform statistical analysis and to illustrate the graphics\textsuperscript{23}.

We intended to perform subgroup analyses on age, duration of infertility, cause of infertility and outcomes at different timepoints after randomization if data were available. We planned a sensitivity analysis by including only studies with a low risk of bias. We also performed a post-hoc sensitivity analysis by excluding participants with missing outcome data\textsuperscript{17}.

### RESULTS

#### Characteristics of included studies

Of the 283 studies identified through the search, 14 RCTs (16 articles) reporting on 3852 women with infertility were included\textsuperscript{25–40} (Figure 1). All studies reported on women with infertility and the detailed causes of this (including unexplained infertility) were provided in all but two studies\textsuperscript{32,34} (Table 1). Funding was reported in three studies\textsuperscript{28,29,31}. Outcome data at different timepoints were extracted from the figures in seven studies by using DigitizeIt 2.2 software\textsuperscript{25,28,31,32,35,37,40}.

Of the 14 included RCTs, the most frequent comparison was tubal flushing using water-based vs oil-based contrast medium ($n = 6$)\textsuperscript{26–28,32,35,36}, followed by tubal flushing using water-based medium succeeded by oil-based contrast medium vs water-based contrast medium alone.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Cause of infertility</th>
<th>Sample size (n)</th>
<th>Follow-up (months)</th>
<th>Intervention and control</th>
<th>Method of tubal flushing</th>
<th>Contrast medium</th>
<th>Co-intervention during/after tubal flushing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Fadhli (2006)&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Canada</td>
<td>Unexplained infertility; endometriosis</td>
<td>88</td>
<td>12</td>
<td>Water + oil Laparoscopy</td>
<td>Dilute solution of methylene blue dye; lipiodol (10–20 mL)</td>
<td>Excision of endometriotic lesions when necessary</td>
<td></td>
</tr>
<tr>
<td>Alper (1986)&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Canada/USA</td>
<td>Oligo-ovulation (33%); tubal factor (29%); endometriosis (8%); unexplained or mild male infertility (30%)</td>
<td>131</td>
<td>6</td>
<td>Oil HSG</td>
<td>Lipiodol (10–20 mL)</td>
<td>Ovulation disorders treated with clomiphene citrate</td>
<td></td>
</tr>
<tr>
<td>de Boer (1988)&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Netherlands</td>
<td>Unexplained or mild male infertility</td>
<td>175</td>
<td>6</td>
<td>Oil HSG</td>
<td>Ethiodol (10 mL)</td>
<td>Only hormonal therapy was used</td>
<td></td>
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<tr>
<td>Dreyer (2017)&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Netherlands</td>
<td>Unexplained or mild male infertility (87%); tubal factor (8%); other cause (5%)*</td>
<td>1119</td>
<td>6</td>
<td>Oil HSG</td>
<td>Lipiodol (5–10 mL)</td>
<td>According to prespecified indications: IUI (17.9%), IVF/ICSI (1.4%), ovulation induction (0.5%), laparoscopy (6.2%) or hysteroscopy (4.4%)</td>
<td></td>
</tr>
<tr>
<td>Johnson (2004)&lt;sup&gt;29&lt;/sup&gt;</td>
<td>New Zealand</td>
<td>Unexplained infertility (61%); endometriosis (39%)</td>
<td>158</td>
<td>6</td>
<td>Oil HSG</td>
<td>Lipiodol (10 mL)</td>
<td>None (but four women had IVF)</td>
<td></td>
</tr>
<tr>
<td>Letterie (1990)&lt;sup&gt;30&lt;/sup&gt;</td>
<td>USA</td>
<td>Unexplained infertility (100%)</td>
<td>40</td>
<td>12</td>
<td>Water + oil Laparoscopy</td>
<td>Laparoscopic tubal testing; ethiodol (20 mL)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Lindborg (2009)&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Sweden</td>
<td>Unexplained or mild male infertility (77%); tubal factor (23%)</td>
<td>334</td>
<td>6</td>
<td>Water No flushing</td>
<td>HyCoSy</td>
<td>Echovist (&lt;15 mL)</td>
<td>None</td>
</tr>
<tr>
<td>Lindequist (1994)&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Denmark</td>
<td>Tubal factor (46%); unexplained or mild male infertility (54%)</td>
<td>242</td>
<td>9</td>
<td>Oil HSG</td>
<td>Lipiodol (5–10 mL)</td>
<td>None</td>
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<tr>
<td>Nugent (2002)&lt;sup&gt;33&lt;/sup&gt;</td>
<td>UK</td>
<td>Unexplained infertility</td>
<td>34</td>
<td>6</td>
<td>Oil HSG</td>
<td>Lipiodol (mean, 5.8 mL)</td>
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<tr>
<td>Ogata (1993)&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Japan</td>
<td>Tubal factor (29%); endometriosis (8%)</td>
<td>302</td>
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<td>Oil HSG</td>
<td>Lipiodol, volume NR</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Rasmussen (1991)&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Denmark</td>
<td>Tubal factor (46%); unexplained or mild male infertility (54%)</td>
<td>398</td>
<td>10</td>
<td>Oil HSG</td>
<td>Lipiodol (5–10 mL)</td>
<td>None</td>
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</table>

