Systematic Review

The impact of endometrial mechanical stimulation in women with normal hysteroscopic findings undergoing IVF/ICSI: a meta-analysis

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Abstract

Background: To investigate whether hysteroscopic endometrial mechanical stimulation improves pregnancy outcomes in patients undergoing in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI). Methods: We conducted a systematic search in electronic databases including PubMed, Embase, Cochrane Library, Web of Science from their inception to Feb 20th, 2021, as well as a manual search. All publications on the impact of hysteroscopic endometrial mechanical stimulation on IVF/ICSI outcomes were retrieved. Two reviewers independently screened the retrieved studies using stringent inclusion and exclusion criteria; data were subsequently extracted, and risk of bias was assessed. Meta-analysis of the selected studies was performed using Revman 5.3. Results: Eight studies involving 1494 patients were eligible for inclusion, including 5 randomized controlled trials and 3 prospective non-randomized simultaneous controlled experimental studies. We found that compared with the control group, hysteroscopic endometrial mechanical stimulation effectively increased live birth rate [risk ratio (RR) = 2.15, 95% confidence interval (CI) (1.78, 2.60), p < 0.00001] and clinical pregnancy rate [RR = 1.95, 95% CI (1.28, 2.98), p = 0.002], and also decreased abortion rate [RR = 0.54, 95% CI (0.35, 0.86), p = 0.009]. Subgroup analyses revealed that, hysteroscopic endometrial mechanical stimulation administered in the luteal phase in patients undergoing their first IVF/ICSI cycle was associated with significantly higher live birth rate and clinical pregnancy rate, as well as a significantly lower abortion rate. Discussion: Endometrial mechanical stimulation may improve live birth rate, clinical pregnancy rate and reduce abortion rate in patients with normal hysteroscopic findings who are undergoing IVF/ICSI. The benefits may be even greater if this therapy is given in the luteal phase and in patients who are in their first IVF/ICSI cycle. However, due to the limited quantity and quality of the included studies and variable stimulation methods, these findings should be interpreted with caution, and more high-quality studies are needed to confirm this conclusion.

Keywords: Hysteroscopy; Endometrial mechanical stimulation; IVF; ICSI; Meta analysis

1. Introduction

As the prevalence of infertility increases year by year, the number of patients seeking assisted reproduction is also increasing. Despite advances in assisted reproductive technology (ART), the clinical pregnancy rate is only about 30% [1], and thus, it is imperative to improve the success rate of ART. Endometrial receptivity is a key factor influencing embryo implantation. Good blastocyst development and simultaneous development of endometrial receptivity are essential for implantation 6–10 days after ovulation, i.e., at the mid-secretory phase of menstrual cycle. Although in most cases this occurs naturally, desynchrony between blastocyst and endometrial development is noted in some women, thus affecting embryo implantation [2]. Embryo implantation is an inflammatory process; in 1907, Loeb first reported that scratching the guinea pig uterus during the pre-pregnancy phase of estrous cycle resulted in rapid growth of decidual cells, and subsequent studies proposed that the decidual growth might be attributed to the inflammatory response triggered by local injury to the endometrium [3]. In 2003, Barash et al. [4] proposed that endometrial mechanical stimulation by endometrial biopsy could improve endometrial receptivity and thus facilitate embryo implantation. The underlying mechanism is poorly understood, which may involve endometrial decidualization caused by histamine release in response to local damage to the endothelium; a large number of cytokines and growth factors involved in the process of embryo implantation are secreted during the repair of endometrial lesions [4], and local injury increases endometrial receptivity by regulating the expression of multiple genes, which may contribute to the success of embryo implantation [5].

Over the past 20 years, many studies have been conducted on endometrial mechanical stimulation by means of pipelle biopsy tube, small curette, hysteroscopy, or hys-
teroscopy combined with surgical instrumentation [6]. Endometrial mechanical stimulation is simple and can be performed by many gynecologists, but the procedure may cause pain and carries the risk of higher cost, endometrial injury and etc. [7]. Also, mixed results have been reported on its effect on pregnancy outcomes after embryo transfer. Some studies observed that endometrial mechanical stimulation might improve the implantation rate and live birth rate and reduce the miscarriage rate [8], while others did not find any benefits for embryo implantation [9]. Hysteroscopy provides a direct visualization of the uterine cavity and is the gold standard for the diagnosis of uterine diseases, which avoids the disadvantages of other mechanical stimulation methods that cannot detect uterine lesions. With advances in hysteroscopy techniques, hysteroscopic procedures can be performed in an outpatient setting without any anesthesia. It is of clinical relevance to determine whether it is necessary to administer endometrial mechanical stimulation that may increase the risks of pain, higher cost, and injury in patients with normal hysteroscopic findings [7], and whether this procedure can increase clinical pregnancy rate. Although several meta-analyses have been published, there is a lack of study assessing the effect of endometrial mechanical stimulation on embryo implantation in patients with normal hysteroscopic findings. Thus, this meta-analysis was performed to provide a more scientific basis for clinical decision-making.

