Endometrial scratch injury before intrauterine insemination: is it time to re-evaluate its value? Evidence from a systematic review and meta-analysis of randomized controlled trials

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Objective: To assess the impact of endometrial scratch injury (ESI) on the outcomes of intrauterine insemination (IUI) stimulated cycles.
Design: Systematic review and meta-analysis.
Setting: Not applicable.
Patient(s): Infertile women undergoing one or more IUI stimulated cycles.
Intervention(s): Randomized controlled trials (RCTs) were identified by searching electronic databases. We included RCTs comparing ESI (i.e., intervention group) during the course of IUI stimulated cycle (C-ESI) or during the menstrual cycle preceding IUI treatment (P-ESI) with controls (no endometrial scratch). The summary measures were reported as odds ratio (OR) with 95% confidence-interval (CI).
Main Outcome Measure(s): Clinical pregnancy rate, ongoing pregnancy rate, multiple pregnancy rate, ectopic pregnancy rate, miscarriage rate.
Result(s): Eight trials were included in the meta-analysis, comprising a total of 1,871 IUI cycles. Endometrial scratch injury was associated with a higher clinical pregnancy rate (OR 2.27) and ongoing pregnancy rate (OR 2.04) in comparison with the controls. No higher risk of multiple pregnancy (OR 1.09), miscarriage (OR 0.80), or ectopic pregnancy (OR 0.82) was observed in patients receiving ESI. Subgroup analysis based on ESI timing showed higher clinical pregnancy rate (OR 2.57) and ongoing pregnancy rate (OR 2.27) in patients receiving C-ESI and no advantage in patients receiving P-ESI.
Conclusion(s): Available data suggest that ESI performed once, preferably during the follicular phase of the same cycle of IUI with flexible aspiration catheters, may improve clinical pregnancy and ongoing pregnancy rates in IUI cycles. Endometrial scratch injury does not appear to increase the risk of multiple pregnancy, miscarriage, or ectopic pregnancy. (Fertil Steril® 2018;109:84–96. ©2017 by American Society for Reproductive Medicine.)
Key Words: Endometrial injury, endometrial scratch, infertility, intrauterine insemination, pregnancy rate

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Intrauterine insemination (IUI) is currently considered the first line of treatment for subfertile couples because of its low cost, psychological burden, and easy access (1, 2). It is indicated to treat a variety of reproductive issues, including unexplained subfertility, minimal to mild endometriosis, male subfertility, and physical disability/psychosexual problems (3, 4). However, despite continuing investigations of ovarian stimulation protocols (1, 5) and luteal phase support (1, 6), pregnancy rates with IUI are still limited and quite variable, ranging from 10% to 25% (7). Investigators have ascribed these mixed results to defects in the implantation process (2, 8).

Endometrial scratch injury (ESI) is a technique that has been proposed to improve implantation in women undergoing treatment with assisted reproduction technology (ART) (9–11). Endometrial scratch injury consists of a voluntary endometrial trauma aimed at inducing an acute inflammatory process, prompting the local release of growth factors and proinflammatory cytokines (2, 8). The trauma can be achieved simply by a Pipelle biopsy, curette, or hysteroscope at low cost and with no need of analgesia or anaesthesia (9, 12, 13).

Presently ESI is offered in women undergoing in vitro fertilization (IVF) cycles (9, 10). Its application in patients undergoing IUI is far less common and less extensively documented (14). The only systematic review performed on this topic (14), which summarized evidence up to October 2015, included women who were both undergoing IUI and attempting to conceive via sexual intercourse, and found poor evidence quality in support of ESI use. Indeed, the results provided by Lensen et al. (14) reflected a high risk of bias due to the heterogeneity among their populations and poor methodological quality of the studies.

From October 2015 to date, several new randomized controlled trials (RCTs) have evaluated ESI before IUI (2, 8, 15, 16). Because the cumulative number of patients and studies almost doubled over this span of time, a new summary of evidence is needed. Our updated, systematic review and meta-analysis assessed the impact of ESI on the outcomes of IUI stimulated cycles.

MATERIALS AND METHODS

Study Design

We conducted a systematic review and meta-analysis of all RCTs investigating the impact of endometrial scratch injury on IUI outcomes. The review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (17). As this study was a systematic review and meta-analysis of published data, formal ethics approval was not required.

Inclusion Criteria

The included studies were limited to RCTs with results published in English. The populations comprised infertile women undergoing one or more IUI stimulated cycles. The intervention under study was endometrial injury during the course of an IUI stimulated cycle or during the menstrual cycle preceding the IUI treatment. Infertile women undergoing IUI stimulated cycles but not receiving an endometrial injury composed the control groups.

Outcomes

Our primary goal was to compare the outcomes of IUI stimulated cycles in patients receiving ESI with those of patients not receiving the intervention (controls). The secondary goal was to evaluate the influence of ESI timing on IUI outcomes by cross-matching patients receiving ESI concomitant to the IUI cycle (C-ESI) with those receiving ESI in the cycle preceding IUI (P-ESI) versus control patients who received no ESI. We also evaluated pain and potential complications associated with ESI.

The outcome measures were defined as follows. Clinical pregnancy rate (CPR) per cycle was defined as the presence of a gestational sac on transvaginal ultrasound or other definitive clinical signs. Ongoing pregnancy rate (OPR) per cycle was defined as the presence of a living intrauterine fetus on transvaginal ultrasound at 12 weeks' gestation. Multiple pregnancies (MPR) per cycle were defined as the presence of more than one gestational sac on transvaginal ultrasound. Miscarriage rate (MR) per clinical pregnancy was defined as fetal loss before 20 weeks' gestation. Ectopic pregnancy rate (EPR) per clinical pregnancy was defined as a pregnancy implanting outside the uterus.

Search Strategy

A systematic literature search was conducted on the electronic databases PubMed, Embase, ScienceDirect, the Cochrane library, Clinicaltrials.gov, the Cochrane Central Register of Controlled Trials, the EU Clinical Trials Register, and World Health Organization International Clinical Trials Registry Platform up to July 18, 2017 (without date restriction). The search used specific key words and database indexing terminology. The key search terms included endometrial injury *OR* endometrial scratch *OR* endometrial biopsy *OR* endometrial sampling [Mesh/Emtree] *AND* insemination *OR* IUI.

Study Selection and Data Extraction

Two authors (A.V., M.N.) independently screened the titles and abstracts of the studies obtained via our search strategy, and each independently obtained and assessed the text of the potentially relevant studies for inclusion in the review. A manual search of the reference lists of the retrieved studies and available review articles was successively performed to avoid missing any relevant publications. The same authors (A.V., M.N.) also independently extracted data from the studies about their features and included populations (country, time when the study was performed, number of participants, and main inclusion criteria), ovarian stimulation cycles (drugs employed for ovarian stimulation, timing of ovulation induction), and IUI outcomes. If more than one study was published for the same cohort with identical end points, the report containing the most comprehensive information on the population was included to avoid overlapping populations. One other author (C.S.) independently reviewed

the selection and data extraction processes. The results were compared, and any disagreements were discussed and resolved by consensus.