*Continued over.*
Table 1 Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Cause of infertility</th>
<th>Sample size (n)</th>
<th>Follow-up (months)</th>
<th>Co-intervention during/after tubal flushing</th>
<th>Intervention and control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spring (2000)</td>
<td>USA</td>
<td>Tubal-, male-, ovulatory-, age-, anovulatory, cervical, endometriosis (35%); ovulation dysfunction (19%); unexplained infertility (25%); drug-associated factor (11%); other factor (6%)</td>
<td>666</td>
<td>12</td>
<td>Water + oil HSG; Sinografin (2-5 ml); ethiodol (2-5 ml)</td>
<td>Ovulatory medication (53.3%)</td>
</tr>
<tr>
<td>Steiner (2003)</td>
<td>USA</td>
<td>Ovulatory dysfunction (35%); endometriosis (12%); unexplained infertility (15%); drug-associated factor (10%); other factor (16%)</td>
<td>56</td>
<td>18</td>
<td>Water + oil HSG; Sinografin (2-5 ml); ethiodol (2-5 ml)</td>
<td>Ovulatory medication (53.3%)</td>
</tr>
<tr>
<td>Yang (1989)</td>
<td>China</td>
<td>Unexplained or mild male infertility (45%); endometriosis (15%); drug-associated factor (10%); other factor (24%)</td>
<td>109</td>
<td>8</td>
<td>Water + oil HSG; Sinografin (2-5 ml); ethiodol (2-5 ml)</td>
<td>None</td>
</tr>
</tbody>
</table>

Only first author of each study is given. *All patients had low risk of tubal pathology. †Detailed data were not available owing to incomplete reporting of baseline data. ‡52.7% diatrizoate meglumine and 26.8% iodipamide meglumine. HSG, hysterosalpingography; HyCoSy, hysterosalpingo-contrast sonography; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in-vitro fertilization; NR, not reported; oil, oil-based contrast medium; water, water-based contrast medium.

There were three studies comparing tubal flushing using oil-based contrast medium with no tubal flushing29,33,34, one comparing tubal flushing using water-based followed by oil-based contrast medium with the use of oil-based contrast medium only36, and one comparing tubal flushing with water-based contrast medium with no tubal flushing31 (Table 1). Clinical pregnancy within 6 months was the most commonly reported outcome (n = 12). The network plots for different outcomes are presented in Figure S1.

Quality of evidence of individual studies

With regard to selection bias, 64% (n = 9)25,26,28–31,36–38 of included RCTs reported adequate methods of random sequence generation and 36% (n = 5)28,29,31,33,38 reported adequate methods of allocation concealment, while 7% (n = 1)37 had no concealment (Table 2). As blinding was not possible owing to the nature of the interventions, we scored the risk of performance bias as unclear in all RCTs. Given that all the fertility outcomes are objective outcomes, it is unlikely that the non-blinded design would affect the outcome measurement, therefore, the risk of detection bias was low in all the included studies. Five RCTs25,26,30,32,34 had a high risk of attrition bias owing to the considerable proportion of missing outcome data. One RCT36 was scored at high risk of other bias because the age distribution was imbalanced in the groups.