2. Materials and methods

2.1 Study sample

2.1.1 Inclusion criteria

(1) study type: randomized controlled trials (RCTs) and non-RCTs; (2) study subjects: infertile patients undergoing in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI), regardless of nationality, ethnicity, or duration of illness; no acute inflammation or systemic disease; (3) interventions: hysteroscopy combined with endometrial mechanical stimulation followed by IVF/ICSI in the treatment group; while hysteroscopy or other examination excluded endometrial lesions and IVF/ICSI subsequently in the control group; (4) outcome measures: live birth rate, clinical pregnancy rate, and abortion rate; (5) published studies or with publication year; with adequate description of sample size and results.

2.1.2 Exclusion criteria

(1) retrospective studies; (2) studies with no control group, or with significant baseline differences between groups; (3) duplicate publications, studies with flawed design, incomplete data, or were of low-quality; (4) studies with insufficient descriptions despite contact with the author; (5) studies with incorrect and uncorrectable statistical methods or unusable data; (6) animal experiments, case reports or literature reviews.

2.2 Methods

2.2.1 Search strategy

The following electronic databases were searched from their inception to Feb 20th, 2021: PubMed, Embase, Cochrane Library, and Web of Science; and manual search was also performed. The search terms were ("Hysteroscopy"[Mesh]) OR (Hysteroscopy*) OR (Endoscopy*) OR (mini-hysteroscopy*) OR (minihysteroscopy*) AND ((endometrial biopsy) OR (endometrial injury) OR (endometrial trauma)) OR (mock embryo transfer) OR (endometrial sampling) OR (endometrial local injury) OR (endometrial priming) OR (endometrial harm) OR (endometrial wound) OR (endometrial lesion) OR (endometrial damage) AND ((assisted reproductive) OR (IVF) OR (in vitro fertilization) OR (in vitro fertil*) OR (ICSI) OR (intracytoplasmic sperm injection) OR (embryo* AND transfer*) OR (blastocyst* AND transfer*) OR (FET) OR ("Reproductive Techniques, Assisted"[Mesh])). A total of 912 studies published in English were retrieved.

2.2.2 Study selection and data extraction

Study selection and data extraction was conducted by two reviewers independently. First, they screened the title and abstract for potentially relevant studies. Next, they read through the entire study to evaluate its eligibility for inclusion. Then, resultant studies from the two reviewers were compared; any discrepancies between the two reviewers were resolved through discussion with a third reviewer, who was an expert in the field. Data were extracted from each study according to the data extraction table. If there was any missing data, the corresponding author was contacted to obtain the required information. If a study group had multiple articles based on similar patients and using the same measures, only the largest or most recent article was included. The data extracted comprised the following: (1) basic information such as name of first author and year of publication; (2) study design, and parameters for risk of bias assessment; (3) basic patient characteristics, such as sample size (treatment/control group), patient age, and nationality; (4) details of intervention strategies, including timing of hysteroscopy and specific methods of endometrial mechanical stimulation; (5) outcome data including live birth rate (i.e., the ratio between the number of live births beyond 22 weeks of gestation and the total number of transfers); clinical pregnancy rate (clinical pregnancy defined as the ultrasound presence of a fetal heartbeat in the gestational sac); and abortion rate (i.e., the ratio between the number of early pregnancy losses and the total number of clinical pregnancies).

2.2.3 Assessment of risk of bias

We utilized the Cochrane risk-of-bias tool [10] to evaluate the included RCTs. For non-RCTs, the methodological index for non-randomized studies (MINORS) [11] was used to assess risk of bias.
2.3 Statistical analysis

We used Review Manager 5.3 (The Cochrane Collaboration, Oxford, UK) [12] to perform meta-analysis. Continuous variables were presented as mean differences (MD), while categorical variables were reported as relative risks (RR). For each outcome measure, point estimates and 95% confidence intervals (95% CI) were also calculated. Heterogeneity across studies was evaluated using the I^2 statistic. Statistical significance was set at α = 0.05. If p < 0.05 or I^2 > 50%, a random-effect model was applied; otherwise, a fixed effect model was used. Subgroup analyses were performed to detect the source of significant clinical heterogeneity. According to the Cochrane Handbook for Systematic Reviews of Interventions, publication bias should not be tested by funnel plot asymmetry when fewer than 10 studies are included in the meta-analysis, because the power of the tests is too low to distinguish chance from real asymmetry. In our review, only 8 studies were included and thus funnel plot was not assessed.