Risk of Bias

Two reviewers (A.M., M.N.) independently judged the methodological quality of the studies included in this meta-analysis using the Cochrane Collaboration's tool for bias risk assessment (18). Their recommended approach for assessing the risk of bias in studies is a two-part tool that addresses seven specific domains: sequence generation and allocation concealment (*selection bias*), blinding of participants and providers (*performance bias*), blinding of outcome assessor (*detection bias*), incomplete outcome data (*attrition bias*), selective outcome reporting (*reporting bias*), and other sources of bias (*other bias*). None of the included studies was blinded to patients, clinicians, or assessors, but this factor was unlikely to generate bias because of the impossibility of blinding ESI. Performance bias was considered as low for all the included studies, and detection bias was evaluated according to the presence or absence of systematic differences between groups potentially affecting the outcomes determined by the assessors (i.e., heterogeneity in ovarian stimulation before IUI). For the estimation of reporting bias, we evaluated the study protocols, when available. When they were not available, we compared the end points of each study with the results provided by the investigators to identify any possible inconsistencies. For the "other bias" domain, all studies without a recorded protocol in national or international registry were considered at high risk of bias. Any discrepancies in an author's judgment were referred to a third reviewer (A.D.S.S.) and were resolved by consensus.

Statistical Analysis

The statistical analysis was performed using Review Manager version 5.2 (Cochrane Collaboration, Software Update). Dichotomous variables were analyzed using odds ratio (OR) and 95% confidence interval (95% CI). $P<.05$ was considered statistically significant. To assess heterogeneity, the I^2 statistic was used. (The value of I^2 describes the percentage of variability in point estimates that is due to heterogeneity rather than sampling error.) We considered the degree of heterogeneity to be low when I^2 was $<30\%$, moderate if between 30% and 50%, and high if $>50\%$. When the heterogeneity was moderate or high, we reported both the random and the fixed outcomes to emphasize the role of heterogeneity among the studies. When the heterogeneity was low, the fixed and the random models gave similar values, and the results were reported only in a fixed effects model using the more conservative value.

In addition, the influence of individual studies on the overall results was explored by serially excluding each study and different study subgroups (according to the authors' methodological quality judgment) in a sensitivity analysis. Moreover, a subgroup analysis was performed to evaluate the specific influence of different ESI timings on the pooled OR.

We aimed to assess publication bias (related to size of the trials) with the use of a funnel plot (a plot of the effect estimate from each study against the standard error) if at least 10 studies were included in the meta-analysis, according to Cochrane Handbook's recommendations (*Cochrane Handbook* 10.4.3.1, "Recommendations on Testing for Funnel Plot Asymmetry"). Nevertheless, not enough studies were included in the final meta-analysis (eight studies).

Grading of Evidence

Two authors (A.V. and M.N.) independently assessed the body of evidence for the primary outcome of the meta-analysis using GRADE (Grading of Recommendations Assessment Development and Evaluation Working Group) (19) methodology. (The GRADE Pro software is available at https://gradepro.org/.) The GRADE criteria allow the evaluation of certainty of evidence in terms of study design, risk of bias, indirectness, inconsistency, imprecision, large effect size, plausible confounding, dose response gradient, and publication bias. We did not evaluate the dose response gradient (intervention was a dichotomous variable). We aimed to exclude outlier studies from the final assessment of quality of evidence if they significantly reduced the heterogeneity of the analyzed populations (but without producing weakening of the final sample size or alterations in conclusive results). However, the degree of heterogeneity was extremely low, so no studies were excluded. Disagreements between reviewers were resolved by discussion and adjudication of a third reviewer (A.D.S.S.).

RESULTS

Study Selection

The literature search, based on our predefined key search items, identified 3,554 publications after removing duplicates. The titles of these publications were screened, resulting in 96 studies considered potentially eligible to be included in the review. Of the total of relevant publications identified, 83 studies were excluded after examination of their abstracts, and 13 studies were further evaluated. After the evaluation of the full publication text, five RCTs were additionally excluded: one study comparing the effects of office hysteroscopy with endometrial scratch versus office hysteroscopy on IUI outcomes (13), two clinical trials that were ongoing at the time of data collection (20, 21), and two additional studies deemed ineligible for only investigating the effect of ESI on natural conception (22, 23). In the end, a total of eight studies (2,8,15,16,24–27) were included in the present meta-analysis after applying our inclusion criteria (see Supplemental Fig. 1, available online).

Included Studies

The eight studies included comprised a total of 1,871 IUI cycles and 1,523 participants, with sample sizes (of IUI cycles) ranging from 144 cycles (2) to 415 cycles (27). Patients received ESI in 998 IUI cycles, and ESI was not performed in 873 IUI cycles. The total number of cycles with C-ESI was 747, and the number with P-ESI was 251. Five studies

TABLE 1

Endometrial scratch injury in intrauterine insemination: general features of the studies.

Study	Country	Period	Participants	Main inclusion criteria	Ovarian stimulation	Intervention and timing	Controls	Outcomes
Abdelhamid, 2013 (24)	United Arab Emirates	03/2010–03/2012	150 women undergoing IUI	Unexplained infertility Age 22–35 y Semen count not less than 15 mil/mL, motility Grade a + b not less than 40% before wash	Letrozole, 2.5 mg/d on days 3–7 of menstrual cycle, then rFSH, 75 IU R-hCG (250 mg) at follicle size 18–19 mm	Tao brush endometrial sampling Group A (n = 50): on days 8–9 of same cycle Group B (n = 50): on days 8–9 of the cycle preceding IUI	Group C (n = 50): no intervention	CPR, MPR
Zarei et al., 2014 (26) [IRCT201207 0810210N1][a]	Iran	01/2011–05/2012	146 women undergoing IUI (total of 231 IUI cycles) Dropout of two women in group A	Unexplained infertility Age 18–40 y Mild male factor infertility (semen count between 5–15 mil/mL, total motility not less than 40%) Mild endometriosis	CC, 100 mg/d on days 5–9 of menstrual cycle, then rFSH, 100 IU U-hCG (10,000 IU) when serum E_2 level <1,500 pg/mL	Novak curette biopsy Group A (n = 72; IUI cycles = 126): on days 6–8 of the cycle preceding IUI	Group B (n = 72; 105 IUI cycles): no intervention	CPP, OPR, MR, MPR
Maged et al., 2016 (27)	Egypt	01/2010–01/2015	146 women undergoing IUI	Unexplained infertility Age <40 y FSH level ≤12 mIU/mL At least 1 patent tube Normal semen analysis (>20 mil/mL, >50% total motility, >30% normal forms	CC, 100 mg/d on days 3–7 of menstrual cycle, then hMG, 150 IU U-hCG (5,000 IU) when >2 follicles at ≥17 mm or urinary LH surge	No. 8 neonatal feeding tube Group A (n = 77; IUI cycles = 200): 24–36 h before IUI	Group B (n = 77; 215 IUI cycles): no intervention	CPR, MR, EPR, MPR
Wadhwa et al., 2015 (25) [CTRI/2013/04/ 003521][a]	India	08/2012–03/2014	251 women undergoing IUI Dropout of 11 women in	Age 18–38 y At least 1 patent tube Mild male	CC or CC + hCG or CC + hCG + hMG	Endometrial aspiration cannula Group A (n = 75): before day 6 of same cycle	Group B (n = 75): no intervention	CPR, MR, MPR

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TABLE 1

Continued.

