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

Amerigo Vitagliano, M.D.,[a] Attilio Di Spiezio Sardo, M.D.,[b] Gabriele Saccone, M.D.,[c] Gaetano Valenti, M.D.,[d] Fabrizio Sapia, M.D.,[d] Mohan S. Kamath, M.S.,[e] Mija Blaganje, M.D., Ph.D.,[f] Alessandra Andrisani, M.D.,[a] and Guido Ambrosini, M.D.[a]

[a] Department of Women and Children's Health, Unit of Gynecology and Obstetrics, University of Padua, Padua; [b] Department of Public Health and [c] Department of Neuroscience Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples; [d] Department of General Surgery and Medical Surgical Specialties, University of Catania, Catania, Italy; [e] Reproductive Medicine Unit, Christian Medical College Hospital, Vellore, India; and [f] Department of Gynecology, University Medical Centre Ljubljana, Ljubljana, Slovenia

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

Received March 19, 2018; revised April 17, 2018; accepted April 26, 2018.
A.V. has nothing to disclose. A.D.S.S. has nothing to disclose. G.S. has nothing to disclose. G.V. has nothing to disclose. F.S. has nothing to disclose. M.S.K. has nothing to disclose. M.B. has nothing to disclose. A.A. has nothing to disclose. G.A. has nothing to disclose.
Reprint requests: Amerigo Vitagliano, M.D., Department of Women and Children's Health, Unit of Gynecology and Obstetrics, University of Padua, Padua, Italy (E-mail: amerigovitagliano.md@gmail.com).

Fertility and Sterility® Vol. 110, No. 4, September 2018 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2018.04.040

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