Endometrial scratch injury for women with one or more previous failed embryo transfers: a systematic review and meta-analysis of randomized controlled trials

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Objective: To investigate endometrial scratch injury (ESI) as an intervention to improve IVF outcome in women with a history of ET failure.
Design: Systematic review and meta-analysis.
Setting: Not applicable.
Patient(s): Infertile women undergoing IVF after one or more failed ET.
Intervention(s): We included all randomized controlled trials of women undergoing IVF after one or more failed ET, where the intervention group received ESI and controls received placebo or no intervention. Pooled results were expressed as relative risk (RR) with a 95% confidence interval (95% CI). The review protocol was registered in PROSPERO before starting the data extraction (CRD42017082777).
Main Outcome Measure(s): Live birth rate (LBR), clinical pregnancy rate (PR), multiple PR, miscarriage rate, ectopic pregnancy (EP) PR.
Result(s): Ten studies were included (1,468 participants). The intervention group showed higher LBR (RR 1.38, 95% CI 1.05–1.80) and clinical PR (RR 1.34, 95% CI 1.07–1.67) in comparison to controls, without difference in terms of multiple PR, miscarriage rate, and EP PR. Double luteal ESI with pipelle was associated with the greatest effect on LBR (RR 1.54, 95% CI 1.10–2.16) and clinical PR (RR 1.30, 95% CI 1.03–1.65). The ESI was beneficial for patients with two or more previous ET failure, but not for women with a single previous failed ET. No effect was found in women undergoing frozen-thawed ET cycles.
Conclusion(s): The ESI may improve IVF success in patients with two or more previous ET failures undergoing fresh ET. The ESI timing and technique seem to play a crucial role in determining its effect on embryo implantation. (Fertil Steril® 2018;110:687–702. ©2018 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Endometrial scratching, endometrial biopsy, injury timing, infertility, implantation failure

In vitro fertilization is the gold standard treatment for causes of infertility, including tubal obstruction, severe male factor, poor ovarian reserve, and unexplained infertility of long duration (1, 2). An upward trend in IVF demand has been recorded in high income countries (3), with a recent survey showing a record of 1 in 20 Japanese babies born through IVF technique in year 2015 (data provided by Japan Society of Obstetrics and Gynecology).

Despite the rapid growth of IVF and considerable innovations in assisted reproductive technique (ART) (i.e., implantation genetic screening to assure transferring euploid embryos) (4, 5), failure of implantation still occurs in most IVF cycles (60%–70%) (6–8). It is

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assumed that up to two-thirds of implantation failures could be secondary to defects in endometrial receptivity (9, 10).

Endometrial scratch injury (ESI) is an intervention widely offered to enhance endometrial receptivity in women with a history of IVF failure (11). The ESI can be simply achieved by common biopsy devices (i.e., pipelle, curette), with no need for analgesia (11, 12). The rationale of performing ESI is to trigger a local acute inflammation, with the release of cytokines and growth factors that could enhance the implantation process (13, 14). Nevertheless, since the first study published in 2003 (15), the impact of ESI on IVF success is still subject of debate (16, 17). Important, there is still no agreement on the most appropriate timing (day of the menstrual cycle) and technique (number of performed endometrial injuries and the optimal device) to be used (16, 18). In addition, although performing ESI before the first IVF cycle is discouraged at present (17, 19), due to lack of evidence, it is still unclear after how many failed ET attempts ESI may be beneficial (16, 17).

The aim of our study was to summarize evidence on ESI effectiveness in women with a history of one or more failed ET attempts. In addition, we evaluated the impact of ESI timing and technique (number of injuries and devices) on IVF outcome.

MATERIALS AND METHODS

Study Design and Registration

This is a systematic review of all randomized controlled trials (RCTs) investigating the effects of ESI on IVF outcomes in women with at least one previous ET failure. Study protocol was registered in PROSPERO before starting the data extraction (CRD42017082777). The review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (20).

Search Strategy

Electronic databases (Medline, Sciencedirect, Scopus, Embase, the Cochrane library, Clinicaltrials.gov, European Union Clinical Trials Register, and World Health Organization International Clinical Trials Registry Platform) were searched from their inception until November 2017. The key search terms were as follows: endometrial injury OR endometrial scratch OR endometrial biopsy OR endometrial sampling OR endometrial damage [Mesh/Emtree] AND IVF OR ICSI OR embryo transfer OR embryo implantation AND failure OR impairment OR defect.

Inclusion Criteria

The inclusion criteria are as follows: studies reported in English language; randomized controlled trials; infertile women undergoing a single IVF-ET cycle (with fresh or frozen embryos) after at least one previous ET failure; endometrial injury during the course of IVF-ET cycle or during the menstrual cycle preceding IVF-ET; infertile women undergoing a single IVF-ET cycle (after at least one previous ET failure) not receiving the intervention (i.e., no intervention or placebo); primary outcome (live birth rate); secondary outcomes (clinical pregnancy rate [PR], miscarriage rate [MR], multiple PR, ectopic pregnancy [EP] PR); and (7) outcomes measures: live birth rate (per patients [LBR], defined as the delivery of one or more living infants), clinical PR (per patients, defined as the visualization of a gestational sac on transvaginal ultrasound or other definitive clinical signs), multiple pregnancies (per patients, defined as the presence of more than one gestational sac on transvaginal ultrasound), MR (per clinical pregnancy, defined as fetal loss prior to the 20th week of gestation), ectopic pregnancy (EP) PR (per clinical pregnancy, defined as a pregnancy that implants outside of the uterus).

Study Selection and Data Extraction

Titles and abstracts were independently screened by two authors (A.V., A.A.). The same authors independently assessed studies for inclusion and checked the reference lists of retrieved studies. The results of the study selection process were then matched and any difference was discussed. Two other authors (G.V., F.S.) extracted data about study features, populations (number and inclusion criteria), intervention (tools and timing), cointerventions (i.e., hysteroscopy, antibiotics) IVF cycles (ovarian stimulation protocols, embryos transferred, luteal phase support), and study outcomes. One author (A.V.) reviewed the entire data extraction process. When insufficient information was reported in the articles, we contacted authors (by e-mail) to ask for additional data.

Risk of Bias

Two authors (A.V., A.A.) independently assessed the methodological quality of included studies by using the Cochrane Collaboration's tool for bias risk assessment (21). Seven domains related to risk of bias were evaluated: random sequence generation; allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessors (detection bias); incomplete outcomes (attrition bias); selective data reporting (reporting bias); other sources of bias (other bias). Authors' judgments were expressed as "low risk", "high risk" or "unclear risk" of bias for each domain. As none of the included studies was blinded but such factor was unlikely to generate bias, "performance bias" was considered a low risk for all the included studies. In addition, "detection bias" was evaluated according to quality of outcomes measures definition (clear/unclear/inappropriate) and possible confounding factors in the detection of ESI effect (i.e., cointerventions). For the estimation of "selective data reporting," we evaluated study protocols, when available. If not available, studies were judged at unclear risk of bias. Authors' scores were compared and disagreements were resolved by consensus.

Data Analysis

Statistical analysis was performed independently by two authors (A.V., G.S.) using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update). The results were compared and any difference was resolved by discussion with a third reviewer (A.D.S.S.). All analyses were carried out with an intention-to-treat approach (number of events per women

randomized), using the random effects model (of DerSimonian and Laird). Results were expressed using risk ratio (RR) with a 95% confidence interval (95% CI). Significance level was set at $P<.05$. Heterogeneity was assessed using Higgins I^2.