Study	Country	Period	Participants	Main inclusion criteria	Ovarian stimulation	Intervention and timing	Controls	Outcomes
			group A Dropout of 11 women in group B	factor infertility		Group B (n = 75): on days 19–24 of cycle preceding IUI		
Baha Eldin et al., 2016 (16) [NCT02542280][a]	Egypt	07/2013–08/2015	360 women undergoing IUI Dropout of 11 + 5 women in group A	Age 20–35 y At least 1 patent tube Mild male factor infertility	CC, 100 mg/d on days 2–6 of menstrual cycles, + hMG 75 IU (from day 3/7 on alternating days) U-hCG (5,000 IU) at follicle size ≥18 mm	Pipelle Group A (n = 169): on days 5–7 of same cycle	Group B (n = 175): no intervention	CPR
Soliman and Harira, 2017 (8)	Egypt	03/2013–05/2015	233 women undergoing IUI Dropout of 7 women	Unexplained infertility Mild male factor infertility	CC, 100 mg/d on days 2–6 of menstrual cycle, then hMG, 75 IU U-hCG (10,000 IU) for ovulation triggering	Embryo mucus aspiration catheter Group A (n = 106): on day 7 of same cycle	Group B (n = 106): no intervention	CPR, OPR, MR
Ashrafi et al., 2017 (15) [IRCT2015072711 41N19][a]	Iran	01/2013–01/2014	169 women undergoing IUI Dropout of 19 women	≥2 previous IUI failures Age <40 y Normal uterine anatomy and HSG result Normal semen analysis	CC, 100 mg/d, or letrozole, 2.5 mg/d, on days 3–7 of menstrual cycle, and hMG, 75–150 IU (from days 6 to 8) U-hCG (10,000 IU) at follicle size ≥18 mm	Pipelle Group A (n = 75): on days 8–9 of same cycle	Group B (n = 75): no intervention	CPR, MR
Goel et al., 2017 (2) [CTRI/2015/12/00 6419][a]	India	07/2014–07/2016	144 women undergoing IUI	Age 21–35 y BMI 18.5–29.9 kg/m^2 Euthyroid state FSH <10 mIU/mL At least 1 patent tube	CC, 50 mg/d on days 2–6 of menstrual cycle U-hCG (5,000 IU) at follicle size ≥18 mm	Karman cannula no. 4 Group A (n = 72): on day 8 of same cycle	Group B (n = 72): no intervention	CPR, OPR, MR, EPR

Note: BMI = body mass index; CC = clomiphene citrate; CPR = clinical pregnancy rate; E_2 = estradiol; EPR = ectopic pregnancy rate; FSH = follicle-stimulating hormone; hMG = human menopausal gonadotropin; HSG = hysterosalpingography; IUI = intrauterine insemination; LH = luteinizing hormone; MPR = multiple pregnancy rate; MR = miscarriage rate; OPR = ongoing pregnancy rate; rFSH = recombinant follicle-stimulating hormone; R-hCG = recombinant human chorionic gonadotropin; U-hCG = urinary human chorionic gonadotropin.

[a] Registered trial with identification code.

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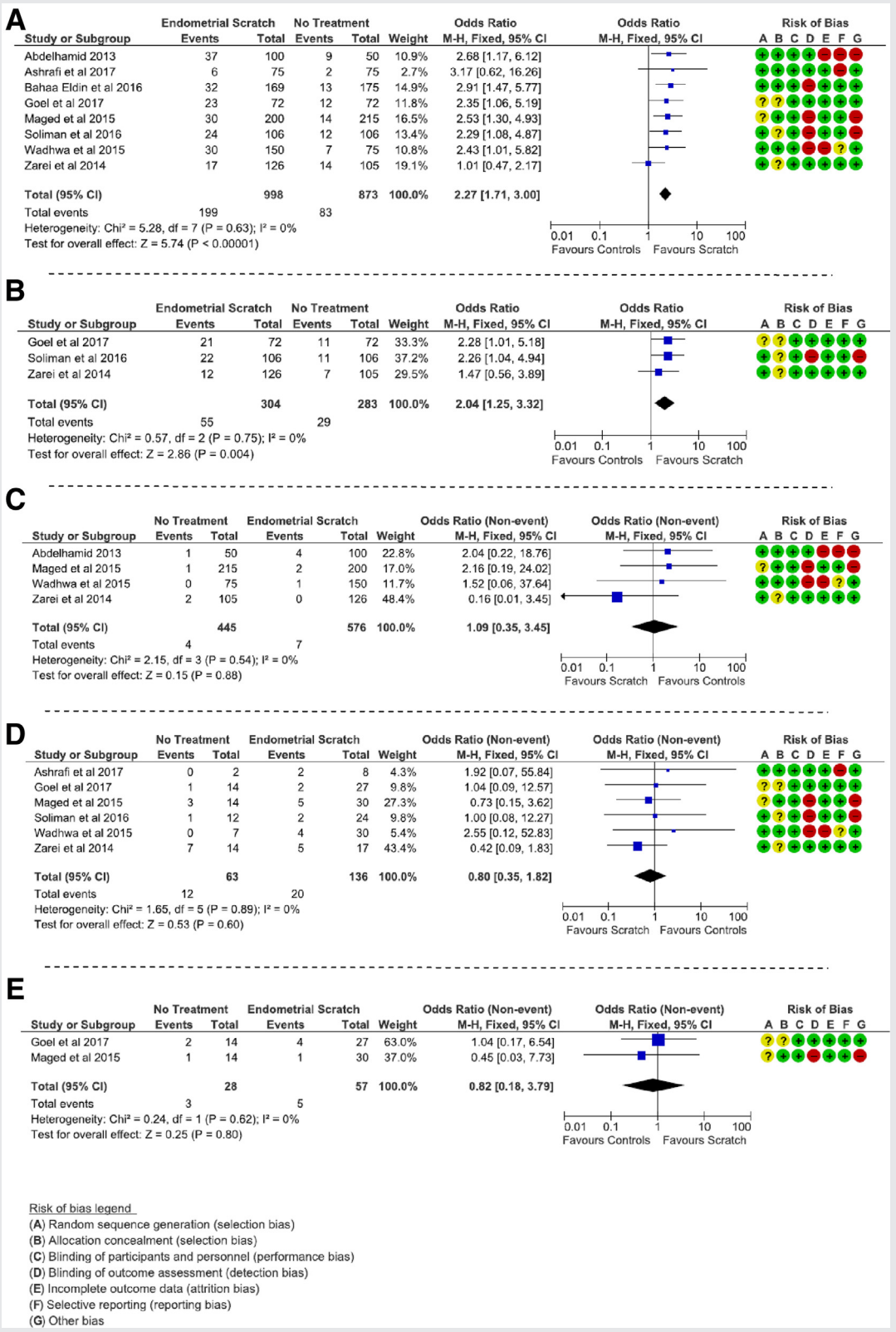
FIGURE 1



Endometrial scratch versus no intervention. (**A**) Clinical pregnancy rate. (**B**) Ongoing pregnancy rate. (**C**) Multiple pregnancy rate. (**D**) Miscarriage rate. (**E**) Ectopic pregnancy rate.