The majority (>70%) of the evidence for comparisons between tubal flushing using oil-based contrast medium vs no flushing, water-based contrast medium vs no flushing and tubal flushing with oil- vs water-based contrast medium were at low risk of bias, but the evidence for the comparisons between the combination group (water-based followed by oil-based contrast medium) and the other groups was prone to bias, as at least 25% of the evidence was at high risk of bias (Figure S2).

Network consistency and contribution

When considering clinical pregnancy at the longest follow-up time in each study in the analysis, we found significant global and local inconsistency (Table S1 and Figure S3). Therefore, we avoided pooling the outcomes at different timepoints21. Instead, we chose clinical pregnancy at the most commonly used timepoint (6 months) as an alternative main outcome, and presented outcomes at other timepoints in subgroup analyses. After separating outcomes at different timepoints, no significant global or local inconsistency was observed (Table S1 and Figure S3). Therefore, time of outcome measurement is an important source of inconsistency in this network meta-analysis. The contribution of direct evidence to the network for different outcomes is presented in Figure S4.

Network and pairwise meta-analysis

Clinical pregnancy

Twelve RCTs reported clinical pregnancy within 6 months in a total of 2884 women. The network meta-analysis
regard to clinical pregnancy within 9, 12 and 18 months, within 6 months from randomization (Figure S6). With showed similar findings to those for clinical pregnancy (Figure S5). was no evidence of the existence of small-study effects. meta-analyses for these comparisons (Figure 2). There meta-analyses were similar to those of the network and 2.5%, respectively. The findings of the pairwise contrast medium alone, water-based contrast medium alone of water- and oil-based contrast media, oil-based con- SUCRA values for tubal flushing with a combination water-based tubal flushing and the other interventions. (Figure 2) showed that tubal flushing with oil-based contrast medium increased the odds of clinical pregnancy within 6 months after randomization compared with no tubal flushing (odds ratio (OR), 2.28 (95% CI, 1.50–3.47); moderate certainty of evidence), while there was insufficient evidence of a difference between tubal flushing using water-based contrast medium and no tubal flushing (OR, 1.36 (95% CI, 0.91–2.04); low certainty of evidence). This suggests that, if the 6-month clinical pregnancy rate following no tubal flushing is assumed to be 16%, the clinical pregnancy rates following tubal flushing with oil-based contrast medium and water-based contrast medium would be 30% (95% CI, 22–40%) and 21% (95% CI, 15–28%), respectively. Compared with water-based contrast medium, the use of oil-based medium resulted in a higher OR for clinical pregnancy within 6 months (OR, 1.67 (95% CI, 1.38–2.03); moderate certainty of evidence). This suggests that if the 6-month clinical pregnancy rate following tubal flushing with water-based contrast medium is assumed to be 28%, the clinical pregnancy rate following tubal flushing with oil-based contrast medium would be 39% (95% CI, 35–44%). There was very low certainty of evidence for the comparison between additional oil-based tubal flushing after water-based tubal flushing and the other interventions. SUCRA values for tubal flushing with a combination of water- and oil-based contrast media, oil-based contrast medium alone, water-based contrast medium alone and no tubal flushing were 83.0%, 82.0%, 31.7% and 2.5%, respectively. The findings of the pairwise meta-analyses were similar to those of the network meta-analyses for these comparisons (Figure 2). There was no evidence of the existence of small-study effects (Figure S5).

Subgroup analysis of clinical pregnancy within 3 months showed similar findings to those for clinical pregnancy within 6 months from randomization (Figure S6). With regard to clinical pregnancy within 9, 12 and 18 months, Comparison

