ORIGINAL ARTICLE: ASSISTED REPRODUCTION

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® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Endometrial injury, endometrial scratch, infertility, intrauterine insemination, pregnancy rate

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Received July 30, 2017; revised September 11, 2017; accepted September 18, 2017.
A.V. has nothing to disclose. M.N. has nothing to disclose. G.S. has nothing to disclose. S.G. has nothing to disclose. S.G.V. has nothing to disclose. A.S.L. has nothing to disclose. P.S.L. has nothing to disclose. C.S. has nothing to disclose. G.B.N. has nothing to disclose. A.D.S.S. has nothing to disclose.
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Fertility and Sterility® Vol. ■, No. ■, ■ 2017 0015-0282/$36.00
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https://doi.org/10.1016/j.fertnstert.2017.09.021

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

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