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(2, 8, 15, 16, 27) compared C-ESI with no intervention, one study (26) compared P-ESI with no intervention, and two studies (24, 25) compared C-ESI, P-ESI, and no treatment. A summary of the main characteristics of the included studies is available in Table 1.

Types of patients. Maged et al. (27) enrolled patients with primary or secondary unexplained infertility. Zarei et al. (26) recruited couples with unexplained infertility, mild male factor infertility, or mild endometriosis. In three studies (15, 24, 25) the couples had unexplained infertility, mild male factor infertility, or ovulatory dysfunction. Three studies (2, 8, 16) enrolled couples with mild male factor infertility or unexplained infertility.

In five studies (8, 15, 16, 24, 25) the analysis was conducted on a single IUI cycle attempt. In three studies (2, 26, 27) the patients underwent up to three IUI attempts. In Soliman and Harira (8) and Ashrafi et al. (15) all patients recruited had one or at least two previous IUI failures, respectively.

Types of IUI cycles. For follicle recruitment, all the studies used a 5-day regimen of either clomiphene citrate at 100 mg/day, except Goel et al. (2) who used 50 mg/day, or letrozole at 2.5 mg/day in the early follicular phase (mainly from days 2 to 6 or days 3 to 7). Only Bahaa Eldin et al. (16) combined clomiphene citrate with human menopausal gonadotropin (hMG) at 75 IU on alternating days. After priming with clomiphene citrate or letrozole, ovarian stimulation was continued with the administration (single, double, or daily) of hMG or recombinant follicle-stimulating hormone (FSH), except in two studies: Goel et al. (2) administered only clomiphene citrate before ovulation induction, and Wadhwa et al. (25) administered only clomiphene citrate to a subgroup of patients.

Ovulation induction was triggered with 5,000–10,000 IU of urinary human chorionic gonadotropin (U-hCG) in all studies, except for a subgroup in Wadhwa et al. (25), on the basis of estradiol levels (>1,500 pg/mL) (26), urinary luteinizing hormone (LH) surge (27), or transvaginal ultrasound showing preovulatory follicles (2, 8, 15, 16, 24, 25).

Type of intervention. In all the studies ESI was performed once. The majority of trials used a flexible aspiration catheter (Pipelle, neonatal feeding tube, Endocell aspiration cannula, embryo mucus aspiration catheter, or Karman cannula), except Abdelhamid (24), who employed a cytobrush (a Tao brush), and Zarei et al. (26) who used a Novak curette (to perform a small biopsy on the anterior and posterior uterine wall).

For timing, C-ESI was performed between days 5 and 9 in six studies (2, 8, 15, 16, 24, 25). Maged et al. (27) performed C-ESI 24 to 36 hours before IUI. For P-ESI, two studies (24, 26) performed the intervention in the interval between days 6 and 9. Wadhwa et al. (25) performed the intervention on days 19 to 24 (of the cycle preceding IUI).

Assessment of the Risk of Study Bias

Selection bias. All of the studies used an adequate method of random sequence generation, except for Goel et al. (2) and Maged et al. (27), whose studies were judged at unclear risk of selection bias because they did not provide their randomization information. Moreover, in three studies (2, 8, 26) the method of allocation concealment was not reported, so they were judged to be at unclear risk of selection bias. The remaining studies (15, 16, 24, 25, 27) were considered at low risk of bias for this domain.

Performance bias. Blinding of personnel and participants was not possible for the types of intervention performed, so performance bias was unlikely to influence the outcomes evaluated. Nevertheless, all studies were judged at low risk of bias.

Detection bias. Two studies (8, 25) were considered at high risk or unclear risk of detection bias, respectively, due to the heterogeneity in the ovarian stimulation protocols in the study population and because of concerns about their calculation of MR (by subtracting biochemical pregnancies from clinical pregnancies). Another study (27) was considered to be at high risk of bias due to the heterogeneity of results between the first and second IUI attempts in terms of CPR and OPR (no beneficial effect at the first attempt, and large beneficial effect at the second attempt). One additional study (16) was judged to be at high risk of bias due to the inclusion of polycystic ovary syndrome patients, potentially affecting the comparison between, groups. The remaining studies (2, 15, 24, 26) were judged to be at low risk of bias.

Attrition bias. Two studies (8, 24) were judged to be at high risk of attrition bias because of missing data outcomes. Abdelhamid (24) did not report the mean β-human chorionic gonadotropin values, and Soliman and Harira (8) had 15 patients in the ESI group drop out. The other studies were at low risk of attrition bias.

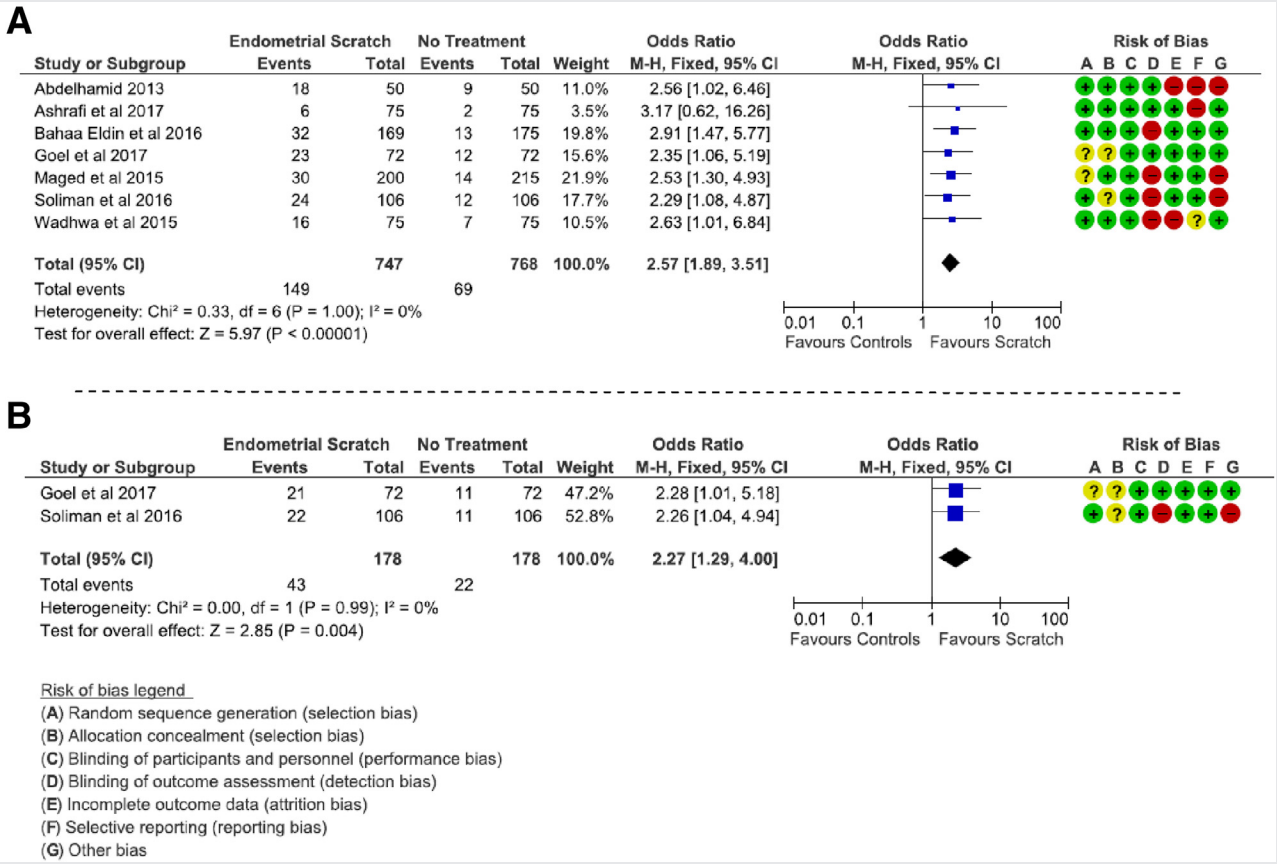
Reporting bias. Two studies (24, 25) were judged at high risk of bias for selective data reporting. Abdelhamid (24) reported data about clinical and multiple pregnancies, even stating that patients were evaluated until the pregnancy test. Wadhwa et al. (25) did not report the precise number of patients who received different ovarian stimulation protocols. The other studies (2, 8, 15, 16, 26, 27) were considered at low risk of reporting bias.