A subgroup analysis was performed to evaluate the impact of different interventions (timing [follicular vs, luteal], number [single vs. double], type of device [soft device, curette]), patients' history of previous ET failures (1 failed ET, ≥ 2 failed ET), type of IVF-ET cycle (fresh, frozen-thawed), and cointerventions (i.e., hysteroscopy, antibiotics, oral contraceptive (OC) pill, prednisolone) and on pooled results. In addition, we performed a sensitivity analysis by serially excluding each study and different study subgroups (according to the methodological quality) from the pooled analysis. We aimed to assess the publication bias for the primary outcome by using the funnel plot if at least 10 studies were included in pooled analysis, according to Cochrane Collaboration (Cochrane Handbook, 10.4.3.1 Recommendations on testing for funnel plot asymmetry).

Grading of Evidence

The body of evidence was assessed by two authors (A.V., A.A.) using GRADE (Grading of Recommendations Assessment Development and Evaluation working group) methodology. The final score was obtained by evaluating the following domains: study design, risk of bias, indirectness, inconsistency, imprecision, large effect size, plausible confounding, and publication bias. Dose-response gradient was not evaluated as intervention was dichotomous.

RESULTS

Study Selection

After titles and abstracts screening, 19 studies were assessed for eligibility. Eight studies were excluded after the evaluation of full-text: five were not RCT (22–26); the Liu et al. (19) study included patients at their first IVF attempt; two additional trials (14, 27) included unselected women undergoing IVF; and the Salhepour et al. (28) study was excluded because endometrial injury was not inflicted by using biopsy devices (but by infusing a saline solution through the cervical canal). Thus, 10 trials (29–38) were included in the present systematic review (Supplemental Fig. 1, available online).

Included Studies

The 10 trials included 1,468 participants, of which 733 were assigned to the intervention group and 735 to the control group. All studies were open-label (for participants, personnel and outcomes assessors), except for one trial (38) (double-blinded). Three studies (33, 34, 36) were multicenter trials. The study characteristics are reported in Table 1.

Participants. Five studies (30, 32, 34, 37, 38) included women with at least one previous failed ET attempt. An additional four trials (29, 33, 35, 36) included women with at least two previous ET failures, whereas Baum et al. (31) enrolled only women with three or more previous failed ET cycles. The mean number of previous failed ET was between two and three in all studies, except in two (Inal et al. [32], between 1 and 2 cycles; Baum et al. [31], between 8 and 9 cycles). Information was not provided in the Singh et al. (35) study. All trial embedded patients with previous good ovarian response and/or previous failed transfer of good quality cleavage stage embryos/blastocysts. Reasons for infertility included male factor, tubal infertility, endometriosis, unexplained infertility, and anovulation in all studies. Data were not provided in three articles (29, 34, 35) (Table 1).

Intervention. All patients received ESI during the menstrual cycle preceding the ET. In five studies ESI was performed twice (during the luteal phase [32, 34, 37] or once during the follicular phase and once during the luteal phase [30, 31]) and in the remaining studies it was performed once (29, 35, 36, 38) or during the follicular phase (33). Biopsy was obtained through flexible biopsy devices—pipelle (29–32, 34, 36, 37) or Karman's cannula (35), except in the Shohayaeb and El-Khayat (33) study (by curette). Only in three trials (31, 34, 38) control patients received placebo (introduction of a catheter inside cervix without tissue sampling).

Cointerventions. Patients underwent hysteroscopy (during the cycle preceding ET) in two studies (30, 33). Doxicicline (200 mg/d for 7 days) was added in the study by Narvekar et al. (30). In the study by Singh et al. (35) all women received antibiotics after ESI (ciprofloxacin 500 mg/daily for 5 days), whereas in another study (32) antibiotics (dose and drug not described) were administered only to patients allocated to intervention. In addition, Gibreel et al. (34) used OC pills for cycle scheduling. Finally, Inal et al. (32) administered oral prednisolone before ET.

IVF-ET cycles. All women underwent a single homologous IVF-ICSI cycle with fresh ET, except in two studies (vitrified warmed ET cycle with 6 mg/d oral E_2 valerate preparation [36] or natural cycle vitrified warmed ET [38]). Pituitary block was achieved by using the same scheme (GnRH-agonists long protocol [29, 32, 34, 35]) or various schemes within the same study population (including GnRH-agonists ultralong/flare up protocols and GnRH-antagonists flexible scheme [30, 31, 34, 35]). Ovarian stimulation was started on days 2–3 of the cycle after ESI with recombinant FSH (29, 30, 35, 37) or recombinant FSH/hMG, mainly adapting dose of gonadotropins (150–375 IU daily) on patients' characteristics (in one study (29) patients received a fixed daily dose of 225 IU FSH). Ovulation was triggered with 5,000–10.000 IU of urinary hCG or 250 μg of recombinant hCG when at least two/three follicles exceeded the mean diameter of 17–18 mm. Oocyte retrieval was performed 34–37 hours after ovulation induction and oocytes were fertilized by IVF/intracytoplasmic sperm injection (ICSI) (except in the study by Inal et al. (32) using only ICSI). Subsequently, a variable number (≤ 3) good quality cleavage stage embryos or blastocysts were transferred (only cleavage stage embryos in six studies (29–33, 36); cleavage stage embryos or blastocysts in the remaining studies (34, 35, 37, 38). Luteal phase support was achieved by administering vaginal P (200–800 mg/d) alone or in combination with IM P (25 mg/d or 100 mg twice a week) from the day of oocyte pick-up. Inal et al. (32) administered

TABLE 1

General features of the studies.

Author and year	Study design, country and time of realization	Participants and main inclusion criteria (n)	Ovarian stimulation (drugs and techniques)	Intervention group	Control group	Outcomes
Karimzadeh et al. 2009 (29)	Single center RCT Iran nr	115 patients undergoing IVF-ICSI 2–6 failed IVF-ET cycles with ≥10 high-grade embryos transferred Mean number of failed cycles: Group A: 2.52 ± 1.42 Group B: 2.18 ± 0.54 No previous poor ovarian response (defined as day 3 FSH >10 IU/mL or <4 follicles at hCG) Age 20–40 years No history of blood disease No uterine malformation, endometriomas, and hydrosalpinx	GnRH-ag long protocol (busereline 0.25–0.5 mg/d) Recombinant FSH 225 IU from day 2 Urinary hCG (10,000 IU) at follicle size 18 mm (≥2) Oocyte retrieval 34–36 h after hCG 2/3 day 2/3 embryos transferred Luteal phase support with vaginal P (800 mg/d)	Single ESI on days 21–26 Pipelle Group A (n = 58 women; 4 lost to follow-up; 6 did not undergo ET) Cointerventions: none	No intervention Group B (n = 57 women; 5 lost to follow-up; 7 did not undergo ET) Cointerventions: none	Clinical PR
Narvekar et al. 2010 (30)	Single center RCT India May 2007 to July 2008	100 patients undergoing IVF-ICSI ≥1 failed IVF-ET cycles with ≥4 high-grade embryos transferred Mean number of failed cycles: Group A: 2.3 ± 0.52 Group B: 2.5 ± 0.7 Previous good ovarian response Age ≤37 years No history of endometrial tuberculosis and Asherman syndrome No submucous fibroids/fibroids distorting uterine cavity No hydrosalpinx	GnRH-ag long/short (leuprorelin 0.2–0.5 mg/d) or GnRH-ant (ganirelix 0.25 mg) flexible protocol Recombinant FSH 150–250 IU from day 3 urinary hCG (5.000 IU) at follicle size 18 mm (≥3) Oocyte retrieval 35 h after hCG ≤4 day 3 high-grade embryos transferred Luteal phase support with vaginal P (600 mg/d)	Double ESI on days 7–10 and 24–25 Pipelle Group A (n = 49 women; 1 received P-ESI once) Cointerventions: hysteroscopy, antibiotics	No intervention Group B (n = 51 women) Cointerventions: hysteroscopy, antibiotics	Clinical PR Live birth rate Miscarriage rate Multiple PR
Baum et al. 2012 (31)	Single center RCT Israel July 2006 to June 2009	36 patients undergoing IVF-ICSI ≥3 failed IVF- ET cycles Mean number of failed cycles:	GnRH-ag long/short or GnRH-ant protocol Urinary hCG (5,000 UI)) at follicle size of 18 mm (>2)	Double ESI on days 9–12 and 21–24 Pipelle Group A (n = 18 patients; 1 did not receive COS;	Placebo (cervical pipelle, without biopsy) Group B (n = 18 patients; 1 not receive COS; 1 did	Clinical PR Live birth rate Miscarriage rate

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TABLE 1

Continued.

