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-

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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 found 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 (Hysteroscop*) OR (Endoscop*) OR (mini-hysteroscop*) OR (minihysteroscop*)) 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 reproducti*) OR (IVF) OR (*in vitro* fertili*) 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.
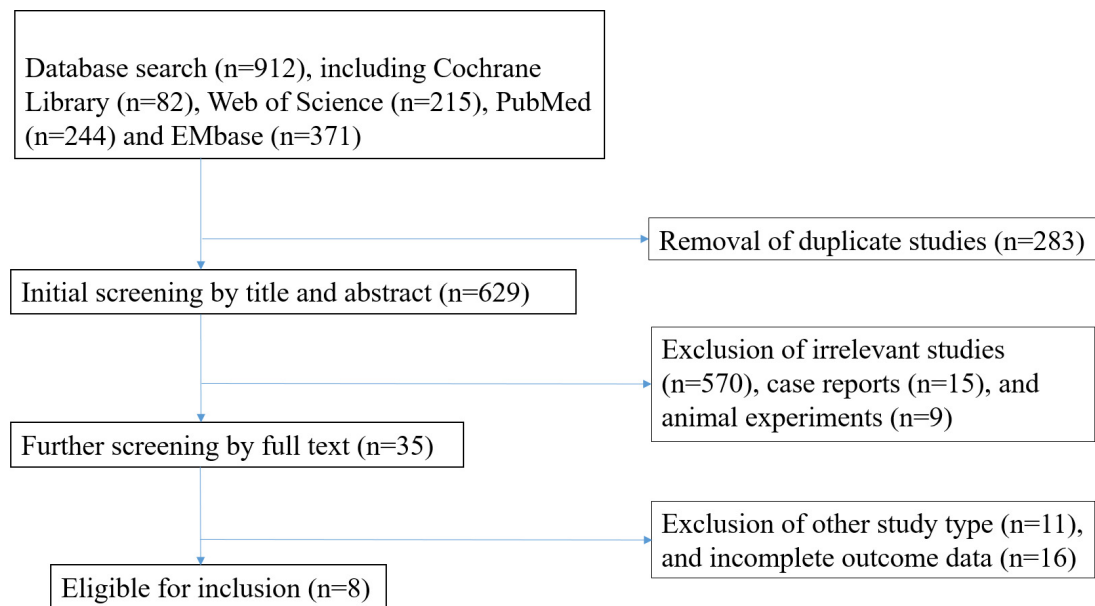
Fig. 1. Flow chart of study selection.

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 $\alpha = 0.05$. 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.

3.2 Basic characteristics and quality assessment

Tables 1,2 (Ref. [6,8,13–18]) presented the basic characteristics of the included studies. A total of 1494 patients from 8 countries or regions were included; of the 8 articles, 2 [17,18] had impact factors greater than 3 points, while the quality of the other articles was relatively low. Fig. 2 presented the assessment of risk of bias for the included RCTs. All RCTs described the process of random sequence generation, and all were of low risk; 3 RCTs [8,13,14] used sealed envelopes for allocation concealment and were rated as low risk, while the other 2 RCTs [16,18] did not mention allocation concealment and were rated as uncertain risk; only 1 RCT [13] achieved double-blindness and was rated as low risk, while the other RCTs were rated as high risk because blinding was not feasible; no loss to follow-up was reported in 3 RCTs [8,13,14], and the loss to follow-up rate was lower than 20% in the other 2 RCTs [16,18], so all RCTs were rated as low risk in terms of data integrity; the study protocol was not available in all RCTs, and thus the risk of selective reporting was considered as uncertain; all RCTs appeared to be free of other sources of bias, and were regarded as low risk. The methodological quality assessment of non-RCTs was presented in Table 3 (Ref. [6,15,17]). All non-RCTs scored at least 12, and therefore all could be included in our meta-analysis.

Table 1. Basic characteristics of the included studies.

Study	Study design	Study quality	Country	No. of patients (T/C)	Mean age (T/C, years)	Interventions T	C	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	②③④
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	①②③④⑤⑥
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	①②③⑥
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	①②③⑥
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	②③④⑤
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	①③④⑤⑥
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	①③④⑤
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	①③④
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	①③⑤

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 Live birth 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 in both RCTs [RR = 2.14, 95% CI (1.76, 2.60), $p < 0.00001$] and non-RCTs [RR = 2.29, 95% CI (1.10, 4.80), $p = 0.003$] (Fig. 4). Hysteroscopic endometrial mechanical stimulation significantly improved the live birth rate 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).