Other bias. The absence of a registered protocol in agreement with the study's performance was considered an additional source of bias. For three studies (8, 24, 27) a protocol registration was not available. For the remaining five studies (2, 15, 16, 25, 26) a protocol registration was found in international/national registers (Supplemental Fig. 2, available online).

Effects of Intervention

ESI versus no intervention. For CPR, the analysis involved a total number of 1,871 IUI cycles (n = 998 with ESI, and n = 873 with no intervention) from eight studies (2,8,15,16,24–27), with 282 clinical pregnancies recorded (n = 199 in patients receiving ESI, and n = 83 in controls). The cumulative CPR was 15.07%. The overall results statistically significantly favored ESI (OR 2.27; 95% CI, 1.71–3.00; $P<.00001$), with no heterogeneity among studies ($I^2 = 0$) (Fig. 1A).

FIGURE 2



Endometrial scratch in the same cycle versus no intervention. (**A**) Clinical pregnancy rate. (**B**) Ongoing pregnancy rate.

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For OPR, three studies (2, 8, 26) with 587 participants were included, of whom 304 were in the ESI group and 283 in control group. Cumulative number of ongoing pregnancies was 84 (14.21%). The pooled OPR associated with ESI result was considerably greater in comparison with the control group (OR 2.04; 95% CI, 1.25–3.32; $I^2 = 0$; $P = .004$) (see Fig. 1B).

The MPR of 1,021 IUI cycles (576 with ESI, and 445 with no intervention) from four studies (24–27) was analyzed. The total number of events was low (n = 11, MPR 1.08%) with no statistically significant differences among the groups (OR 1.09; 95% CI, 0.35–3.45; $I^2 = 0$; $P = .88$) (see Fig. 1C).

For MR, 32 miscarriages among 199 clinical pregnancies (from six studies: 2, 8, 15, 25–27) were observed (16.08%). No difference emerged from comparisons of intervention and control groups (OR 0.80; 95% CI, 0.35–1.82; $I^2 = 0$; $P = .60$) (see Fig. 1D).

Two studies (2, 27) comparing C-ESI with no intervention reported eight ectopic pregnancies. The EPR was high (9.41%), but no statistically significant differences were found between the intervention and control groups (OR 0.82; 95% CI, 0.18–3.79; $I^2 = 0$; $P = .80$) (see Fig. 1E).

C-ESI versus no intervention. For CPR, the analysis involved a total of 1,515 IUI cycles (n = 747 with C-ESI, and n = 768 with no intervention) from seven studies (2, 8, 15, 16, 24, 25, 27). The cumulative CPR was 14.39%. The pooled CPR results were statistically significantly higher in the patients who received C-ESI in comparison with the control group (OR 2.57; 95% CI, 1.89–3.51; $I^2 = 0$; $P < .00001$) (Fig. 2A).

For OPR, two studies (2, 8) with 356 participants were included (n = 176 in each group). The cumulative number of ongoing pregnancies was 65 (cumulative OPR 18.26%). Pooled OPR results were considerably greater in the ESI group compared with controls (OR 2.27; 95% CI, 1.29–4.00, $I^2 = 0$; $P = .004$) (see Fig. 2B).

For MPR, among 665 IUI cycles analyzed from three studies (24, 25, 27), only seven events were observed (MPR 1.05%) with no statistically significant differences found the among groups (OR 2.29; 95% CI, 0.51–10.35; $I^2 = 0$; $P = .28$).

The MR comprised 19 miscarriages among 164 clinical pregnancies (11.58%) (from five studies: 2, 8, 15, 25, 27). No difference emerged from comparisons of the intervention and control groups (OR 1.17; 95% CI, 0.42–3.26; $I^2 = 0$; $P = .76$).

The EPR results were analogous to those reported in the previous section.

P-ESI versus no intervention. For CPR, the analysis involved a total of 481 IUI cycles (n = 251 with P-ESI, and n = 230 with

TABLE 2

Evidence profile: endometrial scratch injury compared with no intervention in patients undergoing IUI cycles.

Outcomes	Anticipated absolute effects (95% CI)[a] Risk without ESI	Risk with ESI	Relative effect OR (95% CI)	No. of participants (no. of RCTs)	Quality of the evidence (GRADE)[b]
Clinical pregnancy rate	95/1,000	193/1,000 (152–240)	2.27 (1.71–3.00)	1,871 (8)	⊕⊕◯◯, Low[c,d,e]
Ongoing pregnancy rate	102/1,000	189/1,000 (125–275)	2.04 (1.25–3.32)	587 (3)	⊕⊕◯◯, Low[d,e,f]
Multiple pregnancy rate	9/1,000	10/1,000 (3–30)	1.09 (0.35–3.45)	1,021 (4)	⊕⊕◯◯, Low[d,e,g]
Miscarriage rate	190/1,000	158/1,000 (76–300)	0.80 (0.35–1.82)	199 (6)	⊕◯◯◯, Very low[d,e,h,i]
Ectopic pregnancy rate	107/1,000	90/1,000 (21–313)	0.82 (0.18–3.79)	85 (2)	⊕◯◯◯, Very low[d,e,j,k]

Note: Question: Should ESI be used for patients undergoing IUI cycles? Patient or population: women undergoing IUI stimulated cycles. Intervention: ESI. Comparison: No ESI. CI = confidence interval; ESI = endometrial scratch injury; OR = odds ratio; IUI = intrauterine insemination; RCT = randomized controlled trial.

