

# Cervical mucus removal before embryo transfer in women undergoing in vitro fertilization/intracytoplasmic sperm injection: a systematic review and meta-analysis of randomized controlled trials

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**Objective:** To appraise critically the published randomized controlled trials (RCTs) reporting on the effectiveness of cervical mucus removal before embryo transfer.

**Design:** Systematic review and meta-analysis of RCTs.

**Setting:** Assisted reproduction technology (ART) units.

**Patient(s):** Women undergoing embryo transfer after in vitro fertilization/intracytoplasmic sperm injection (IVF-ICSI).

**Intervention(s):** Cervical mucus removal followed or not by cervical irrigation immediately before embryo transfer.

**Main Outcome Measure(s):** Clinical pregnancy, implantation and live-birth rates.

**Result(s):** Eight RCTs involving 1,715 women were systematically analyzed. There was substantial heterogeneity among the included trials. There was no statistically significant difference in terms of pregnancy, implantation, or live-birth rates.

**Conclusion(s):** A meta-analysis from the available moderate to low quality trials provides very little evidence of an overall benefit of cervical mucus removal before embryo transfer for women undergoing IVF/ICSI. Due to problems of clinical diversity, statistical heterogeneity, and risk of bias, additional pragmatic multicenter RCTs are needed to evaluate the possible small benefit of cervical mucus removal before embryo transfer. (Fertil Steril® 2014;101:1302-7. ©2014 by American Society for Reproductive Medicine.)

**Key Words:** Cervical mucus, embryo transfer, live birth rate, pregnancy rate

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Embryo transfer involves placing the embryo(s) obtained before assisted reproduction technology (ART) into the uterus via a catheter advanced through the cervical canal. Despite the significant improvements in ART toward obtaining high-quality

embryos (1, 2), fewer than one-third of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) cycles progress to a clinical pregnancy or a live birth (3, 4).

Different aspects of the embryo transfer protocol have been studied in

relation to the outcomes of women undergoing IVF/ICSI. These factors can be divided in three main categories depending on the timing relative to the embryo transfer: pretransfer = dummy embryo transfer (5, 6), cervical and endometrial preparation (7-9); during transfer = catheter choice (10), ultrasound guidance (11), site of embryo placement (12); and posttransfer = bed rest (13), fibrin sealant (14), mechanical closure of the cervix (15).

Cervical mucus has been suggested to interfere with adequate embryo

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transfer in different ways: blocking the passage of embryos through the tip of the catheter (16), dragging the embryos back from the releasing site (17), or contaminating the intra-uterine environment with microorganisms (18, 19). It has been recommended that cervical mucus should be removed before embryo transfer to increase the rates of pregnancy and live birth (17, 20).

These possible advantages of removing the cervical mucus might be counteracted by the increase in transfer difficulty, which has been suggested as being associated with decreased pregnancy rates (21). In addition, touching the cervix and the endocervix might stimulate uterine contractions, with a consequent negative effect on pregnancy rates (22). Our study critically appraised the published randomized controlled trials (RCTs) reporting on the outcome of cervical mucus removal before embryo transfer in women undergoing IVF/ICSI.

## MATERIALS AND METHODS

Two of the present authors independently performed a literature search based on the PICO Method (23) for the following medical subject headings (MeSH): “embryo transfer,” “cervical mucus,” “pregnancy rate,” “in vitro fertilization,” and “intracytoplasmic sperm injection” in combination with the free terms “cervical discharge,” “aspiration,” “removal,” “irrigation,” or “outcome.” In addition to the standard medical databases (Medline, EMBASE, Science Citation Index Expanded, and Cochrane Central Register of Controlled Trials), we screened Google Scholar for grey literature. We used the “related citations” function, and we searched the references of the included studies to identify additional studies.