Fig. 2. Assessment of risk of bias for the included RCTs.

3.3.2 Clinical pregnancy rate

Eight studies were included for this analysis [6,8,13–18]. Due to significant heterogeneity across these studies [$p < 0.00001$, $I^2 = 84\%$], 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 in both RCTs [RR = 2.36, 95% CI (1.18, 4.72), $p = 0.02$] and non-RCTs [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 = 1.77, 95% CI (1.41, 2.23), $p < 0.00001$], those in their first IVF/ICSI 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
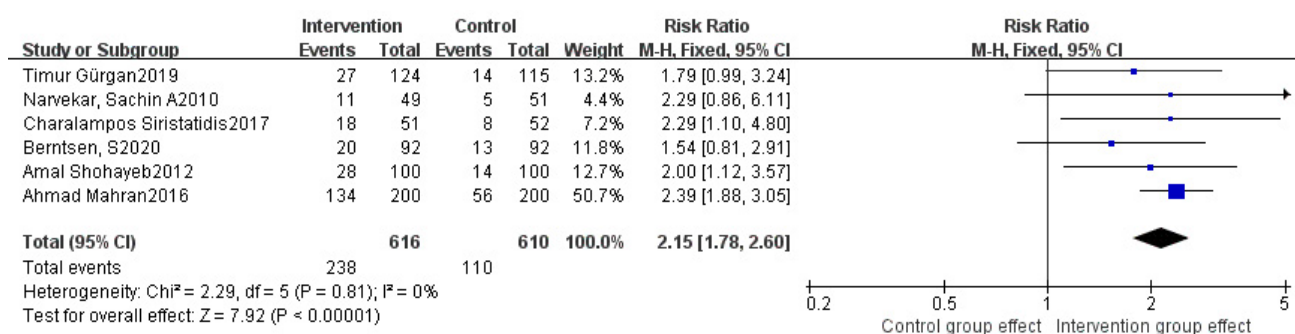
Study or Subgroup	Intervention Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Timur Gürgan2019	27	124	14	115	13.2%	1.79 [0.99, 3.24]
Narvekar, Sachin A2010	11	49	5	51	4.4%	2.29 [0.86, 6.11]
Charalampos Siristatidis2017	18	51	8	52	7.2%	2.29 [1.10, 4.80]
Berntsen, S2020	20	92	13	92	11.8%	1.54 [0.81, 2.91]
Amal Shohayeb2012	28	100	14	100	12.7%	2.00 [1.12, 3.57]
Ahmad Mahran2016	134	200	56	200	50.7%	2.39 [1.88, 3.05]
Total (95% CI)		616		610	100.0%	2.15 [1.78, 2.60]
Total events	238		110			

Heterogeneity: Chi² = 2.29, df = 5 (P = 0.81); I² = 0%
Test for overall effect: Z = 7.92 (P < 0.00001)

Risk Ratio M-H, Fixed, 95% CI — 0.2 0.5 1 2 5 — Control group effect / Intervention group effect

Fig. 3. Comparison of live birth rate between intervention group and control group.

Study or Subgroup	Intervention group Events	Total	Control group Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 RCT study						
Ahmad Mahran2016	134	200	56	200	50.7%	2.39 [1.88, 3.05]
Amal Shohayeb2012	28	100	14	100	12.7%	2.00 [1.12, 3.57]
Berntsen, S2020	20	92	13	92	11.8%	1.54 [0.81, 2.91]
Narvekar, Sachin A2010	11	49	5	51	4.4%	2.29 [0.86, 6.11]
Timur Gürgan2019	27	124	14	115	13.2%	1.79 [0.99, 3.24]
Subtotal (95% CI)		565		558	92.8%	2.14 [1.76, 2.60]
Total events	220		102			

Heterogeneity: Chi² = 2.27, df = 4 (P = 0.69); I² = 0%
Test for overall effect: Z = 7.60 (P < 0.00001)

3.2.2 non-RCT study						
Charalampos Siristatidis2017	18	51	8	52	7.2%	2.29 [1.10, 4.80]
Subtotal (95% CI)		51		52	7.2%	2.29 [1.10, 4.80]
Total events	18		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.21 (P = 0.03)