3. Results

3.1 Study selection

A total of 912 relevant studies were initially retrieved. After careful screening, 8 studies [6,8,13–18] met the eligibility criteria including 5 RCTs [8,13,14,16,18] and 3 prospective non-randomized simultaneous controlled experimental studies [6,15,17]. Totally 1494 patients were included for analysis. The search process and the number of studies obtained in each step were presented in a flow chart in Fig. 1.
| Study                        | Study design | Study quality | Country               | No. of patients (T/C) | Mean age (T/C, years) | Interventions                                                                 | Outcome measures |
|-----------------------------|--------------|---------------|-----------------------|-----------------------|-----------------------|-------------------------------------------------------------------------------|---------------------|
| Berntsen, S 2020 [16]       | RCT          | IF 1.868      | Denmark               | 95/95                 | 34.0 ± 4.5/34.7 ± 4.0 | hysteroscopy + endometrial injury in the follicular phase of the cycle before ovulation induction | none               |
| Timur Gürgan 2019 [18]      | RCT          | IF 3.218      | Turkey                | 124/115               | 34.31 ± 3.83/33.64 ± 4.25 | hysteroscopy + endometrial injury in the follicular phase of the cycle before ovulation induction | none               |
| Dejan Mitić 2018 [6]a       | Prospective  | MIN 22        | Serbia                | 40/151                | 32.78 ± 4.12/33.61 ± 3.65 | hysteroscopy + endometrial injury in the follicular phase before ovulation induction | none               |
| Dejan Mitić 2018 [6]b       | Prospective  | MIN 22        | Serbia                | 40/41                 | 32.78 ± 4.12/34.00 ± 3.49 | hysteroscopy + endometrial injury in the follicular phase before ovulation induction | hysteroscopy alone |
| Charalampos Siristatidis 2017 [15] | Prospective | MIN 22        | Greece                | 51/52                 | 36 (27–42)/36 (28–41) | hysteroscopy + endometrial injury in the follicular phase of the cycle before implantation | none               |
| Ahmad Mahran 2016 [8]        | RCT          | IF 0          | Egypt                 | 200/200               | 31.4 ± 0.7/30 ± 0.7   | hysteroscopy + endometrial injury in the follicular phase of the cycle before implantation | hysteroscopy alone |
| Amal Shohayeb 2012 [13]      | RCT          | IF 1.868      | Egypt/Saudi Arabia    | 100/100               | 30.7 ± 4.5/30.6 ± 4.5 | hysteroscopy + endometrial injury in the follicular phase of the cycle before implantation | hysteroscopy alone |
| Narvekar, Sachin A 2010 [14] | RCT          | IF 0          | India                 | 49/51                 | 32.16 ± 3.4/32.36 ± 3.3 | follicular-phase hysteroscopy + intraoperative endometrial injury + luteal-phase endometrial injury before implantation | hysteroscopy alone |
| Huang, S. Y. 2011 [17]      | Prospective  | IF 3.235      | Taiwan                | 6/24                  | 34 ± 3.0/35 ± 4.1     | hysteroscopy + endometrial injury in the follicular phase before ovulation induction | none               |

Notes: RCT, randomized controlled trial; prospective, prospective non-randomized simultaneous controlled experimental study; IF, impact factor; MIN, methodological index for non-randomized studies; T, treatment group; C, control group; a, in the study of Dejan Mitić 2018, the intervention group included 40 patients who received LEI (local endometrial injury) during hysteroscopy, and the control group included 151 patients who did not receive hysteroscopy or LEI; b, in the study of Dejan Mitić 2018, the intervention group included 40 patients who received LEI during hysteroscopy, and the control group included 41 patients who received hysteroscopy without LEI.