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b] GRADE Working Group grades of evidence. High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[c] Four studies at unclear/high risk of selection bias, four studies at unclear/high risk of detection bias, two studies at high risk of attrition bias, two studies at high/unclear risk of reporting bias, and three studies at high risk of other bias.

[d] Heterogeneity in endometrial scratch injury techniques/timing and in ovarian stimulation protocols.

[e] Possible small study effect.

[f] Three studies at unclear risk of selection bias, and one study at high risk of detection bias and other bias.

[g] Two studies at unclear risk of selection bias, one study at high risk of detection bias, one study at high risk of attrition bias, two studies at high/unclear risk of reporting bias, and two studies at high risk of other bias.

[h] Four studies at unclear/high risk of selection bias, two studies at high risk of detection bias, one study at high risk of attrition bias, two studies at high/unclear risk of reporting bias, and two studies at high risk of other bias.

[i] Small number of cases (n = 199) and events (n = 32).

[j] One study at unclear risk of selection bias, and one study at unclear risk of selection bias and high risk of other bias.

[k] Small number of cases (n = 85) and events (n = 8).

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no intervention) from three studies (24–26). The cumulative CPR was 16.63%. The pooled CPR results were higher in patients who received P-ESI in comparison with the control group, but were not statistically significant with the random effect model (I^2 = 37%; fixed effect: OR 1.70; 95% CI, 1.04–2.79; *P*=.04; random effect OR 1.75; 95% CI, 0.92–3.33; *P*=.09) (Supplemental Fig. 3, available online).

For OPR, one study (26) with 231 participants was included. The study showed no difference in OPR between the P-ESI group and the controls (OR 1.47; 95% CI, 0.56–3.89; *P*=.43).

For MPR, among 481 IUI cycles analyzed from three studies (24–26), only five events were observed (MPR 1.04%) with no differences among the groups (I^2 = 37%; fixed effect OR 0.65; 95% CI, 0.13–3.30; *P*=.61; random effect OR 0.69; 95% CI, 0.06–8.11; *P*=.76).

The MR comprised 13 miscarriages among 52 clinical pregnancies (25%) (from two studies (25, 26). No differences were observed between the intervention and control groups (OR 0.54; 95% CI, 0.15–1.99, I^2 = 0; *P*=.35).

No data were available for comparing the EPR.

C-ESI versus P-ESI. For OPR and MPR, two studies (24, 25) with 250 participants were analyzed (125 in each group). No differences were found in pooled OPR (OR 1.04; 95% CI, 0.59–1.84; I^2 = 0; *P*=.88) (Supplemental Fig. 4, available online) or MPR (OR 0.71; 95% CI, 0.14–3.68; I^2 = 0; *P*=.68) between the two groups.

For MR, 4 miscarriages among 30 clinical pregnancies (13.33%) were found by one study (25), with no difference between the C-ESI and P-ESI groups (OR 0.33; 95% CI, 0.03–3.64; *P*=.60).

No data available for comparing CPR or EPR.

Sensitivity Analysis

Primary outcomes. The serial exclusion of each study from the meta-analysis of ESI versus no intervention did not produce statistically significant changes in CPR (from OR 2.24; 95% CI, 1.69–2.98; to OR 2.56; 95% CI, 1.89–3.47), with the exclusion of Ashrafi et al. (15) and Zarei et al. (26). It produced no changes in OPR (from OR 1.91; 95% CI, 1.04, 3.51; to OR 2.27; 95% CI, 1.29–4.00), with the exclusion of Goel et al. (2) and Soliman and Harira (8). It produced no changes in MPR (from OR 0.87; 95% CI, 0.23–3.36; to OR 1.96; 95% CI, 0.46–8.42), with the exclusion of Maged et al. (27) and Zarei et al. (26). It produced no changes in MR (from OR 0.70; 95% CI, 0.29–1.67; to OR 1.10; 95% CI, 0.39–3.06), with the exclusion of Wadhwa et al. (25) and Zarei et al. (26). It produced no changes in EPR (from OR 1.04; 95% CI, 0.17–6.54; to OR 0.45; 95% CI, 0.03–7.73), with the exclusion of Maged et al. (27) and Goel et al. (2). Similarly, the exclusion of all studies with a high risk of bias in at least two domains (8,17,24–26) did not cancel the benefits observed in the ESI group (OR 1.75; 95% CI, 1.04–2.93; *P*<.03).

Secondary outcomes. The sensitivity analysis for all the evaluated end points produced no changes in the comparison between C-ESI and no treatment. A statistically significant increase in CPR of patients receiving P-ESI (OR 2.51; 95% CI, 1.29–4.89; $P=.007$; $I^2 = 0$) was observed by excluding Wadhwa et al. (25). No other change was found in the comparison P-ESI versus controls, and no modifications were obtained from the singular exclusion of each study in the comparison of P-ESI with C-ESI. The sensitivity analysis based on study quality, when possible (due to the low number of studies meta-analyzed for secondary outcomes), provided no substantial changes to the results.

Pain and Complications

None of the studies quantitatively measured the patients' discomfort during ESI (i.e., with a visual analogue scale), and no information was reported about the potential short-term or long-term complications. However, Wadhwa et al. (25) mentioned that no patients receiving ESI treatment reported experiencing severe pain or discomfort. Similarly, Maged et al. (27) reported in the methods section that only mild cramping similar to menstrual pain may be felt during the scratch, and mild spotting may occur after withdrawal of the catheter.

Overall Quality of Evidence

The overall quality of evidence was rated as low for CPR, OPR, and MPR, and very low for MR and EPR (Table 2). The studies were heterogeneous for ESI timing and methodology, as well as for ovarian stimulation protocols. Moreover, several studies were judged as being at unclear/high risk of selection bias (2, 8, 26, 27), detection bias (8, 16, 25, 27), attrition bias (24, 25), or reporting bias (15, 24, 25), which led us to downgrade the cumulative evidence quality. Finally, possible publication bias due to positive results and small study effect was strongly suspected.

DISCUSSION

The real effectiveness of ESI in improving the reproductive outcomes of patients undergoing ART is widely debated in the literature. Some investigators consider the technique ineffective and prone to patient discomfort and a risk of Asherman's syndrome (10, 28, 29). Others have promoted its effectiveness for improving the rate of embryo implantation, with good tolerability and a low risk of infectious events (27, 30, 31).

Beyond the open debate, a recent international survey (12) performed across Australia, New Zealand, and the United Kingdom demonstrated that ESI is broadly offered by infertility care providers to patients undergoing ART. Nevertheless, ESI recommendations generally are limited to women undergoing IVF, especially after repeated embryo-implantation failures (recommended by 92% of physicians) (12, 32). Indeed, only 3.6% of clinicians currently offer ESI to patients before IUI, suggesting poor knowledge about the beneficial effects of ESI in such patients (12). The prior systematic review investigating this topic (14) raised uncertainties about the capability of ESI to improve CPR and OPR in women undergoing IUI or attempting to conceive via sexual intercourse, but the results provided by Lensen et al. (14) were affected by poor quality of evidence, mainly due to high risk of bias in the included studies—the investigators included data from meeting abstracts (33) and data from an unpublished master's thesis (34)—and the high degree of heterogeneity: only some patients received ovarian stimulation, some patients attempting natural conception (22), and others were undergoing IUI (24). However, since the publication of the Lensen et al. review (14) four additional RCTs have been published (2, 8, 15, 16). Reports for this technique have doubled in last 2 years, necessitating a new summary. We analyzed the impact of ESI on the outcomes of patients undergoing IUI stimulated cycles, based exclusively on data from RCTs.