Total (95% CI)		616		610	100.0%	2.15 [1.78, 2.60]
Total events	238		110			

Heterogeneity: Chi² = 2.29, df = 5 (P = 0.81); I² = 0%
Test for overall effect: Z = 7.92 (P < 0.00001)
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%

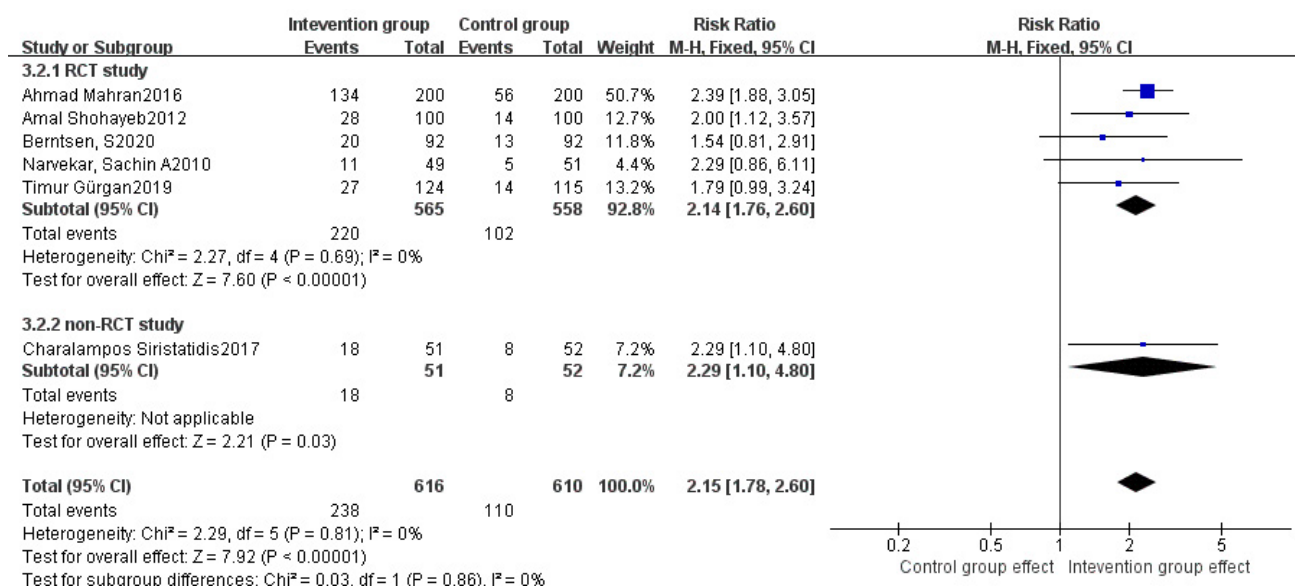Risk Ratio M-H, Fixed, 95% CI — 0.2 0.5 1 2 5 — Control group effect / Intevention group effect

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

Study or Subgroup	Intervention group Events	Total	Control group Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 ≥1 previous failed cycles						
Amal Shohayeb2012	28	100	14	100	12.7%	2.00 [1.12, 3.57]
Berntsen, S2020	20	92	13	92	11.8%	1.54 [0.81, 2.91]
Charalampos Siristatidis2017	18	51	8	52	7.2%	2.29 [1.10, 4.80]
Narvekar, Sachin A2010	11	49	5	51	4.4%	2.29 [0.86, 6.11]
Timur Gürgan2019	27	124	14	115	13.2%	1.79 [0.99, 3.24]
Subtotal (95% CI)		416		410	49.3%	1.90 [1.41, 2.56]
Total events	104		54			

Heterogeneity: Chi² = 0.88, df = 4 (P = 0.93); I² = 0%
Test for overall effect: Z = 4.22 (P < 0.0001)

3.3.2 First IVF/ICSI						
Ahmad Mahran2016	134	200	56	200	50.7%	2.39 [1.88, 3.05]
Subtotal (95% CI)		200		200	50.7%	2.39 [1.88, 3.05]
Total events	134		56			

Heterogeneity: Not applicable
Test for overall effect: Z = 7.05 (P < 0.00001)

Total (95% CI)		616		610	100.0%	2.15 [1.78, 2.60]
Total events	238		110			

Heterogeneity: Chi² = 2.29, df = 5 (P = 0.81); I² = 0%
Test for overall effect: Z = 7.92 (P < 0.00001)
Test for subgroup differences: Chi² = 1.37, df = 1 (P = 0.24), I² = 26.9%