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection bias (random sequence generation)</th>
<th>Selection bias (allocation concealment)</th>
<th>Performance bias (blinding of participants and personnel)</th>
<th>Detection bias (blinding of outcome assessment)</th>
<th>Attrition bias (incomplete outcome data)</th>
<th>Reporting bias (selective reporting)</th>
<th>Other bias (other sources of bias)</th>
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<tr>
<td>Al-Fadhli (2006)</td>
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<td>de Boer (1998)</td>
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Odds ratio (95% CI)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water vs none (1 RCT, 334 women)</td>
<td>1.14 (0.71, 1.84)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.14 (0.71, 1.84)</td>
</tr>
<tr>
<td>Oil vs none (2 RCTs, 192 women)</td>
<td>1.36 (0.91, 2.04)</td>
</tr>
<tr>
<td>Johnson (2004)</td>
<td>3.16 (1.50, 6.63)</td>
</tr>
<tr>
<td>Overall</td>
<td>11.67 (0.58, 235.92)</td>
</tr>
<tr>
<td>Oil vs water (5 RCTs, 2065 women)</td>
<td>3.40 (1.65, 6.99)</td>
</tr>
<tr>
<td>Overall</td>
<td>2.28 (1.50, 3.47)</td>
</tr>
<tr>
<td>Oil vs water (5 RCTs, 2065 women)</td>
<td>2.30 (1.20, 4.41)</td>
</tr>
<tr>
<td>Alper (1986)</td>
<td>1.23 (0.54, 2.81)</td>
</tr>
<tr>
<td>De Boer (1998)</td>
<td>1.49 (0.78, 2.85)</td>
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<tr>
<td>Dreyer (2017)</td>
<td>1.64 (1.27, 2.11)</td>
</tr>
<tr>
<td>Lindequist (1994)</td>
<td>1.40 (0.72, 2.70)</td>
</tr>
<tr>
<td>Rasmussen (1991)</td>
<td>2.11 (1.19, 3.72)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.62 (1.33, 1.98)</td>
</tr>
<tr>
<td>Oil vs water (4 RCTs, 293 women)</td>
<td>1.67 (1.38, 2.03)</td>
</tr>
<tr>
<td>Al-Fadhli (2006)</td>
<td>1.43 (0.58, 3.52)</td>
</tr>
<tr>
<td>Latterie (1990)</td>
<td>3.86 (0.67, 22.11)</td>
</tr>
<tr>
<td>Steiner (2003)</td>
<td>2.16 (0.73, 6.36)</td>
</tr>
<tr>
<td>Yang (1989)</td>
<td>1.41 (0.61, 3.22)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.69 (1.02, 2.81)</td>
</tr>
<tr>
<td>Oil vs oil (RCT)</td>
<td>1.01 (0.59, 1.74)</td>
</tr>
</tbody>
</table>

Figure 2 Forest plots of network and pairwise meta-analyses on clinical pregnancy within 6 months after randomization to tubal flushing with oil-based contrast medium (oil), tubal flushing with water-based contrast medium (water), additional tubal flushing with oil-based following flushing with water-based contrast medium (both) or no tubal flushing (none). Odds ratios and 95% CIs of pairwise meta-analyses are illustrated by hollow diamonds while those of network meta-analyses are illustrated by filled diamonds.
neither network meta-analysis nor pairwise meta-analysis showed any statistically significant differences in most comparisons.

As the breakdown outcome data on women of different ages or with different duration or cause of infertility were not available, no subgroup analyses on these variables were performed. Sensitivity analyses of studies with an overall low risk of bias and after excluding participants with missing outcome data showed findings consistent with the main findings of the network meta-analysis for clinical pregnancy within 6 months (Figure S7).

**Live birth and ongoing pregnancy**

Five studies reported on live birth resulting from pregnancy within 6 months in a total of 2043 women. The network meta-analysis (Figure 3) showed that tubal flushing using oil-based contrast medium resulted in higher odds of live birth compared with no tubal flushing (OR, 2.85 (95% CI, 1.41–5.74); low certainty of evidence), while there was insufficient evidence of a difference between tubal flushing using water-based medium and no tubal flushing (OR, 1.31 (95% CI, 0.70–2.44); low certainty of evidence). This suggests that, if the live-birth rate resulting from clinical pregnancy within 6 months following no tubal flushing is assumed to be 16%, the live-birth rates following tubal flushing with oil-based contrast medium and water-based contrast medium would be 35% (95% CI, 21–52%) and 20% (95% CI, 12–32%), respectively. Tubal flushing using oil-based contrast medium resulted in higher odds of live birth than did the use of water-based contrast medium (OR, 2.18 (95% CI, 1.30–3.65); low certainty of evidence). This suggests that, if the live-birth rate following tubal flushing with water-based contrast medium is assumed to be 22%, the live-birth rate following tubal flushing with oil-based contrast medium would be 38% (95% CI, 27–51%). SUCRA values for tubal flushing with oil-based and water-based contrast media and no tubal flushing were 99.9%, 41.1% and 9.0%, respectively. The findings of the pairwise meta-analyses were consistent with those of the network meta-analyses (Figure 3). The results for ongoing pregnancy resulting from pregnancy occurring within 6 months following intervention (four RCTs, 1645 women) were consistent with those for live birth (Figure S6).