Author and year	Study design, country and time of realization	Participants and main inclusion criteria (n)	Ovarian stimulation (drugs and techniques)	Intervention group	Control group	Outcomes
		Group A: 8.8 ± 4.6 Group B: 8.5 ± 3.5 Previous good ovarian response Age 18–41 years No uterine malformations, endometriomas, and hydrosalpinx	Variable number of day 3 embryos transferred Luteal phase support not described	1 did not undergo ET) Cointerventions: none	not undergo ET) Cointerventions: none	
Inal et al. 2012 (32)	Single center RCT Turkey January 2008 to March 2009	100 patients undergoing ICSI ≥1 failed IVF-ET cycles Mean number of failed cycles: Group A: 1.3 ± 0.57 Group B: 1.44 ± 0.6 Previous good ovarian response No hydrosalpinx, thrombophilia, and submucous myoma	GnRH-ag long protocol (leuprorelix 1 mg/d) Recombinant FSH or hMG (dose according to patient characteristics) Urinary hCG (10,000 IU) at follicle size of 18–20 (1) or 17 mm (2) Oocyte retrieval 35–37 h after hCG ≤3 day 3 high-grade embryos transferred Luteal phase support with vaginal P (600 mg/d), IM P (25 mg/d), oral prednisolone (16 mg/d for 5 d) and transdermal E_2 100 μg (alternate days)	Double ESI during luteal phase (7-day interval) Pipelle Group A (n = 50 patients) Cointerventions: antibiotics, prednisolone	No intervention Group B (n = 50 patients) Cointerventions: prednisolone	Clinical PR Live birth rate Miscarriage rate
Shohayeb and El-Khayat 2012 (33)	Multicenter RCT Egypt, Saudi Arabia nr	210 patients undergoing IVF-ICSI ≥2 failed IVF- ET cycles Mean number of failed cycles: Group A: 2.9 ± 1.0 Group B: 2.84 ± 1.04 Previous transfers of good quality embryos Endometrial thickness <5 mm on day 4 Age <39 years No submucous myoma, endometrial polyp, intrauterine synechiae, or uterine malformation	GnRH-ag long protocol (triptorelin 1 mg/dy) or GnRH-ant protocol (centrorelix 0.25 mg/d) Recombinant FSH or hMG (dose according to patient characteristics) Ovulation induction at follicle size of 18 mm (≥3) Oocyte retrieval 36 h after hCG Day 3 embryos transferred (variable number) Vaginal P 400 mg for luteal phase support	Single ESI on days 4–7 Curette Group A (n = 105 patients; 2 lost because of low response; 3 lost because of low embryo quality) Cointervention: hysteroscopy	No intervention Group B (n = 105 patients; 3 lost because of low response; 2 lost because of low embryo quality) Cointervention: hysteroscopy	Clinical PR Live birth rate Miscarriage rate

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TABLE 1

Continued.

Author and year	Study design, country and time of realization	Participants and main inclusion criteria (n)	Ovarian stimulation (drugs and techniques)	Intervention group	Control group	Outcomes
Gibreel et al. 2015 (34) [NCT01245309][b]	Multicenter RCT Egypt; Belgium nr	387 patients undergoing IVF/ICSI ≥1 previous failed IVF-ET Age <40 years Number of failed cycles among groups: Group A: (n = 128, 1 cycle; n = 64, ≥2 cycles) Group B: (n = 124, 1 cycle; n = 70, ≥2 cycles) No previous poor ovarian response. No endocrine disorders No uterine abnormalities and hydrosalpinx No recent endometrial curettage (past 3 months).	GnRH-ag long protocol Gonadotropins and hCG not described 2 day 3 or 1 day 5 embryo transferred Luteal phase support with micronized P twice	Double ESI on days 21 and 23–24 Pipelle Group A (n = 193 patients; 178 received ESI twice; 15 underwent hysteroscopy and ESI once; 3 lost follow-up) Cointervention: contraceptive pill	Placebo (introduction of a sound through cervix stopping before internal os) Group B (n = 194 patients; 182 received placebo twice; 12 underwent hysteroscopy; 2 lost follow-up) Cointervention: contraceptive pill	Clinical PR Live birth rate Multiple PR Miscarriage rate
Singh et al. 2015 (35)	Single center RCT India April 2013 to July 2014	60 patients undergoing IVF-ICSI ≥2 previous failed IVF cycles Number of failed cycles among groups: nr Age <35 years AFC >8, AMH 2–6 ng/mL, FSH <8 m IU/mL No uterine manipulation within past 3 months No severe endometriosis No abnormal uterine cavity No diabetes mellitus, hypertension. and autoimmune diseases	GnRH-ag long protocol (leuprorelix 1 mg/d) Recombinant FSH 150–375 IU/d Recombinant hCG (250 μg) at follicle size >18 mm (2–3) Oocyte retrieval 34–36 h after hCG Day 2–5 embryos transferred (variable number) Luteal phase support with vaginal P (300 mg/d) or IM P (100 mg/d)	Single ESI on days 14–21 Karman's cannula Group A (n = 30 patients) Cointervention: antibiotics	No intervention Group B (n = 30 patients) Cointervention: antibiotics	Clinical PR Live birth rate Miscarriage rate
Shahrokh-Tehraninejad et al. 2016 (36) [201311065181N12R][b]	Multicenter RCT Iran, USA January 2013 to December 2014	120 patients undergoing IVF-ICSI (frozen) ≥2 previous failed IVF cycles Mean number of failed cycles: Group A: 2.3 ± 0.5 Group B: 2.8 ± 0.7 Age <40 years, BMI ≤30	GnRH-ant (buserelin 1.05 mg/d) from luteal phase Oral E_2 valerate (6 mg/d) from day 3 of next cycle Vaginal P (400 mg/d) at 8 mm endometrial thickness	Single ESI on day 21 Pipelle Group A (n = 60 patients) Cointervention: none	No intervention Group B (n = 60 patients) Cointervention: none	Clinical PR Live birth rate Miscarriage rate Ectopic PR

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TABLE 1

Continued.