Risk Ratio M-H, Fixed, 95% CI — 0.2 0.5 1 2 5 — Control group effect / Intervention group effect
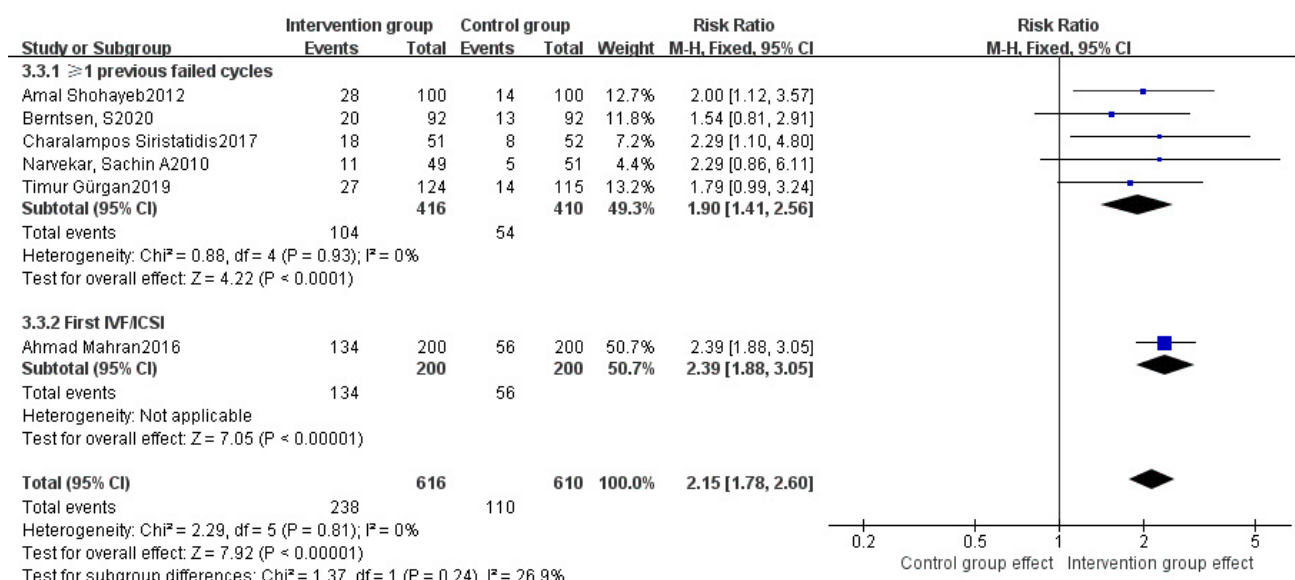
Fig. 5. Subgroup analysis of live birth rate between intervention group and control group stratified by prior history of failed cycles.

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
Charalampos Siristatidis 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 of fundus and posterior wall of uterine cavity was done three times.	first IVF/ICSI	FET
Amal Shohayeb 2012 [13]	Curettage of the fundus and posterior wall once by Novak curette.	≥2 previous failed cycles	FET
Narvekar, Sachin A 2010 [14]	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 mid-line 10–15 mm from the fundus by a claw forceps, the depth and width of the injured site was 2 × 2 mm.	≥2 transfers of good-quality embryos	FET

FET, fresh embryo transfer; TET, thawing embryo transfer; IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm injection.
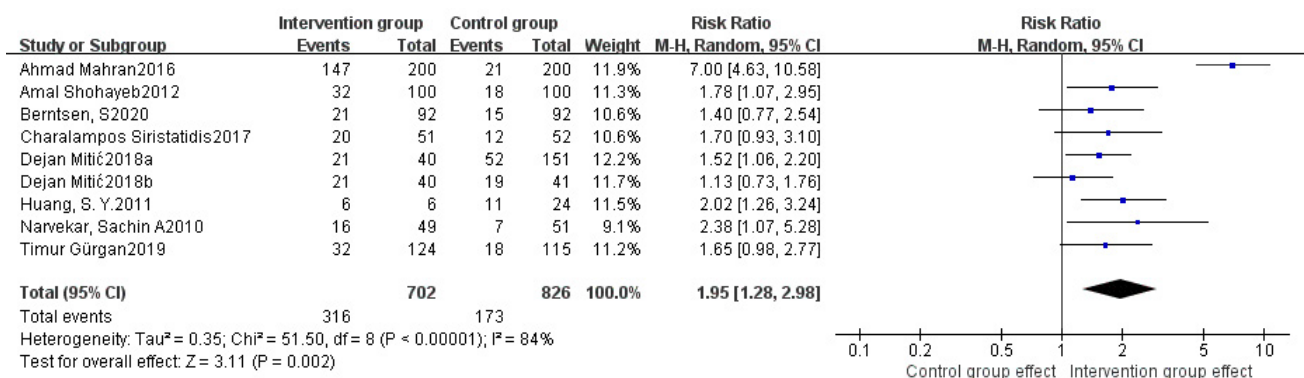
Fig. 6. Comparison of clinical pregnancy rate between intervention group and control group.