**Miscarriage, ectopic pregnancy and adverse events**

There was no conclusive evidence of a difference in any of the comparisons for miscarriage or ectopic pregnancy (Figure S6).

Five studies reported no short-term adverse events following tubal flushing. Pooled analysis of the three studies that reported on intravasation showed that, compared with water-based contrast medium, oil-based contrast medium was associated with higher odds of asymptomatic intravasation (OR, 5.06 (95% CI, 2.29–11.18); three studies; \( I^2 = 0 \)). No cases of pulmonary embolism or death were reported. Three studies reported on pelvic infection, of which two compared tubal flushing with water-based vs oil-based contrast medium. Pooled analysis showed that there was insufficient evidence of differences in the incidence of pelvic infection between these two interventions (OR, 0.23 (95% CI, 0.04–1.27); two studies; \( I^2 = 0 \) (Figure S6).

Only one study reported long-term adverse events, in which three newborns in the group of women who underwent tubal flushing with oil-based contrast medium had skeletal dysplasia, esophageal atresia and chromosomal mosaicism, respectively. No congenital abnormalities were seen in neonates born to women who underwent tubal flushing with water-based medium.

**DISCUSSION**

**Summary of key findings**

For the comparisons between tubal flushing using oil-based contrast medium vs water-based contrast medium or no tubal flushing, the overall certainty of evidence was moderate for short-term clinical pregnancy, low for short-term live birth and low to very low for outcomes beyond 6 months. Tubal flushing using oil-based contrast medium probably increases short-term (6 months) clinical pregnancy rate, and may increase subsequent live-birth rate compared with tubal flushing with water-based contrast medium and no tubal flushing, but it is not certain whether this effect persists beyond 6 months. The evidence on the effectiveness of tubal flushing using water-based contrast medium compared with no tubal flushing was insufficient (low certainty of evidence).
Strengths and limitations

The strengths of this systematic review include that it incorporates evidence from both direct and indirect comparisons, provides a hierarchy of rankings of effectiveness and uses multiple approaches for sensitivity analysis. Moreover, time from randomization was incorporated into the outcome assessments and was identified as a source of inconsistency. Our current outcome-reporting strategy not only reduced the heterogeneity in outcome reporting across trials but also illustrated the trend of effectiveness of different interventions over time.

On the other hand, several limitations of our meta-analysis should be addressed. Firstly, not all trials reported live birth. Despite this, the agreement between the results for live birth and those for clinical pregnancy provided some reassurance for our main conclusion. Secondly, although the majority of the participants were broadly defined as having unexplained infertility, including endometriosis and mild male-factor infertility, the study population also included other causes of infertility; the heterogeneous nature of the study population may have resulted in selection bias. Thirdly, some of the studies had a high risk of selection, attrition or other bias. This resulted in an overall low quality of evidence in some comparisons, especially in the combination group of tubal flushing with oil-based medium following flushing with water-based contrast medium. Finally, the association between available evidence and competing interests of the manufacturer was unclear in most studies. Only three studies\textsuperscript{28,29,36} reported funding sources and all were from academic institutes or societies, including one\textsuperscript{29} with additional support from industry.

Clinical implications

The effect of tubal flushing using oil-based contrast medium has not been evaluated outside HSG. HyCoSy is an accurate test for diagnosing tubal occlusion and performs similarly to HSG\textsuperscript{41}. It prevents women from being exposed to radiation and, therefore, has replaced HSG in fertility workup in many settings. More recently, HyFoSy has become commonly used, and a trial on its diagnostic accuracy and cost-effectiveness in fertility workup is underway\textsuperscript{12}.