Author and year	Study design, country and time of realization	Participants and main inclusion criteria (n)	Ovarian stimulation (drugs and techniques)	Intervention group	Control group	Outcomes
		≥4 grade 1 embryos available Normal uterine cavity No submucosal, intramural, or large (>5 cm) subserosal myoma No endometrioma ≥3 cm, hydrosalpinx, endometrial tuberculosis, active vaginal or cervical infection, diabetes, and systemic lupus erythematosus	Day 3 embryos transferred (variable number)			
Mak et al. 2017 (38) [ChiCTRTRC-12002389][b]	Single center RCT Hong Kong, People's Republic of China March 2013 to April 2016	229 patients undergoing IVF-ICSI (frozen) ≥1 previous failed ET cycles Normal ovulatory cycles No uterine anomaly or pathology such as endometrial polyps, endometriomas >4 cm, or hydrosalpinx Tubal factor Male factor infertility Endometriosis Unexplained infertility	Natural cycle Day 2-6 embryos transferred (1 or 2) Luteal phase support not administered	Single ESI on day LH + 6/8 Pipelle Group A (n = 115 patients; 15 did not receive ESI, 7 did not undergo ET) Cointervention: none	Placebo (sterile cotton wool stick inserted in the cervical os) Group B (n = 114 patients; 10 did not receive ESI, 11 did not undergo ET) Cointervention: none	Clinical PR Ongoing pregnancy/live birth rate[a] Miscarriage rate Multiple PR
Aleyamma et al 2017 (37) [CTRI/2013/003564][b]	Single center RCT India April 2008 to April 2015	111 patients undergoing IVF-ICSI ≥1 previous failed IVF cycle with ≥2 good quality embryos transferred Mean number of failed cycles: Group A: 2.38 ± 0.63 Group B: 2.46 ± 0.90 No previous poor ovarian response (<3 oocytes)	GnRH-ag long/ultra-long/flare-up protocol (leuprorelin 0.5 mg/d/3.75 mg depot) or GnRH-ant flexible protocol (ganirelix 0.25 mg/d) Recombinant FSH 150–300 IU Urinary hCG (5,000 IU) at follicle size >17 mm (≥3)	Double ESI (within 48 hours) in luteal phase Pipelle Group A (n = 55 patients: 11 drop-out [2 patients refused; 7 before oocyte retrieval [functional cysts, poor response, low E_2 on day of trigger, fever on day of trigger]; 2 after	No intervention Group B (n = 56 patients: 9 drop-out [3 lost before oocyte retrieval [poor response], 6 after oocyte retrieval [elective embryo cryopreservation, no M2 oocytes, fertilization failure, sudden panic attack])	Clinical PR Live birth rate Multiple PR Miscarriage rate

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TABLE 1

Continued.

Author and year	Study design, country and time of realization	Participants and main inclusion criteria (n)	Ovarian stimulation (drugs and techniques)	Intervention group	Control group	Outcomes
		Age <38 years, BMI <29 FSH <10 mIU/mL No endometrial pathology, uterine malformations, severe endometriosis, adenomyosis, autoimmune disorders	Oocyte retrieval 35 h after hCG 1–3 day 3–5 embryos transferred Luteal phase support with vaginal P (800 mg/d) plus IM P (100 mg twice weekly)	oocyte retrieval [no M2 oocytes, fertilization failure]) Cointervention: none	Cointervention: none	

Note: AFC = antral follicle count; BMI = body mass index; COS = controlled-ovarian stimulation; ESI = endometrial scratch injury; GnRH-ag = GnRH agonist; GnRH-ant = GnRH antagonist; ICSI = intracytoplasmic sperm injection; nr = not reported; PR = pregnancy rate; RCT = randomized control trial.
[a] Data excluded from quantitative synthesis.
[b] Registred trials: identification code in brackets.

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also oral prednisolone (16 mg/d for 5 days after) and transdermal E_2 (100 mg on alternate days). One study (31) did not report details about embryos (stage at ET) and luteal phase support. The use of preimplantation genetic testing was not reported in any study.

Assessment of the Risk of Study Bias

Selection bias

- Most studies used adequate methods of random sequence generation (computer randomization or random tables), except in two (29, 36; high risk of bias). Allocation concealment was not described in five trials (29, 31, 32, 35, 36) (unclear risk of bias), whereas the remaining studies used opaque sealed envelopes (low risk of bias).

Performance bias

- Because the evaluated outcomes were unlikely to be influenced by the lack of blinding, all studies were judged at low risk of bias.

Detection bias

- Five studies (30, 32–35) were considered at unclear risk of bias due to the presence of cointerventions with uncertain influence on the outcomes evaluated (i.e., hysteroscopy, antibiotics, prednisone).

Attrition bias

- All studies were at low risk of bias, except the one by Singh et al. (35; high risk of bias due to attrition between data outcomes) and the one by Mak et al. (38; unclear risk of bias as live births and ongoing pregnancies were not reported separately).

Reporting bias

- Due to absence of recorded protocol, all studies but three (34, 36, 37) were judged at unclear risk of selective data reporting.

Other bias

- Three studies were judged at low risk of other bias (30, 37, 38). Other studies were at unclear/high risk of bias due to lack of description of population characteristics (i.e., IVF cycle techniques) or due to absence of power analysis/intention to treat analysis (Supplemental Fig. 2, available online).

Synthesis of Results

Primary outcome. A total of 1,124 participants (n = 560 in the intervention group and n = 564 in the control group) from eight studies (30–37) were evaluated. A significantly higher pooled LBR was found in patients receiving ESI (RR

1.38, 95% CI 1.05–1.80, $I^2 = 26\%$, $P = .02$) compared with the control group (Fig. 1A).

Secondary outcomes. The analysis of 1,468 patients (from all the 10 studies [29–37]) found higher clinical PR (RR 1.34, 95% CI 1.07–1.67, $I^2 = 38\%$, $P = .01$) in patients receiving ESI (Fig. 2A). There was with no difference in terms of multiple PR (RR 1.09, 95% CI 0.64–1.85, $I^2 = 0$, $P = .76$), MR (RR 0.97, 95% CI 0.65–1.47, $I^2 = 0$, $P = .90$), and EP PR (RR 3.00, 95% CI 0.12–72.20, I^2 = not applicable, $P = .50$) compared with the control group.

Subgroup analysis

Subgroup analysis was performed for the outcomes LBR and clinical PR ($I^2 = 0$ for MR and multiple PR; I^2 = not applicable for EP PR). This was also done for splitting patients according to type of intervention (ESI number, timing, and device), history of previous failed IVF-ET attempts (1, ≥2), type of ET cycle (fresh vs. frozen), and presence of cointerventions (hysteroscopy, antibiotics, OC pill).

Type of intervention. The maximum effect of intervention was correlated with double luteal ESI (performed with a pipelle), in terms of LBR (RR 1.54, 95% CI 1.10–2.16, $I^2 = 0$, $P = .01$) and clinical PR (RR 1.30, 95% CI 1.03–1.65, $I^2 = 18\%$, $P = .03$). Data from one study (33) showed advantage from single follicular ESI (performed by curette) in terms of LBR (RR 2.36, 95% CI 1.16–4.81, I^2 = not applicable, $P = .03$) and clinical PR (RR 1.78, 95% CI 1.07–1.96, I^2 = not applicable, $P = .03$). No benefit was observed from single luteal ESI and double follicular-luteal ESI (both obtained through flexible devices), in terms of LBR and clinical PR (P = not significant [NS]) (Figs. 1B and 2B).

History of implantation failure. The ESI was associated with higher LBR (RR 1.64, 95% CI 1.21–2.21, $I^2 = 0$, $P = .001$) and clinical PR (RR 1.57, 95% CI 1.22–2.03, $I^2 = 6\%$, $P = .0005$) only in women with two or more previous failed ET. Differently, the pooled analysis of studies on women with a single previous ET failure did not show any difference with controls in terms of clinical PR and LBR (P = NS) (Figs. 1C and 2C).