The inclusion criteria were defined as RCTs evaluating the outcome of cervical mucus removal before embryo transfer in women undergoing IVF/ICSI indexed earlier than October 2013. No filters were set for language, country of origin, blinding, or sample size. We selected our primary end points as clinical pregnancy, implantation, and live-birth rates, and secondary end points as retained embryos, difficult embryo transfer, and catheter bacterial contamination rates.

We used the software package RevMan 5.2.7 (24), provided by the Cochrane Collaboration, for statistical analysis. The risk ratio (RR) with a 95% confidence interval (CI) was calculated using the Mantel-Haenszel method for binary data variables. Heterogeneity was measured using the chi-square test and quantified (25) using  $I^2$ . In case of substantial heterogeneity ( $P < .10$  for chi-square test or  $I^2 > 50\%$ ), we reported the combined outcome calculated using the random effect model (26). We displayed the results from the meta-analysis as forest plots. The left column lists the names of the included studies, and the right column is a plot of the measure of effect for each of these studies incorporating confidence intervals represented by horizontal lines. The overall meta-analyzed measure of effect is plotted as a diamond, the lateral points of which indicate confidence intervals for this estimate.

The risk of bias was assessed by the guideline of the Cochrane Collaboration (27) and illustrated as a risk of bias graph. The summary of the evidence was generated using GradePro (version 3.2 for Windows), a tool provided by the

Cochrane Collaboration (28). No institutional review board approval was required because our study did not involve any patients.

## RESULTS

The systemic literature search identified 251 different studies related to removing the cervical mucus before embryo transfer. The PRISMA flow chart to explain the RCTs selection is shown in Supplemental Figure 1 (available online). The summary of the evidence is presented in Supplemental Figure 2 (available online). Eight RCTs (29–36) evaluating 1,715 women allocated to experimental group or control group for reporting the effect of cervical mucus removal before embryo transfer were included in the systematic review. There were 851 women in the experimental group and 864 women in the control group.

The characteristics of the included trials are shown in Supplemental Table 1 (available online), and the procedure protocols used for the women in all the trials are shown in Supplemental Table 2 (available online). The quality assessment of the included trials are shown in Supplemental Table 3 (available online). Variables used to achieve a combined outcome are shown in Table 1. One study (33) included multiple cycles of the same patients, so we used only the data from the first cycle to avoid bias. Three studies (29, 32, 33) were reported as full articles, and five studies were reported as abstracts (30, 31, 34–36). Two studies (37, 38) were excluded as being duplicate data of two other studies (33, 36) included in the systematic review. Five studies (29–33) reported the outcome of cervical mucus removal alone, and three studies (34–36) reported the outcome of cervical irrigation in addition to cervical mucus removal, so we analyzed them separately. There was complete agreement between authors in terms of included studies and extracted data.

### Methodologic Quality of Included Studies

Based upon the guidelines suggested by the Cochrane Collaboration, the quality of most of the included studies was moderate to poor because of inadequate concealment technique, blinding, and possible reporting bias in abstracts (Supplemental Fig. 3, available online). The combined outcome of all of the variables is given below.

### Clinical Pregnancy Rate

There was substantial heterogeneity [chi-square = 8.28,  $df = 4$ , ( $P = .08$ );  $I^2 = 52\%$ ] among the studies reporting cervical mucus removal. The clinical pregnancy rate was similar (RR 1.25; 95% CI, 0.96–1.63;  $z = 1.63$ ;  $P = .10$ ; Fig. 1) in the experimental group compared with the control group. In a subgroup analysis, three studies (29–31) reported cervical mucus removal by aspiration, and the combined calculation of clinical pregnancy rate was similar between the groups (RR 1.12; 95% CI, 0.85–1.49;  $z = 0.81$ ;  $P = .42$ ; Fig. 1). One study (32) evaluated cervical mucus removal with a cotton swab and reported a statistically significantly increased clinical pregnancy rate (RR 1.73; 95% CI, 1.33–2.27;  $P < .0001$ ) in the experimental group compared with the

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