The costs of HyCoSy with sonographic contrast and HSG with water-based contrast are considered similar\textsuperscript{43}, while HyFoSy may further reduce the cost\textsuperscript{42}. In HSG, oil-based contrast is more expensive than is water-based contrast, with an extra US$ 8198 for an additional ongoing pregnancy in ovulatory women with infertility at low risk for tubal pathology\textsuperscript{44}. Cost-effectiveness should also be considered in shared decision-making.

Several safety concerns regarding tubal flushing have been raised. Firstly, venous intravasation occurs in approximately 2–7% of cases undergoing HSG\textsuperscript{45–47} and seems to occur more frequently when using oil-based contrast medium. Some reports on venous intravasation during ultrasound show a higher incidence (13%)\textsuperscript{48}. While intravasation can potentially result in life-threatening pulmonary embolism, we are unaware of any deaths reported since the 1960s\textsuperscript{49}. This may be owing to fluoroscopy screening or the reduced use of HSG with oil-based contrast worldwide as HyCoSy and HyFoSy become more popular. Secondly, any concerns about the thyroid function of mother and child are based on the effects of iodinated contrast medium\textsuperscript{50,51} and a longer-lasting time of oil-based contrast in the pelvis\textsuperscript{52}. Maternal hypothyroidism can occur after tubal flushing with oil-based contrast\textsuperscript{51}, especially in women with subclinical hypothyroidism before HSG\textsuperscript{53}. With regard to neonatal safety, a Japanese cohort showed that infants born to mothers undergoing HSG using oil-based contrast before conceiving had a higher incidence of thyroid dysfunction (2.4%) than did the unselected population (0.7%)\textsuperscript{50}. Although there is limited evidence on these safety issues, they should be fully discussed during clinical consultations.

Research implications

Future trials should evaluate long-term fertility outcomes after tubal flushing. The effectiveness needs to be tested in trials addressing different populations, including women with advanced age, anovulation or tubal-factor infertility. Safety data on women and their offspring are also needed to address the short- and long-term safety concerns.

The therapeutic effects of contrast media should also be tested in techniques other than HSG, such as HyCoSy, HyFoSy and hydrolaparoscopy as well as laparoscopy, for instance by using tubal flushing with oil-based contrast medium after confirming tubal patency with HyCoSy, or performing preovulatory tubal flushing without any imaging after confirmed tubal patency, followed by intrauterine insemination or timed intercourse, as suggested in some studies\textsuperscript{54,55}. This would be an interesting alternative treatment for in-vitro fertilization in women with unexplained infertility.

The mechanical effects of flushing on the Fallopian tubes seem to be the most reasonable theory to account for its therapeutic effects, as they persist after several menstrual cycles post tubal flushing, and such effects have been observed following the use of both oil-based and water-based contrast in a recent cohort study\textsuperscript{56}. With regard to the difference between different contrast media, we hypothesize that for tubes with mucus plugs or debris, the higher viscosity of the oil-based contrast causes a better flushing effect, maybe owing to a higher pressure during the tubal flushing procedure. A recent study found that the treatment effect of oil-based, as compared with water-based, contrast medium was higher in women suffering from severe pain during tubal flushing\textsuperscript{57}, possibly because the higher intrauterine pressure associated with the dislodgement of mucus plugs and debris might cause more pain. However, we acknowledge that such a hypothesis is difficult to test in animal models or humans. Hypotheses related to other mechanisms, including the effects on...
endometrial receptivity, should be further tested in future research.

Conclusions
In women with infertility undergoing fertility workup, tubal flushing using oil-based contrast medium probably increases clinical pregnancy rates within 6 months and may increase subsequent live-born rates, compared to tubal flushing with water-based contrast medium or no intervention. Available evidence on fertility outcomes beyond 6 months is inadequate to draw firm conclusions.

ACKNOWLEDGMENTS
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REFERENCES
Tubal flushing and fertility outcome


### SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

**Appendix S1** Search strategies

**Table S1** Results of global inconsistency assessment

**Figure S1** Network plots for clinical pregnancy within 3 months (a), 6 months (b), 9 months (c) and 12 months (d), and live birth resulting from pregnancy within 6 months (e), after randomization.

**Figure S2** Risk of bias contributions.

**Figure S3** Inconsistency plots for clinical pregnancy at the longest follow-up time (a), clinical pregnancy within 6 months (b), 3 months (c) and 12 months (d), and live birth resulting from pregnancy within 6 months (e), after randomization.