Type of ET cycle. We found a significant effect of ESI on LBR (RR 1.44, 95% CI 1.05–1.97, $I^2 = 34\%$, $P = .002$) and clinical PR (RR 1.49, 95% CI 1.12–1.99, $I^2 = 41\%$, $P = .006$) in fresh ET cycles. Differently, the two studies (36, 38) on frozen-thawed ET cycles did not find any advantage from ESI (P = NS).

Cointerventions. Studies in which ESI was associated with cointerventions (30, 32–35, 37) showed significantly higher clinical PR (RR 1.49, 95% CI 1.14–1.95, $I^2 = 32\%$, $P = .003$) and LBR (RR 1.53, 95% CI 1.10–2.12, $I^2 = 33\%$, $P = .01$) in comparison with other studies (P = NS). The major effect of ESI was observed in studies in which hysteroscopy was performed before ESI (30, 33) (clinical PR: RR 1.93, 95% CI 1.26–2.97, $I^2 = 0$, $P = .003$; LBR: RR 2.07, 95% CI 1.26–3.42, $I^2 = 0$, $P = .004$), with/without the addition of antibiotic therapy. No benefit from ESI (clinical PR and LBR, P = NS) was found in patients receiving OCs (data from a single study [34]).

Sensitivity analysis

The exclusion of the study by Shohayeb et al. (33) from pooled analysis produced statistical changes to LBR (RR 1.29, 95% CI 0.98–1.70, $I^2 = 20\%$, $P = .07$), but not to clinical PR (RR 1.29, 95% CI 1.02–1.63, $I^2 = 37\%$, $P = .03$). Sensitivity analysis based on study quality (with the exclusion of 2 studies [32, 35] at high/unclear risk of bias in 4 domains) did not provide any substantial change to clinical PR (RR 1.30, 95% CI 1.01–1.67, $I^2 = 43\%$, $P = .04$), but reduced the effect of ESI on LBR (RR 1.34, 95% CI 1.01–1.79, $I^2 = 26\%$, $P = .05$). Differently, no changes in pooled multiple PR and MR (not feasible for the outcome EP PR due to few data) resulted from sensitivity analysis.

Pain and complications

Two studies (29, 31) reported no complications associated with ESI. The remaining studies did not report any information. Similarly, no data was available about patients' discomfort, as well as about long-term complications associated with ESI.

Overall Quality of Evidence

The quality of evidence was rated as low for LBR, clinical PR, MR, and multiple PR, very low for EP PR. We judged the cumulative risk of bias as serious/very serious due to methodological flaws of most studies (5 of 10 studies were at unclear/high risk of bias in at least 3 domains). In addition, the body of evidence was limited by serious imprecision, as well as by serious/very serious indirectness (Table 2). Publication bias was strongly suspected (Funnel plot was not built as <10 studies were evaluated for the primary outcome).

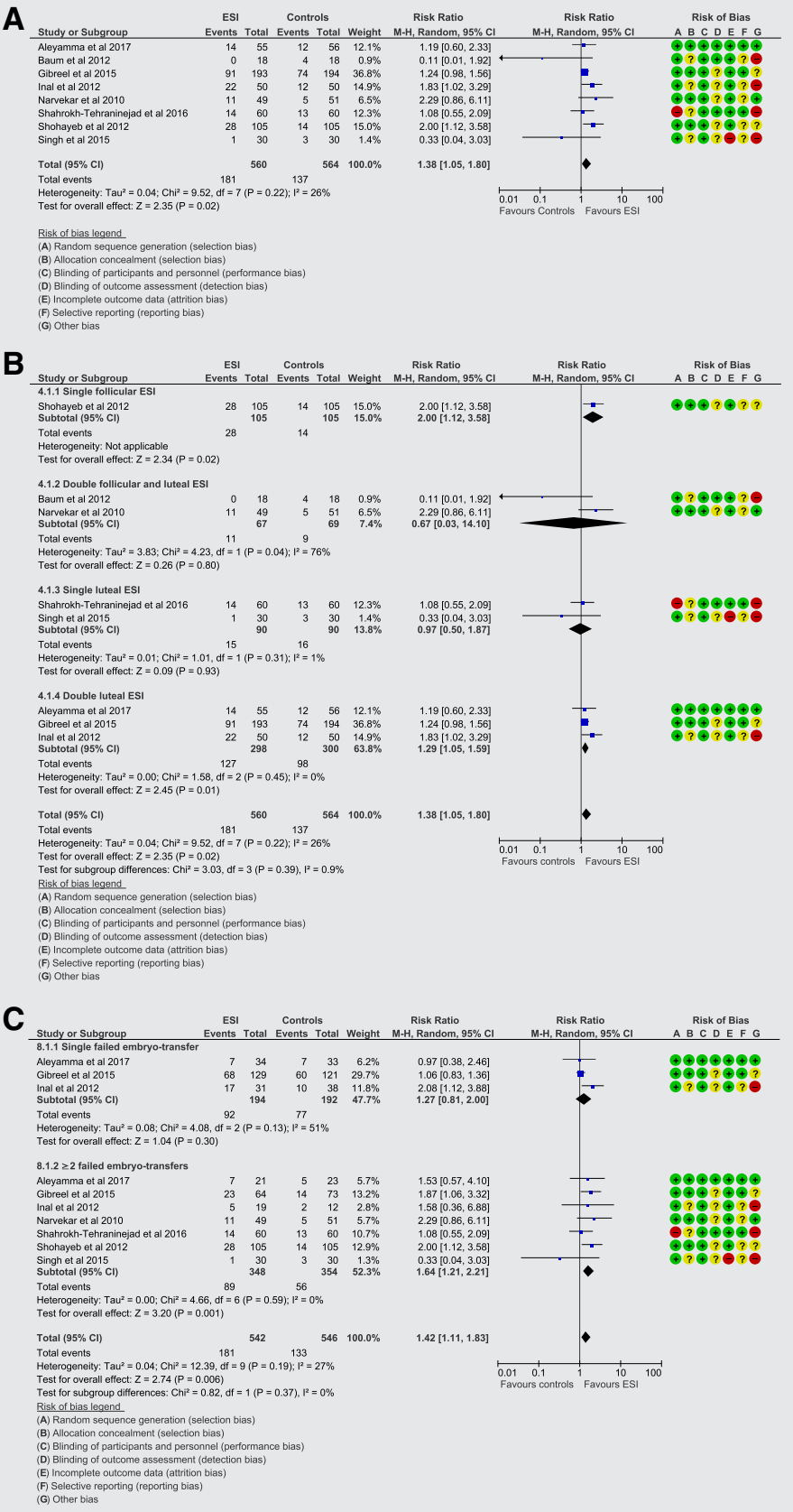
DISCUSSION

Main Findings

The present meta-analysis included 1,468 participants (from 10 RCTs [29–38]) undergoing a single IVF-ET cycle after one or more previous failed attempts. Patients allocated to intervention received ESI once or twice during the cycle preceding ovarian stimulation, whereas controls received no intervention or placebo.

The intervention group showed significantly higher LBR (RR 1.38, 95% CI 1.05–1.80, $P = .02$; GRADE score low) and clinical PR (RR 1.34, 95% CI 1.07–1.67, $P = .01$; GRADE score low) in comparison with controls, without difference in terms of multiple PR, MR, and EP PR (P = NS; GRADE score low/very low). Interestingly, subgroup analysis showed that double luteal ESI with pipelle (data from 3 studies) was associated with the maximum effect on LBR (RR 1.54, 95% CI 1.10–2.16, $P = .01$) and clinical PR (RR 1.30, 95% CI 1.03–1.65, $P = .03$), with minimal inconsistency ($I^2 = 0$ for LBR and $I^2 = 18\%$ for clinical PR). In addition, single follicular ESI through Novak curette (data from 1 study) showed also a benefit on LBR (RR 2.36, 95% CI 1.16–4.81, $P = .03$) and clinical PR (RR 1.78, 95% CI 1.07–1.96, $P = .03$). No effects of single luteal ESI (by pipelle) and double follicular-luteal ESI (by pipelle or Karman's cannula) were observed (P = NS).