Main Findings

Eight RCTs (2,8,15,16,24–27) were included in our systematic review, comprising a total of 1,871 IUI cycles (and 1,523 participants). In 998 IUI cycles the patients received ESI (747 C-ESI and 251 P-ESI), and in 873 IUI cycles no intervention was performed.

Effects of intervention on IUI outcomes. Concerning the primary outcome (including both C-ESI and P-ESI in the intervention group), the overall comparison between ESI and controls showed statistically significant advantages in patients receiving ESI in terms of CPR (OR 2.27; $P<.00001$; data from 1,871 IUI cycles) and OPR (OR 2.04 $P=.004$; data from 587 IUI cycles). Nevertheless, the body of evidence was judged as moderate for CPR and as low for OPR. In addition, ESI was not associated with a higher risk of MPR (OR 1.09; $P=.88$), MR (OR 0.80; $P=.60$), or EPR (OR 0.82; $P=.80$) in comparison with controls, even if the quality of evidence was low (for MPR) or very low (for MR and EPR).

Concerning the secondary outcomes, C-ESI was associated with a statistically significantly higher CPR (OR 2.57; $P<.00001$) and OPR (OR 2.27; $P=.004$) in comparison with the controls. No advantage was shown for P-ESI in terms of CPR (OR 1.75, $P=.09$, random effect model) or OPR (OR 1.47; $P=.43$), while the MPR, MR, and EPR (evaluated only for C-ESI) did not substantially differ from those of the controls. Finally, the comparison between C-ESI and P-ESI, based on data from two studies (24, 25), showed no substantial difference in terms of OPR, MPR, or MR (CPR and EPR were not evaluable). However, the results of the comparison were affected by the small number of participants included in the analysis (n = 250) and the two studies' different methodological concerns (24, 25).

The sensitivity analysis and the analysis of subgroups produced no substantial modifications to the primary outcome results, which confirmed their robustness. The exclusion of one study (25) from the comparison between C-ESI and controls (secondary outcomes) produced a statistically significant increase in the CPR of patients receiving P-ESI (OR 2.51; $P=.007$), suggesting that the result was affected by inconsistent data.

Pain and complications. No studies measured the patients' pain (e.g., with a visual analogue scale) during the ESI procedure. Only Wadhwa et al. (25) reported that no severe pain or discomfort was experienced by patients receiving ESI, but the investigators did not provide quantitative data. In this regard, unpublished data from Mahey et al. (33) included in a recent review (14) showed an average pain sensation (measured with visual analogue scale) of 6/10 when a small (no. 4) Karman cannula was used in the procedure. Thus, even if pain related to ESI is not expected to be severe, this aspect certainly needs further investigation.

In addition, no data about the short-term or long-term complications of ESI were reported in the evaluated studies. The literature lacks this information as well. The concerns raised by some investigators about the potential risk of intrauterine adhesions after ESI should encourage future research to counter such speculations.

Implications

In spite of recent efforts in reproductive surgery (35, 36), targeted drugs (37–39), preimplantation genetics (40), and ovarian stimulation protocols (41, 42), the path from follicle to ongoing pregnancy remains mysterious (43, 44) and burdened by empiricism (45, 46). There is an absolute need for novel, cost-effective, and evidence-based strategies to improve the success of ART.

Endometrial scratch injury is a simple, low-cost procedure (mean cost of 140 Australian dollars = €95.1) (12) that can be performed with a flexible catheter, such as a Pipelle (15). It does not require analgesia, and it can be performed as part of an outpatient regimen (2, 12). The rationale of administering a voluntary endometrial trauma is to induce the local release of cytokines (such as interleukin 6 and 11), growth-factors (including tumor necrosis factor-α and amphiregulin), and enzymes and adhesion molecules (such as laminin α4, integrin α6, matrix metalloproteinase 1, and glycodelin A) (2, 15). The acute inflammatory process creates an angiogenic environment, which may promote embryo-uterine crosstalk and result in successful implantation (16, 27). According to various investigators, ESI may mitigate the detrimental effects of ovarian stimulation of the endometrium and favor endometrial and embryo synchronization (47, 48).

The inflammatory theory may provide a physiological explanation of the benefits of ESI observed in our meta-analysis. However, at present it is still an intriguing hypothesis that has yet to be confirmed by evidence from histologic studies. Nevertheless, the recent literature has suggested that endometrial inflammation, especially if chronic, may be detrimental for embryo implantation and development, potentially leading to female infertility and recurrent pregnancy loss (49–51). Thus, the true physiological and biochemical rationale of ESI's effect on embryo-uterine crosstalk still needs to be elucidated, and solid evidence is needed to draw any conclusions about the benefits of driven inflammation on implantation. In fact, using ESI resulted in no advantage in terms of CPR or OPR in the study with the greatest weight (according to our study quality judgment) (26). It was probably due a lack of benefits from follicular P-ESI (days 6–8 of the cycle preceding IUI) or perhaps to a more vigorous endometrial injury inflicted by the use of a Novak curette.

Strengths and Limitations

Originality, strict inclusion criteria, and rigorous methodology represent points of strength of the present review. We selected only RCTs with women undergoing IUI stimulated cycles with the aim of reducing the bias related to heterogeneity in study designs, population characteristics, and type of IUI cycles (stimulated/not stimulated). Moreover, the low statistical heterogeneity detected between the studies ($I^2 = 0$) represents a further point of strength of our meta-analysis, supporting the substantial consistency of our findings.

However, the present study is not exempt from limitations. First, we performed a meta-analysis exclusively on published data. This exposes our findings to the considerable risk of publication bias, which potentially affects their reliability. Moreover, a moderate degree of heterogeneity within the studies was present in terms of patients' characteristics (percentages of different reproductive disorders), ESI timing and technique (different tools), ovarian stimulation protocols (drugs administered and criteria for ovulation induction), and methodological quality. Such factors may potentially represent additional sources of bias in our final statements.

CONCLUSION

We found poor evidence quality (GRADE of evidence: low) that ESI improves CPR (OR 2.27, $P<.00001$) and OPR (OR 2.04, $P=.004$) in patients undergoing IUI without increasing the risk of multiple pregnancy, miscarriage, or ectopic pregnancy (GRADE score: low/very low). However, the evidence in favor of performing ESI once during the follicular phase of the same cycle of IUI with a flexible aspiration catheter appears to be promising. Conversely, performing P-ESI is supported by inconsistent evidence, as is using other biopsy devices. Moreover, ESI is expected to be safe, although clear evidence about its short-term and long-term complications is warranted. Similarly, few data are available concerning the pain experienced during ESI, which requires future research.