**Figure S4** Contribution plots for clinical pregnancy within 6 months (a), 3 months (b), 9 months (c) and 12 months (d), live birth resulting from pregnancy within 6 months (e) and miscarriage within 6 months (f) after randomization.

**Figure S5** Comparison-adjusted funnel plots for clinical pregnancy within 6 months (a) and 3 months (b) after randomization.

**Figure S6** Network and pairwise meta-analyses for clinical pregnancy at different timepoints (a), live birth at different timepoints (b), ongoing pregnancy resulting from pregnancy within 6 months after randomization (c), miscarriage (d) and ectopic pregnancy and adverse events (e).

**Figure S7** Sensitivity analysis for clinical pregnancy within 6 months when including only studies with low risk of bias (a) and when excluding participants with missing outcome data (b).

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A video abstract of this article is available online.
Eficacia sobre el resultado de fertilidad del lavado de trompas con diferentes medios de contraste: revisión sistemática y metaanálisis en red

RESUMEN

Objetivos
Comparar, en mujeres con infertilidad, la efectividad y seguridad del lavado de trompas con un medio de contraste a base de aceite, un medio de contraste a base de agua o una combinación, y el no lavado de trompas, y evaluar la efectividad del lavado de trompas en el resultado de la fertilidad con el tiempo.

Métodos
Se realizó una revisión sistemática y un metaanálisis en red, mediante búsquedas en las bases de datos electrónicas MEDLINE, EMBASE y el Registro Central Cochrane de Ensayos Controlados, y en otros registros de ensayos, hasta el 25 de septiembre de 2018. Se incluyeron ensayos controlados aleatorizados (ECA) que compararon las siguientes intervenciones entre sí o con la no intervención en mujeres con infertilidad: lavado de trompas con medio de contraste a base de agua, lavado de trompas con medio de contraste a base de aceite o lavado de trompas adicional con un medio a base de aceite después de un lavado de trompas con un medio a base de agua. Los resultados incluyeron el embarazo confirmado ecográficamente, el nacimiento vivo, el embarazo en curso, el aborto espontáneo, el embarazo ectópico y los eventos adversos.

Resultados
De los 283 estudios identificados mediante la búsqueda, se incluyeron 14 ECA que informaron sobre 3852 mujeres con infertilidad. El metaanálisis en red mostró que el lavado de trompas con medio de contraste a base de aceite se asoció con mayores probabilidades de embarazo confirmado ecográficamente dentro de los seis meses posteriores a la aleatorización y mas nacimientos vivos posteriores en comparación con el lavado de trompas con medio a base de agua (razón de momios [RM], 1,67; IC 95%: 1,38–2,03), certeza moderada de evidencia; y RM, 2,18 (IC 95%: 1,50–3,47), certeza baja de evidencia; y RM, 2,85 (IC 95%: 1,41–5,74), certeza baja de evidencia, respectivamente). Estos resultados coincidieron con los del metaanálisis por pares. No hubo evidencia suficiente de una diferencia entre el lavado de trompas con medio de contraste a base de agua y la no intervención para el embarazo clínico dentro de los seis meses (RM, 1,36 [IC 95%: 0,91–2,04]; certeza baja de evidencia). Para los resultados de fertilidad después de los seis meses, no hubo evidencia suficiente de diferencias en cualquier comparación (certeza de evidencia baja a muy baja). En comparación con el lavado de trompas con un medio de contraste a base de agua, el uso de un medio de contraste a base de aceite se asoció con mayores probabilidades de intravasación asimétrica (RM, 5,06 [IC 95%: 2,29–11,18], certeza moderada de evidencia).

Conclusiones
En las mujeres con infertilidad que se someten a un examen de fertilidad, el lavado de trompas con medio de contraste a base de aceite aumenta la probabilidad de las tasas de embarazo clínico dentro de los 6 meses posteriores a la aleatorización y puede aumentar las tasas de nacimientos vivos, en comparación con el lavado de trompas con medio de contraste a base de agua y en comparación con la no intervención. La evidencia sobre los resultados de fertilidad después de los seis meses es inadecuada para establecer conclusiones firmes.