FIGURE 1



Effect of endometrial injury on live birth rate **(A)**. Subgroup analysis on injury type **(B)**. Subgroup analysis on previous ET failures **(C)**.

Vitagliano. Endometrial injury for IVF failures. Fertil Steril 2018.

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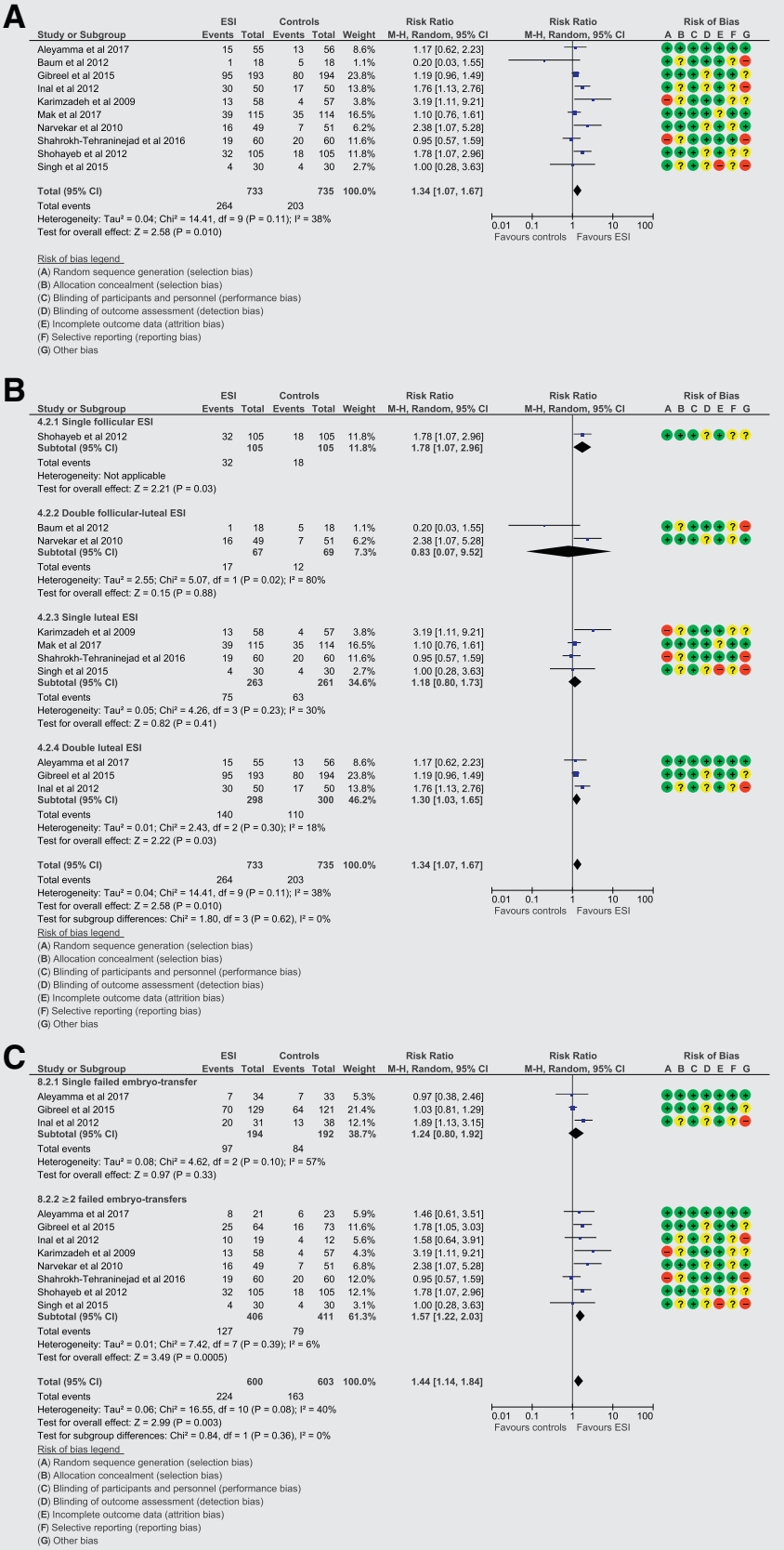
FIGURE 2



Effect of endometrial injury on clinical pregnancy rate **(A)**. Subgroup analysis on injury type **(B)**. Subgroup analysis on previous ET failures **(C)**.

Vitagliano. Endometrial injury for IVF failures. Fertil Steril 2018.

TABLE 2

Evidence profile: endometrial injury compared with no intervention in patients with one or more previous embryo transfer failure.

Characteristic	Anticipated absolute effects (95% CI) Risk with no intervention	Risk with endometrial injury	Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
Ongoing pregnancy/live birth rate	24 per 100	34 per 100 (26–44)	RR 1.38 (1.05–1.80)	1,124 (8 RCTs)	Low[a,b,c]
Clinical pregnancy rate	28 per 100	37 per 100 (30–46)	RR 1.34 (1.07–1.67)	1468 (10 RCTs)	Low[a,b,c]
Miscarriage rate	17 per 100	16 per 100 (11–24)	RR 0.97 (0.65–1.47)	440 (9 RCTs)	Low[a,b,c]
Multiple pregnancy rate	6 per 100	7 per 100 (4–11)	RR 1.09 (0.64–1.85)	827 (4 RCTs)	Low[b,c]
Ectopic pregnancy rate	0 per 100	0 per 100 (0–0)	RR 3.00 (0.12–72.20)	120 (1 RCT)	Very low[d,e]

Note: CI = confidence interval; GRADE = Grading of Recommendations Assessment Development and Evaluation; RR = relative risk; RCT = randomized controlled trial.
[a] Majority of studies at high/unclear risk of bias in four or more domains.
[b] High heterogeneity among study populations, type of intervention, and cointerventions.
[c] The number of participants is insufficient to detect a precise estimate of the effect.
[d] Study at unclear/high risk of bias in three domains.
[e] 120 participants included (with one, an event occurred).

Vitagliano. Endometrial injury for IVF failures. Fertil Steril 2018.

The ESI was beneficial only for patients with two or more previous ET failure (LBR: RR 1.64, 95% CI 1.21–2.21, $I^2 = 0$, $P = .001$; clinical PR: RR 1.57, 95% CI 1.22–2.03, $I^2 = 6\%$, $P = .0005$), but not for women with single previous ET failure (P = NS). In addition, ESI improved IVF success only in women undergoing fresh ET cycles (LBR: RR 1.44, 95% CI 1.05–1.97, $I^2 = 34\%$, $P = .002$; clinical PR: RR 1.49, 95% CI 1.12–1.99, $I^2 = 41\%$, $P = .006$), without any effect on women undergoing frozen-thawed ET cycles (P = NS).

Notably, the final effect of ESI was potentially influenced by the administration of cointerventions (on clinical PR and LBR: positive effect of hysteroscopy with/without antibiotic therapy and negative effect of OCs). No complications associated with ESI were found.

