ORIGINAL ARTICLE: INFERTILITY

Oil-based versus water-based contrast for hysterosalpingography in infertile women: a systematic review and meta-analysis of randomized controlled trials

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Objective: To determine the effect of the using oil-soluble contrast material (OSCM) vs. water-soluble contrast material (WSCM) for hysterosalpingography on pregnancy rates in infertile women.
Design: Systematic review and meta-analysis.
Setting: Not applicable.
Patient(s): Infertile women.
Intervention(s): We included randomized controlled trials comparing pregnancy outcomes in women with infertility undergoing hysterosalpingography using OSCM and WSCM. Paired reviewers independently screened citations, assessed risk of bias of included studies, and extracted data. A random-effects model was used to report all outcomes. The Grading of Recommendations Assessment, Development, Evaluation (GRADE) system was used to quantify absolute effects and quality of evidence.
Main Outcome Measure(s): The primary outcome was ongoing pregnancy per randomized women.
Result(s): Six trials with a total of 2,562 patients were selected. Our meta-analysis showed OSCM was associated with significantly higher rates of ongoing pregnancy compared with WSCM (odds ratio [OR] 1.47, 95% confidence interval [CI] 1.12–1.93; $I^2 = 44\%$, moderate-quality evidence). Three trials reported live birth, but they were not pooled owing to extreme statistical heterogeneity ($I^2 = 86\%$). There was no difference in incidence of miscarriage (OR 0.83, 95% CI 0.56–1.24) or ectopic pregnancy (OR 0.65, 95% CI 0.18–2.36) between OSCM and WSCM groups. Three trials were rated as low risk of bias, whereas three were considered unclear.
Conclusion(s): Women who previously underwent hysterosalpingography using oil contrast had higher rates of ongoing pregnancy compared with women who underwent this procedure using water contrast. There is not enough evidence to either support or oppose the difference between groups concerning miscarriage and ectopic pregnancy. (Fertil Steril® 2018;■:■–■. ©2018 by American Society for Reproductive Medicine.)
Key Words: Hysterosalpingography, infertility, oil-soluble contrast material, water-soluble contrast material

Infertility, defined as the inability to conceive after 1 year of unprotected intercourse, affects 9% of couples worldwide (1, 2). One-third of infertility cases are due to anatomic abnormalities of the female reproductive tract, such as tubal blockage (3). Hysterosalpingography is a commonly used diagnostic modality used in women with infertility, but it has been known that many women conceive within months after hysterosalpingography, suggesting that tubal flushing might be considered a possible therapy option for infertility (4–6).

Traditionally hysterosalpingography was performed using oil-soluble contrast material (OSCM), which was associated with higher rates of ongoing pregnancy than no intervention (7). Oil-soluble contrast material was gradually replaced by water-soluble contrast material (WSCM), at least in

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part because OSCM might promote granulomatous inflammation in the presence of inflamed or obstructed fallopian tubes. Earlier studies indicated that the postexamination pregnancy rates vary depending on the type of contrast medium used (5,8–12). Continuing debate has focused on whether the option of contrast material used in hysterosalpingography could affect subsequent reproductive success.

Five randomized controlled trials (RCTs) (11,13–16) have compared pregnancy rates after hysterosalpingography involving OSCM with those after hysterosalpingography involving WSCM. One trial (15) demonstrated that pregnancy rates were higher in patients who had OSCM used in hysterosalpingography, compared with those who had WSCM. This finding, however, was not replicated in four other trials (11, 13, 14, 16). A meta-analysis including all five trials did not show a significant difference in rates of ongoing pregnancy between OSCM and WSCM groups (7). However, findings from a recent large multicenter RCT reiterated that the use OSCM is associated with higher ongoing pregnancy rates compared with the use of WSCM (17). Moreover, the previous meta-analysis did not conduct interpretation of results based on a formal evaluation of the quality of evidence (using the Grading of Recommendations Assessment, Development, Evaluation tool [GRADE] approach), leaving the credibility of findings uncertain. Thus, the conflicting evidence and the limitations of the previous meta-analyses prompted us to conduct an updated systematic review and meta-analysis.

In this study we conducted a meta-analysis of RCTs to determine the effect of the use of WSCM vs. OSCM on pregnancy rates and other pregnancy outcomes in infertile women undergoing hysterosalpingography.

MATERIALS AND METHODS

Protocol and Guidance

The present report has been prepared following Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines (18). The methods of the systematic review and meta-analysis followed PRISMA guidelines (19). Reporting of statistical data in the study followed Statistical Analyses and Methods in the Published Literature guidelines (20).

Eligibility Criteria

Inclusion criteria. We included RCTs comparing pregnancy outcomes in women with infertility undergoing hysterosalpingography using OSCM and WSCM.

Exclusion criteria. We excluded observational, noncontrolled, or nonrandomized interventional studies, emergency surgery, duplicate publications, and studies not reporting pregnancy outcomes as an endpoint.

Information Sources and Search Strategy

MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were systematically searched. The last electronic search was performed on August 1, 2017. We also hand-searched the references to the retrieved articles and meta-analyses. There were no restrictions on language.

For the search strategy, we used, in various relevant combinations, Medical Subject Headings terms and keywords pertinent to the intervention of interest: "hysterosalpingography," "infertility," "pregnancy," "miscarriage," "live birth," "ongoing pregnancy," "ectopic pregnancy," "controlled trials," and "randomized controlled trial."

Study Selection

After removal of duplicate articles, two reviewers (Y.Z. and F.F.) independently accessed the titles and abstracts of studies identified by the search for eligibility. They then screened the full text of potentially relevant studies. Disagreements were resolved by discussion with a third reviewer (Y.B.).

Data Collection Process

Two investigators (Y.Z. and F.F.) independently extracted relevant data from the included RCTs using a standardized electronic spreadsheet. If the required data could not be extracted, authors were e-mailed with the specific inquiry. Disagreements between the two reviewers were resolved by discussion with a third reviewer (Y.B.). Another reviewer (A.F.) double-checked the extracted data.

Risk of Bias and Quality of Evidence

Two reviewers (Y.Z. and F.F.) independently undertook quality assessment using a Cochrane risk of bias assessment tool. Studies with more than two high-risk components were rated as having a moderate risk of bias, studies with more than four high-risk components as having a high risk of bias, and studies with more than three unclear-risk components as having an unclear risk of bias.

We used the GRADE approach to rate the quality of evidence and generate absolute estimates of effect for the outcomes (21).

Outcomes

The primary outcome was ongoing pregnancy per randomized women, defined as a positive fetal heartbeat on ultrasonographic examination after 12 weeks' gestation.

The secondary outcomes were live birth per randomized women (defined as a live birth after 24 weeks' gestation), miscarriage per pregnancy (defined as the absence of a fetal heartbeat on ultrasonography or spontaneous loss of pregnancy before 12 weeks' gestation), and ectopic pregnancy per pregnancy (defined as an embryo implanted outside the uterine cavity).

Sensitivity Analyses

We performed the following sensitivity analyses for the outcomes: [1] removing one study at a time; [2] using alternative imputation methods; [3] using a fixed-effect model instead of a random-effects model; and [4] using risk ratios instead of odds ratios.