We believe our efforts should be of great interest to the scientific community because of their direct implications for the clinical practice of fertility care providers. Our results support clinicians by providing an updated summary on ESI use in IUI and advising about the uncertainties in the real chances of ESI improving CPR and OPR. Despite the novel evidence provided by our study, there is still a need for further robust, high-quality RCTs to confirm the effectiveness and safety ESI before routinely recommending its use in patients undergoing IUI cycles.

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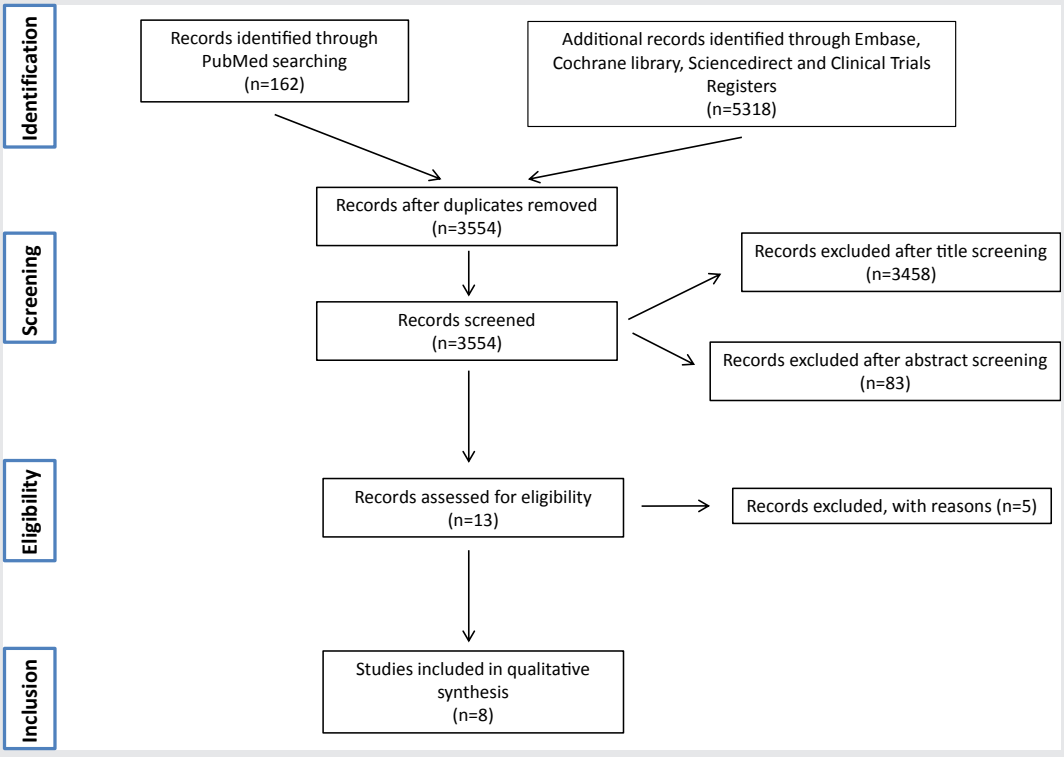
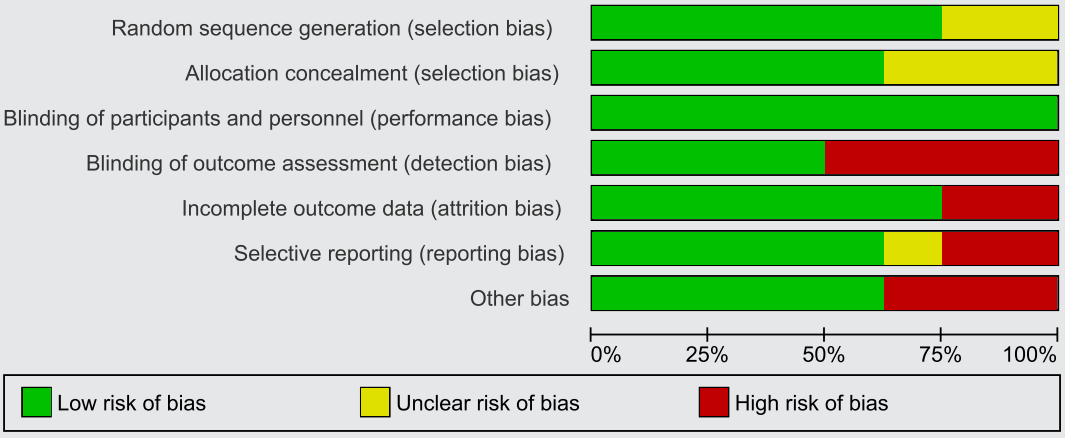
SUPPLEMENTAL FIGURE 1



PRISMA flow diagram.

Vitagliano. Endometrial scratching and insemination. Fertil Steril 2017.

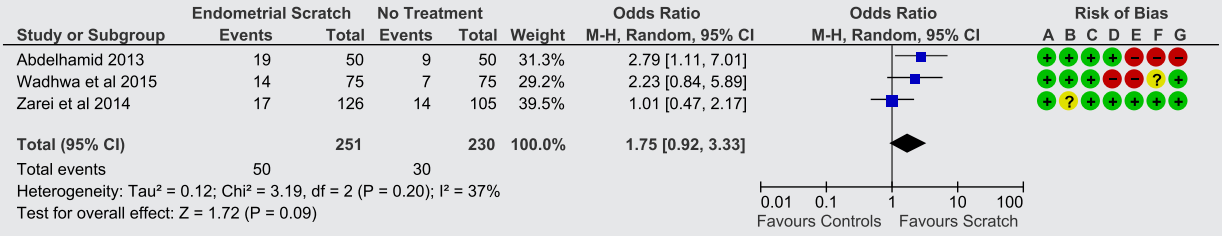
SUPPLEMENTAL FIGURE 2



Risk of bias graph. The authors' judgment about each risk of bias item presented as percentages across the included studies.

Vitagliano. Endometrial scratching and insemination. Fertil Steril 2017.

SUPPLEMENTAL FIGURE 3



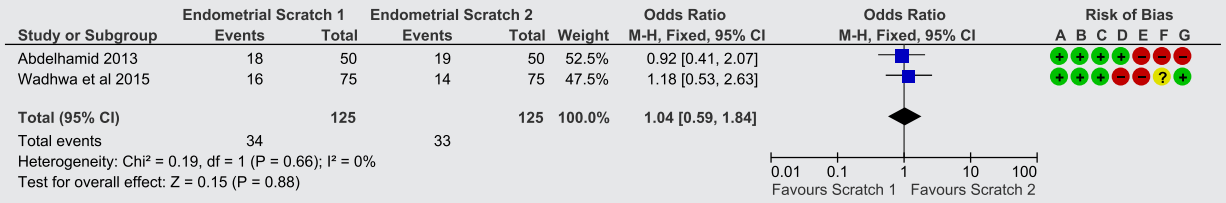
Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Endometrial scratch in the preceding cycle versus no intervention: clinical pregnancy rate.

Vitagliano. Endometrial scratching and insemination. Fertil Steril 2017.

SUPPLEMENTAL FIGURE 4



Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Endometrial scratch in the same cycle versus endometrial scratch in the preceding cycle: clinical pregnancy rate.

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