Implications

Despite the growing scientific advances in reproductive medicine (39–41), implantation remains the rate-limiting step for the success of ART (35, 37). Successful implantation entails a complex series of events, culminating in the incorporation of blastocyst in endometrial stroma. For this process to be accomplished, three prerequisite factors are needed: an embryo with implantation competency, a receptive endometrium, and synchrony between embryo and endometrium (42, 43).

It has been hypothesized that performing ESI during the cycle before ovarian stimulation may enhance endometrial receptivity and promote embryo-endometrium synchronization (12, 37). Specifically, acute endometrial inflammation may promote embryo-uterine crosstalk through the local release of cytokines, growth factors, and adhesion molecules (44, 45). In addition, subsequent endometrial healing may delay endometrial maturation (minimizing the effect of ovarian stimulation), thereby facilitating the synchronization between endometrium and embryo (34, 37).

It is reasonable to assume that the degree of ESI (by gentle devices or curette), the number of ESI (1 or 2) and the time elapsing between ESI and the ET may play a crucial role in determining the impact of this intervention on implantation. Accordingly, our study provides first evidence of the varying scenarios resulting from the combination of different ESI techniques (including devices and number of injuries) and timing.

We insightfully found that, when achieved by flexible biopsy devices, ESI was effective in improving LBR and clinical PR only if performed twice during the luteal phase (but not once during the luteal phase or twice during follicular and luteal phase). In addition, results from a single study (33) showed a positive effect from single follicular ESI achieved by curette.

Even if these results are intriguing, caution is needed in drawing any firm conclusion about the most effective technique for ESI. The study by Shohayeb et al. (33) was potentially affected by different sources of bias (3 domains judged at unclear risk of bias), including a small number of patients (n = 210) and events (n = 42 live births). In addition, no study compared the effect of types of intervention on IVF success, limiting any assumption regarding the most efficient number (single or double), timing (follicular or luteal), and device (soft device or curette) for performing ESI.

Furthermore, we found a positive effect of ESI (in terms of clinical PR and LBR) only in patients with two or more previous failed ET. These results were in agreement with the findings of the most recent systematic review (18) on the topic (although more consistent in our study, after the inclusion of data from 4 additional RCTs [35–38]). In addition, we newly demonstrated that ESI was ineffective in women with a single previous failed ET (even if performed twice by pipelle during the luteal phase). Thus, despite the evidence, which is limited by few data (n = 386 patients), currently there is no rationale to offer ESI with the purpose to overcome a single ET failure.

In addition, we observed a consistent advantage from ESI only in patients undergoing fresh ET cycles. Differently, no effect was found (in LBR and clinical PR) in women undergoing frozen-thawed ET cycles. The results by Sharokh-Tehraninejad et al. (36) and by Mak et al. (38) were in line with the findings of a recent nonrandomized study (46) (including patients with ≤ 3 previous failed ET). In this respect, we may speculate that frozen-thawed ET cycles (rather than fresh

cycles) may provide a more accurate endometrial preparation, reducing the risk of premature endometrial maturation (mainly induced by ovarian stimulation drugs) (47, 48). Thus, the positive impact of ESI on embryo-endometrium synchronization may be irrelevant in this particular case. Therefore, we should stress that these two studies (36, 38) evaluated frozen-thawed ET cycles with supernumerary (vitrified) embryos. Accordingly, the lower quality of residual embryos transferred may have affected any positive impact of ESI on IVF success. In addition, both studies (36, 38) included women with a history of failed fresh and/or frozen-thawed ET cycles. This may represent an additional source of bias in the estimation of the benefits of ESI in women undergoing a frozen-thawed ET cycle after one or more ET failures.

We also pointed out the presence of cointerventions in most studies (30, 32–35) (i.e., hysteroscopy, antibiotic therapy, OC treatment, and oral prednisolone) that may potentially interfere with the effects of ESI on implantation. Hysteroscopy was offered to all patients during the cycle preceding IVF in two studies (30, 33). Interestingly, both studies demonstrated a great advantage from ESI on IVF success (clinical PR: RR 1.93, 95% CI 1.26–2.97, $I^2 = 0$, $P = .003$; LBR: RR 2.07, 95% CI 1.26–3.42, $I^2 = 0$, $P = .004$). Nevertheless, according to the results of a recent systematic review (49), hysteroscopy itself may improve IVF success (mainly by removing the antiadhesive glycoprotein molecules on the endometrial surface and by disrupting cervical adhesions). In addition, the occasional scratching of the hysteroscope on the endometrial surface may inflict various degrees of endometrial damage (50, 51), which may add to the damage generated by ESI. Therefore, even if hysteroscopy was performed in both intervention and control groups, its effects may vary from case to case and its impact on pooled results was not measurable.

Antibiotic therapy was administered in three studies (30, 32, 35) (only in the intervention group in the study by Inal et al. [32]). It is a recent acquisition that subclinical chronic endometritis may often occur in patients affected by infertility, especially in case of previous IVF failures (52, 53). Antibiotic therapy also can restore normal endometrial histology and improve IVF success in these patients (54, 55). Because none of the study investigated chronic endometritis, the impact of antibiotics on IVF outcome could not be quantified.

In addition, OCs were administered in the cycle before IVF in a single study (34). Interestingly, ESI (performed twice with pipelle during the luteal phase) did not provide any effect on LBR and clinical PR in such patients, suggesting a possible interference with OC therapy. We may hypothesize that OCs may preclude the mechanism of "delayed menstruation" promoted by ESI. This may foreclose the synchronization between endometrium and embryo, thereby abolishing the positive effect of ESI on implantation. However, a previous RCT (14) on unselected women undergoing IVF (including some women with previous ET failures) observed different results (positive effect from ESI on LBR). Thus, more evidence is still needed to confirm a potential interaction between OCs and ESI effects on implantation.

Finally, in the study by Inal et al. (32), all patients received oral prednisolone (16 mg/d for 5 days after oocyte retrieval). Due to its well-known immunomodulating action (56, 57), a potential interference of prednisolone with ESI effect cannot be excluded. Nevertheless, Inal et al. (32) reported more clinical PR and LBR in the intervention group, apparently contradicting such hypothesis.

Points of Strength and Limitations

The present systematic review is the largest and most comprehensive (of published and unpublished data) investigating the impact of ESI on IVF-ET success in women with history of implantation failure. We provide the first evidence on the influence of different ESI timing (follicular, luteal), number (single, double), and devices for ESI (soft device, curette) on IVF outcome. We also evaluated the impact of ESI on different subgroups of patients (i.e., with history of single or repeated ET failure) and different types of IVF-ET cycles (fresh, frozen-thawed).

We excluded data from studies including women with unselected number of previous ETs (i.e., including also women at their first IVF attempt) to avoid additional bias due to patients' inconsistency at the time of randomization. However, the considerable heterogeneity between original studies in patients' characteristics, tools for the identification of uterine diseases, techniques for IVF-ET cycles, type of embryos transferred (cleavage stage embryos vs. blastocysts), and cointerventions represent the main point of weakness of this present study. In addition, the lack of genetic testing of preimplantation embryos and of search for chronic endometritis did not rule out embryo aneuploidy and endometrial inflammation as causes for implantation failure. In addition, the low number of included studies evaluating specific outcomes (i.e., LBR available for 1,124 of 1,468 patients) and subgroups (i.e., ESI in follicular phase, single ESI, and frozen-thawed ET cycles) requires a cautious interpretation of our findings due to possibility of type II error. Finally, as trials involved a variable number of embryos transferred, we did not perform an aggregate analysis for the outcome implantation rate to avoid unit of randomization error. For all such reasons, the overall quality of evidence was rated as low/very low.