1embryo implantation; 2biochemical pregnancy; 3clinical pregnancy; 4live birth; 5abortion; 6multiple pregnancy.
3.3 Results of meta-analysis

3.3.1 Livebirth rate

Six studies were included for this analysis [8, 13–16, 18]. Due to sufficient homogeneity across studies (p = 0.81, I^2 = 0%), a fixed-effect model was applied. The live birth rate was significantly higher in the treatment group compared with that of the control group [RR = 2.15, 95% CI (1.78, 2.60), p < 0.00001] (Fig. 3). Similar results were obtained in all subgroup analyses stratified by RCT vs. non-RCT, and prior history of failed cycles. A significantly higher live birth rate was noted in the treatment group compared with that of the control group both in patients with at least one failed cycle [RR = 1.90, 95% CI (1.41, 2.56), p < 0.0001] and in patients undergoing their first IVF/ICSI cycle [RR = 2.39, 95% CI (1.88, 3.05), p < 0.00001] (Fig. 5).

3.3.2 Clinical pregnancy rate

Eight studies were included for this analysis [6, 8, 13–18]. Due to significant heterogeneity across these studies (p < 0.0001, I^2 = 84%), a random-effect model was used. A significant difference in clinical pregnancy rate was noted between the treatment group and the control group [RR = 1.95, 95% CI (1.28, 2.98), p = 0.002] (Fig. 6). Similar results were obtained across all subgroup analyses stratified by timing of stimulation (follicular and/or luteal phases), RCT vs. non-RCT, and prior history of failed cycles. Endometrial mechanical stimulation administered in the luteal phase was associated with a significantly higher clinical pregnancy rate when compared with the control group [RR = 7.00, 95% CI (4.63, 10.58), p < 0.00001] (Fig. 7). A significantly higher clinical pregnancy rate was observed in the treatment group than that of the control group both in patients with at least one failed cycle [RR = 1.77, 95% CI (1.41, 2.23), p < 0.0001], those in their first IVF/ICSI cycle [RR = 1.53, 95% CI (1.21, 1.94), p = 0.0005] (Fig. 8). Hysteroscopic endometrial mechanical stimulation significantly improved the clinical pregnancy rate in patients with at least one failed cycle [RR = 7.00, 95% CI (4.63, 10.58), p < 0.00001] and those undergoing their first/second IVF cycle [RR = 1.35, 95% CI (1.01, 1.80), p < 0.04] (Fig. 9).

3.3.3 Abortion rate

Five studies were included for this analysis [8, 13, 15, 17, 18]. Due to statistical homogeneity across studies (p = 0.89, I^2 = 0%), a fixed-effect model was applied. The abortion rate was significantly lower in the treatment group compared with that of the control group [RR = 0.54, 95% CI (0.35, 0.86), p = 0.009] (Fig. 10). According to subgroup analyses stratified by RCT vs. non-RCT, and prior history of failed cycles, significant differences favoring the treatment group were found in RCTs and in patients undergoing their first IVF/ICSI cycle, whereas the differences were not statistically significant in non-RCTs and in patients with at least one failed cycle. A significantly lower abortion rate was noted in the treatment group compared with that of the control group in RCTs [RR = 0.51, 95% CI (0.3, 0.88), p = 0.02], but only numerically lower in non-RCTs [RR = 0.62, 95% CI (0.27, 1.43), p = 0.26] (Fig. 11). A significantly lower abortion rate was observed in the treatment group compared with that of the control group in patients undergoing their first IVF/ICSI cycle [RR = 0.45, 95% CI (0.22, 0.90), p = 0.02], but only numerically lower in those with at least one failed cycle [RR = 0.62, 95% CI (0.34, 1.14), p = 0.12] (Fig. 12).

4. Discussion

Endometrial mechanical stimulation is a procedure that is easy to perform. In 2003, Barash et al. [4] proposed that endometrial mechanical stimulation might improve endometrial receptivity and thus facilitate embryo implantation. Since then, a series of related studies have been published, in which endometrial mechanical stimulation was achieved by curette scratching, pipelle biopsy, hysteroscopy, or hysteroscopy combined with surgical instrumentation. Given its simplicity, it may become a very

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Fig. 2. Assessment of risk of bias for the included RCTs.
Fig. 3. Comparison of live birth rate between intervention group and control group.