CONCLUSIONS

In conclusion, we found low quality evidence that ESI may improve LBR and clinical PR in women with two or more previous failed ET undergoing fresh IVF-ET cycles. Therefore, ESI did not increase IVF success in women with a history of a single failed ET (independently from the timing and device used), nor in patients undergoing frozen-thawed ET.

We found no evidence of a negative impact of ESI on multiple PR, MR, and EP PR. Similarly, no complications have been associated with the procedure.

Given the limitations of available studies (including serious imprecision and indirectness), we recommend further well-designed RCTs on ESI, focusing on patients with homogeneous characteristics (i.e., ovarian reserve, cause of infertility, ovarian stimulation protocols, stage and number of

embryos transferred, type of luteal phase support, and number of failed ET) and avoiding bias due to cointerventions (hysteroscopy, antibiotic therapy, and OC) and due to the lack of preimplantation genetic testing. In addition, as all the studies performed ESI during the menstrual cycle preceding IVF-ET (during the follicular or the luteal phase), future studies evaluating the impact of ESI during the course of IVF-ET cycle (i.e., during ovarian stimulation) are warranted. Finally, future RCTs comparing types of intervention are still needed to establish the most effective number (single or double), timing (follicular or luteal), and device (soft device or curette) for performing ESI.

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Lesión por rascado endometrial para mujeres con uno o más fracasos previos en transferencias de embriones: Una revisión sistemática y meta-análisis de los estudios controlados aleatorizados

Objetivo: Investigar la lesión por rascado endometrial (ESI) como una intervención para mejorar el resultado de FIV en mujeres con historia de fracaso en transferencias de embriones.

Diseño: Revisión sistemática y meta-análisis.

Entorno: No aplica.

Paciente (s): Mujeres estériles sometidas a FIV después de uno o más fracasos previos en transferencias de embriones.

Intervención (s): Se incluyen todos los estudios controlados aleatorizados de mujeres sometidas a FIV después de uno o más fracasos en transferencias de embriones, donde al grupo con intervención se le practicó ESI y los controles recibieron placebo o ninguna intervención. Los resultados agrupados se expresaron como riesgo relativo (RR) con un intervalo de confianza del 95% (95% CI). El protocolo de revisión fue registrado en PROSPERO antes de iniciar la extracción de los datos (CRD42017082777).

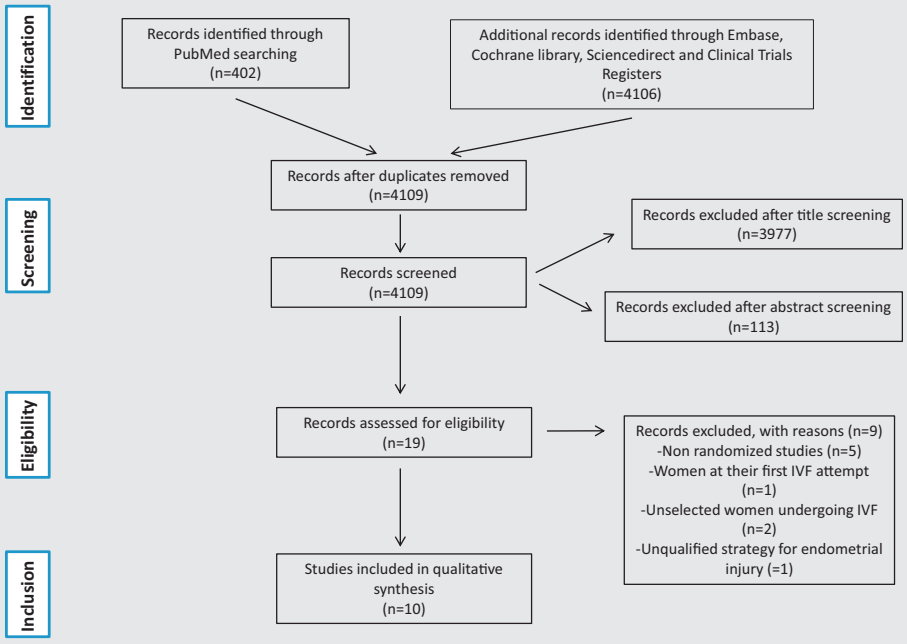
Principales variables de resultado: Tasa de nacido vivo (LBR), tasa de gestación clínica (PR), tasa de gestación múltiple, tasa de aborto y tasa de gestación ectópica (EP) PR.

Resultado (s): Se incluyeron 10 estudios (1468 participantes). El grupo con intervención mostró una LBR (RR 1.38, 95% CI 1.05-1.8) y una PR (RR 1.34, 95% CI 1.07-1.67) más elevadas comparado con los controles, sin diferencias en términos de gestación múltiple, tasa de aborto o EP. Doble ESI en fase lútea con Pipelle estuvo asociada con el mayor efecto sobre LBR (RR 1.54, 95% CI 1.10-2.16) y PR (RR 1.54, 95% CI 1.10-2.16). La ESI fue de beneficio en mujeres con dos o más fracasos en transferencias de embriones, pero no en mujeres con un único fracaso previo de transferencia embrionaria. No se encontró ningún efecto en mujeres sometidas a ciclos de transferencia de embriones descongelados.

Conclusión (s): El ESI puede mejorar el éxito de FIV, en mujeres con dos o más fracasos previos en transferencias de embriones, sometidas a transferencias en fresco. El momento y técnica de la ESI parecen jugar un papel fundamental en la determinación de su efecto sobre la implantación embrionaria.

Palabras clave: Rascado endometrial, biopsia endometrial, momento de la lesión, infertilidad, fallo de implantación.

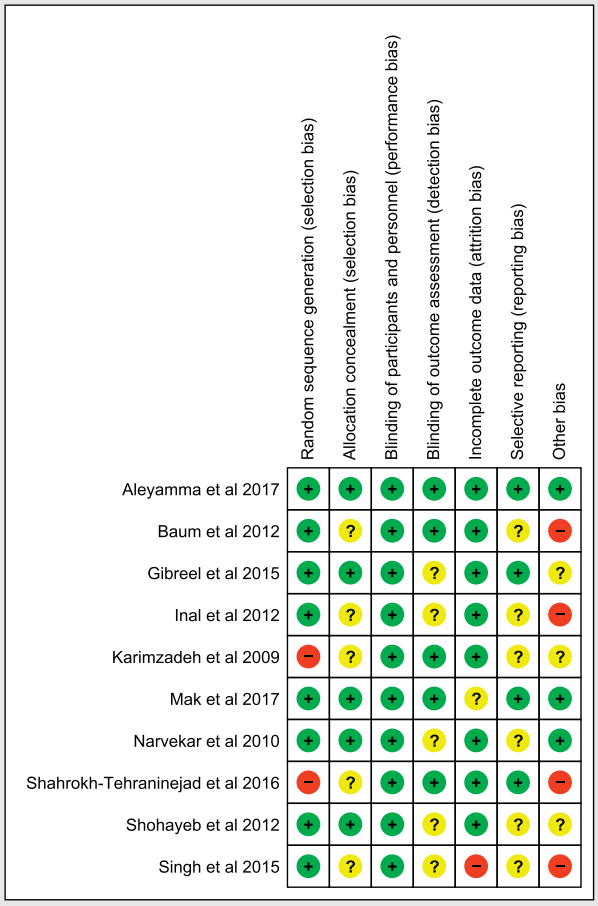
SUPPLEMENTAL FIGURE 1



PRISMA flow diagram.

Vitagliano. Endometrial injury for IVF failures. Fertil Steril 2018.

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 injury for IVF failures. Fertil Steril 2018.

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