| Study or Subgroup | intervention | Control | Risk Ratio | Risk Ratio |
|-------------------|--------------|---------|------------|------------|
|                   | Events       | Total   | Total      | M-H Fixed  | 95% CI     |
| Timur Gurgan2016  | 27           | 124     | 115        | 13.2%      | 1.79 [0.69, 3.24] |
| Nevekar, Sachin A2010 | 11          | 40      | 51         | 4.4%       | 2.29 [0.68, 8.11] |
| Charalampous Krikonis et al.2010 | 10         | 51      | 52         | 7.2%       | 2.29 [1.10, 4.00] |
| Bertelsen, 2020   | 20           | 82      | 13         | 11.8%      | 1.54 [0.61, 3.81] |
| Amel Eshrayyeh2012 | 100          | 100     | 100        | 12.7%      | 2.00 [1.02, 3.97] |
| Ahmad M. Mahran2018 | 134          | 200     | 195        | 50.7%      | 2.39 [1.60, 3.90] |
| **Total (95% CI)** | **616**     | **610** | **610**    | **100.0%** | **2.15 [1.78, 2.60]** |
| **Total events**   | **230**      | **110** |            |            |

**Heterogeneity:** Chi² = 2.29, df = 5 (P = 0.69), P = 0%

**Test for overall effect:** Z = 7.52 (P < 0.0001)

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Fig. 4. Subgroup analysis of live birth rate between intervention group and control group stratified by RCT vs. non-RCT.

| Study or Subgroup | intervention | Control | Risk Ratio | Risk Ratio |
|-------------------|--------------|---------|------------|------------|
|                   | Events       | Total   | Total      | M-H Fixed  | 95% CI     |
| 3.2.1 RCT study   |              |         |            |            |
| Ahmad M. Mahran2016 | 100          | 100     | 100        | 12.7%      | 2.00 [1.12, 3.57] |
| Amel Eshrayyeh2012 | 100          | 100     | 100        | 12.7%      | 2.00 [1.12, 3.57] |
| Bertelsen, 2020   | 20           | 100     | 100        | 12.7%      | 2.00 [1.12, 3.57] |
| Charalampous Krikonis et al.2010 | 10         | 51      | 52         | 7.2%       | 2.29 [1.10, 4.00] |
| Vanezis, Sachin A2010 | 10          | 51      | 52         | 7.2%       | 2.29 [1.10, 4.00] |
| Timur Gurgan2015   | 10           | 51      | 52         | 7.2%       | 2.29 [1.10, 4.00] |
| **Total (95% CI)** | **565**     | **595** | **595**    | **92.4%**  | **2.14 [1.76, 2.60]** |
| **Total events**   | **220**      | **102** |            |            |

**Heterogeneity:** Chi² = 2.29, df = 5 (P = 0.69), P = 0%

**Test for overall effect:** Z = 7.80 (P < 0.0001)

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3.2.2 Non-RCT study

| Study or Subgroup | intervention | Control | Risk Ratio | Risk Ratio |
|-------------------|--------------|---------|------------|------------|
|                   | Events       | Total   | Total      | M-H Fixed  | 95% CI     |
| Charalampous Krikonis et al.2010 | 10          | 51      | 52         | 7.2%       | 2.29 [1.10, 4.00] |
| **Total (95% CI)** | **616**     | **610** | **610**    | **100.0%** | **2.15 [1.78, 2.60]** |
| **Total events**   | **230**      | **110** |            |            |

**Heterogeneity:** Chi² = 2.29, df = 5 (P = 0.69), P = 0%

**Test for overall effect:** Z = 7.80 (P < 0.0001)

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Fig. 5. Subgroup analysis of live birth rate between intervention group and control group stratified by prior history of failed cycles.

| Study or Subgroup | intervention | Control | Risk Ratio | Risk Ratio |
|-------------------|--------------|---------|------------|------------|
| 3.3.1 1 or more previous failed cycles |              |         |            |            |
| Amel Eshrayyeh2012 | 100          | 100     | 100        | 12.7%      | 2.00 [1.12, 3.57] |
| Bertelsen, 2020   | 20           | 100     | 100        | 12.7%      | 2.00 [1.12, 3.57] |
| Charalampous Krikonis et al.2010 | 10         | 51      | 52         | 7.2%       | 2.29 [1.10, 4.00] |
| Vanezis, Sachin A2010 | 10          | 51      | 52         | 7.2%       | 2.29 [1.10, 4.00] |
| Timur Gurgan2015   | 10           | 51      | 52         | 7.2%       | 2.29 [1.10, 4.00] |
| **Total (95% CI)** | **565**     | **595** | **595**    | **92.4%**  | **2.14 [1.76, 2.60]** |
| **Total events**   | **220**      | **102** |            |            |

**Heterogeneity:** Chi² = 2.29, df = 5 (P = 0.69), P = 0%

**Test for overall effect:** Z = 7.52 (P < 0.0001)

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3.3.2 First IVF/ICSI

| Study or Subgroup | intervention | Control | Risk Ratio | Risk Ratio |
|-------------------|--------------|---------|------------|------------|
| Ahmad M. Mahran2016 | 100          | 100     | 100        | 12.7%      | 2.00 [1.12, 3.57] |
| **Total (95% CI)** | **616**     | **610** | **610**    | **100.0%** | **2.15 [1.78, 2.60]** |
| **Total events**   | **230**      | **110** |            |            |

**Heterogeneity:** Chi² = 2.29, df = 5 (P = 0.69), P = 0%

**Test for overall effect:** Z = 7.52 (P < 0.0001)

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3.3.3 Other IVF/ICSI

| Study or Subgroup | intervention | Control | Risk Ratio | Risk Ratio |
|-------------------|--------------|---------|------------|------------|
|                   | Events       | Total   | Total      | M-H Fixed  | 95% CI     |
|                   |              |         |            |            |
| **Total (95% CI)** | **616**     | **610** | **610**    | **100.0%** | **2.15 [1.78, 2.60]** |
| **Total events**   | **230**      | **110** |            |            |

**Heterogeneity:** Chi² = 2.29, df = 5 (P = 0.69), P = 0%

**Test for overall effect:** Z = 7.52 (P < 0.0001)

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**Test for subgroup differences:** Chi² = 1.97, df = 1 (P = 0.24), P = 20.9%
### Table 2. Treatment-related details of the included studies.

| Study                        | Specific methods                                                                 | Participants                          | Embryo transfer |
|------------------------------|----------------------------------------------------------------------------------|---------------------------------------|-----------------|
| Berntsen, S 2020 [16]        | Hysteroscopic biopsy forceps stimulate posterior uterine wall.                   | ≥1 previous failed cycles             | FET             |
| Timur Gürgan 2019 [18]       | First on the fundus by cutting transversally into the endometrium. Later, three or four vertical incisions were performed 0.5 cm apart, on the anterior and posterior walls of the uterus, 1–1.5 cm away from the fundus and with one cut for each lateral wall by scissors. | ≥3 previous failed cycles             | FET or TET according to the patient’s indications |
| Dejan Mitić 2018 [6]         | 10–15 mm in length throughout the whole endometrial thickness in a transversal direction with a springle bipolar electrode. | First/second IVF                     | FET             |
| Charalampous Siristidis 2017 [15] | Three cuttings of 0.5 cm on the front endometrial wall, 1 cm lower of the endometrial fundus level. | ≥2 previous failed cycles             | FET             |
| Ahmad Mahran 2016 [8]        | Pipelle endosampler catheter scratching off fundus and posterior wall of uterine cavity was done three times. | First/second IVF                     | FET             |
| Amal Shohayeb 2012 [13]      | Curettage of the fundus and posterior wall once by Novak curette.                | ≥2 previous failed cycles             | FET             |
| Narvekar, Sachin 2010 [14]   | A Pipelle endosampler catheter was rotated 360 degrees and moved up and down four times after withdrawing the piston. | ≥1 previous failed cycles             | FET             |
| Huang, S. Y. 2011 [17]       | A local injury on the posterior endometrium at ≥2 transfers of good-quality embryos mid-line 10–15 mm from the fundus by a claw forceps, the depth and width of the injured site was 2 × 2 mm. | First IVF/ICSI                       | FET             |

FET, fresh embryo transfer; TET, thawing embryo transfer; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection.

![Fig. 6. Comparison of clinical pregnancy rate between intervention group and control group.](image)

promising clinical approach to improve pregnancy outcomes in patients undergoing IVF/ICSI. However, its role in ART is controversial. Some believe that it should be used with caution because this is an invasive procedure and may cause pain and discomfort, higher cost and increase the risk of endothelial injury leading to Asherman syndrome [7]. But others argue that there is evidence supporting the efficacy of endometrial mechanical stimulation in improving the implantation rate and live birth rate and reducing the miscarriage rate [8]. Recent meta-analyses [19,20] also reported mixed results on the role of endometrial mechanical stimulation. For this reason, we performed a meta-analysis to assess the impact of endometrial mechanical stimulation on IVF/ICSI outcomes in patients with normal...
Table 3. Assessment of risk of bias for the included non-RCTs.

| Study                                      | A clearly stated aim | Inclusion of consecutive patients | Prospective collection of data | Endpoints appropriate to the aim of the study | Unbiased assessment of the study endpoint | Follow-up period appropriate to the aim of the study | Loss to follow-up less than 5% | Prospective calculation of the study size | Score |
|-------------------------------------------|----------------------|-----------------------------------|--------------------------------|-----------------------------------------------|------------------------------------------|-----------------------------------------------|-------------------------------|-----------------------------------------------|-------|
| Dejan Mitić 2018 [6]a                    | 2                    | 2                                 | 2                              | 2                                             | 2                                        | 2                                             | 2                             |                                               | 0     |
| Dejan Mitić 2018 [6]b                    | 2                    | 2                                 | 2                              | 2                                             | 2                                        | 2                                             | 2                             |                                               | 0     |
| Charalampos Siristatidis 2017 [15]       | 2                    | 2                                 | 2                              | 2                                             | 2                                        | 2                                             | 2                             |                                               | 0     |
| Huang, S. Y. 2011 [17]                   | 2                    | 2                                 | 2                              | 2                                             | 2                                        | 1                                             | 2                             |                                               | 0     |

Additional criteria in the case of comparative study

| Study                                      | An adequate control group | Contemporary groups | Baseline equivalence of groups | Adequate statistical analyses | Score |
|-------------------------------------------|----------------------------|---------------------|-------------------------------|-------------------------------|-------|
| Dejan Mitić 2018 [6]a                    | 2                         | 2                   | 2                             | 2                             | 22    |
| Dejan Mitić 2018 [6]b                    | 2                         | 2                   | 2                             | 2                             | 22    |
| Charalampos Siristatidis 2017 [15]       | 2                         | 2                   | 2                             | 2                             | 22    |
| Huang, S. Y. 2011 [17]                   | 2                         | 2                   | 2                             | 2                             | 21    |

Notes: a, in the study of Dejan Mitić 2018, the intervention group included 40 patients who received LEI (local endometrial injury) during hysteroscopy, and the control group included 151 patients who did not receive hysteroscopy or LEI; b, in the study of Dejan Mitić 2018, the intervention group included 40 patients who received LEI during hysteroscopy, and the control group included 41 patients who received hysteroscopy without LEI.
Fig. 7. Subgroup analysis of clinical pregnancy rate between intervention group and control group stratified by timing of stimulation.

hysteroscopic findings, so as to provide more evidence for real-world clinical practice.

In contrast to prior studies [20], only patients with normal hysteroscopic findings were included in our study, and this homogeneity of participants may provide targeted guidance for clinical management of such patients. Our analyses indicated that endometrial mechanical stimulation might improve live birth rate, clinical pregnancy rate and reduce abortion rate in patients with normal hysteroscopic findings.

According to subgroup analyses stratified by timing of stimulation, endometrial mechanical stimulation given in the follicular and/or luteal phase was associated with higher clinical pregnancy rates, and the benefit was even greater when given in the luteal phase. It has been shown that mechanical stimulation in the presence of progestins in the luteal phase may induce more effective decidualization response [21]. And endometrial mechanical stimulation on days D21-24 of menstrual cycle may trigger an inflammatory response characterized by an influx of macrophages and an increase in pro-inflammatory cytokines, which is positively correlated with pregnancy outcomes [22]. Besides, endometrial mechanical stimulation administered in the luteal phase may relieve patient discomfort [23]. Thus, endometrial mechanical stimulation in the luteal phase is a promising approach for clinical use. However, as only one study involving endometrial mechanical stimulation in the luteal phase was included in this meta-analysis, more studies are needed to clarify whether stimulation in the luteal phase is superior to that given in the follicular phase.

Moreover, subgroup analyses stratified by study type (RCT vs. non-RCT) indicated that, significantly higher live birth rate and clinical pregnancy rate were noted in both RCTs and non-RCTs, but not in non-RCTs. Due to the low incidence of abortion and the small sample size of studies reporting abortion rate, it may be insufficient to identify statistically significant difference in abortion rate, and more relevant RCTs or non-RCTs are needed to confirm the reliability of this finding.

Besides, we also performed subgroup analyses stratified by prior history of failed cycles. Hysteroscopic endometrial mechanical stimulation significantly improved the live birth rate and clinical pregnancy rate both in patients undergoing their first IVF/ICSI cycle and in those having at least one failed cycle. The clinical pregnancy rate was even higher in patients in their first IVF/ICSI cycle. It has been reported that hysteroscopic endometrial mechanical stimulation may improve pregnancy outcomes in patients who have failed previous cycles [24]. In our study, for the first IVF/ICSI cycle, luteal-phase me-
Mechanical stimulation, which was given after endometrial lesions had been excluded by hysteroscopy, dramatically improved clinical pregnancy rate. Therefore, hysteroscopy combined with luteal-phase mechanical stimulation may be considered prior to the first IVF/ICSI cycle. However, as only one study involving luteal-phase endometrial mechanical stimulation in patients undergoing their first IVF/ICSI cycle was included in this meta-analysis, more studies are required to better define its role in clinical practice.

We acknowledge that our analysis has several limitations. Firstly, as some patients declined to receive the intervention, complete randomization was sometimes not

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**Fig. 8.** Subgroup analysis of clinical pregnancy rate between intervention group and control group stratified by RCT vs non-RCT.

| Study or Subgroup | Intervention Group | Control Group | Risk Ratio | Test for Overlap | Risk Ratio |
|-------------------|-------------------|---------------|------------|-----------------|------------|
|                   | Events            | Total         | Weight     | M-H, Random     | 5% CI      |
|                   | Events            | Total         |            |                 |            |
| 2.3.0 RCT study   | 147               | 21            | 200        | 11.9%           | 7.00 [4.63, 10.58] |
| 2.3.1 non RCT study | 20               | 51            | 52         | 10.6%           | 1.71 [0.93, 3.11] |

**Fig. 9.** Subgroup analysis of clinical pregnancy rate between intervention group and control group stratified by prior history of failed cycles.

| Study or Subgroup | Intervention Group | Control Group | Risk Ratio | Test for Overlap | Risk Ratio |
|-------------------|-------------------|---------------|------------|-----------------|------------|
|                   | Events            | Total         | Weight     | M-H, Random     | 5% CI      |
|                   | Events            | Total         |            |                 |            |
| 2.2.2 First IVF/ICSI | 147             | 200          | 200        | 11.9%           | 7.00 [4.63, 10.58] |

**Figures**

- Fig. 8: Subgroup analysis of clinical pregnancy rate between intervention group and control group stratified by RCT vs non-RCT.
- Fig. 9: Subgroup analysis of clinical pregnancy rate between intervention group and control group stratified by prior history of failed cycles.
feasible and three non-RCTs were included in our analysis, which may compromise the level of evidence. Secondly, no interventions were given in the control group of some RCTs, and thus blinding of participants was not feasible. And different stimulation methodologies were used in the included studies, such as different instruments (hysteroscopic sci-
sors, biopsy forceps, bipolar electrodes, Novak curette or pipelle tube), sites (the posterior wall of the uterus alone; the fundus, anterior/posterior walls and both sides; or the fundus and posterior wall), as well as length, width, depth and quantity of stimulation. As these differences may induce variable endometrial responses and then have different effects on pregnancy outcomes, performance bias may exist. Most published studies were performed in patients with abnormal hysteroscopic findings and the incidence of unexpected hysteroscopic lesions was up to 45.1% [25]; the presence of hysteroscopic abnormalities may confound the baseline characteristics of participants, and such studies cannot be included in our analysis. And thus, only a small number of studies were included, which may cause a lack of effective way to guide the method for endometrial mechanical stimulation. Thirdly, fresh embryo transplantation was performed in 7 of the 8 included studies, and only in the Timur Gürgan 2019 [18] study fresh or thawed embryo transplantation was performed according to patient’s preferences. Thus, our findings have limited implications for patients undergoing frozen-thawed embryo transplantation. Finally, only one study assessing luteal-phase endometrial mechanical stimulation prior to the first IVF/ICSI cycle in patients with normal hysteroscopic findings was included in this meta-analysis, and the stability of our findings may be affected by the large sample size and high weights of this study. Thus, more high-quality studies are needed.

5. Conclusions

In conclusion, based on the available evidence, endometrial mechanical stimulation may improve live birth rate, clinical pregnancy rate and reduce abortion rate in patients with normal hysteroscopic findings who are undergoing IVF/ICSI. The benefits may be even greater if this therapy is given in the luteal phase and in patients who are in their first IVF/ICSI cycle in patients with normal hysteroscopic findings. However, due to the limited quantity and quality of the included studies, more high-quality RCTs are required to confirm these findings and further define the appropriate indications, optimal timing, instrument, site and extent of endometrial mechanical stimulation.

Author contributions

HC, LYL and JL designed the research study. LYL and JL performed the research and collected the data. LZX provided help and advice to LYL and JL. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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