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.

Non-comparative study

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.
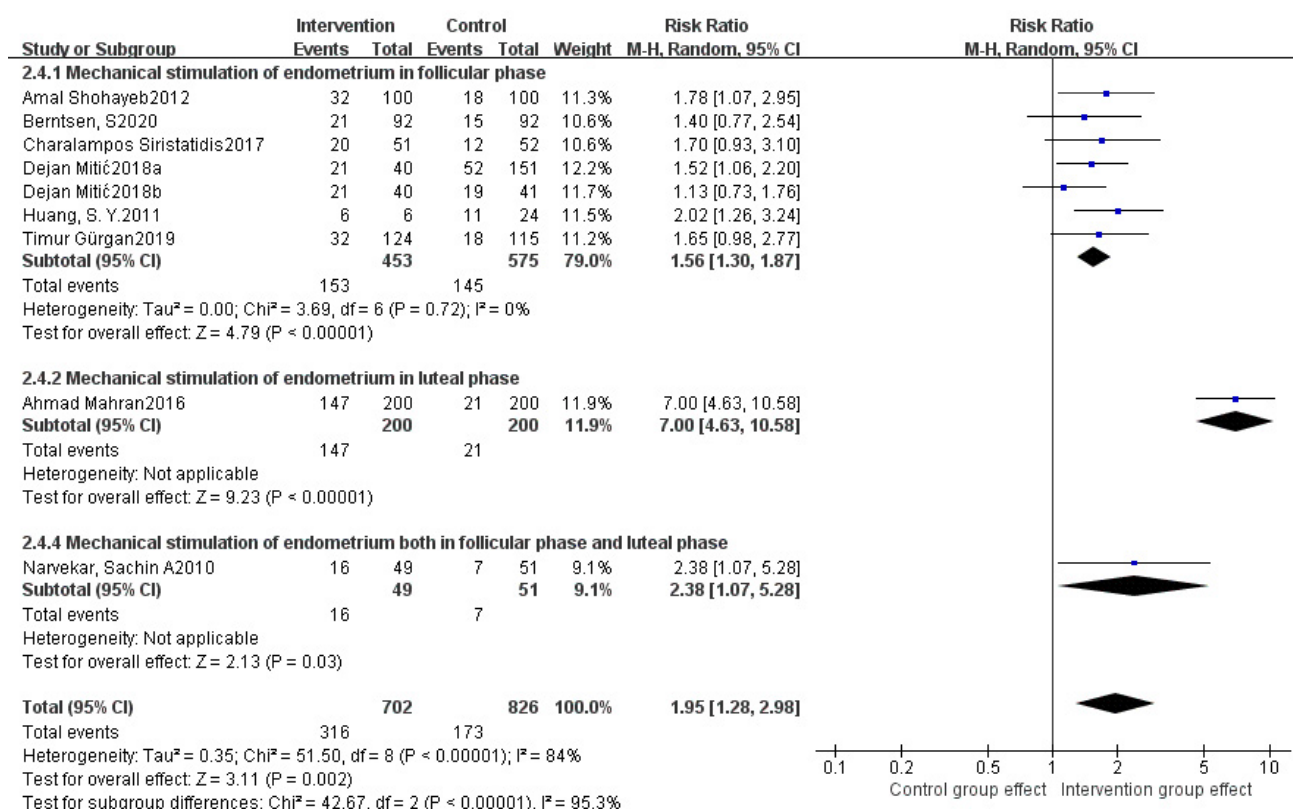
Fig. 7. Subgroup analysis of clinical pregnancy rate between intervention group and control group stratified by timing of stimulation.

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 the treatment group compared with those of the control group in both RCTs and non-RCTs, and a significantly lower abortion rate was also found in the treatment group in 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. A significantly lower abortion rate was found in patients undergoing their first IVF/ICSI cycle, but not in those with at least one failed 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-
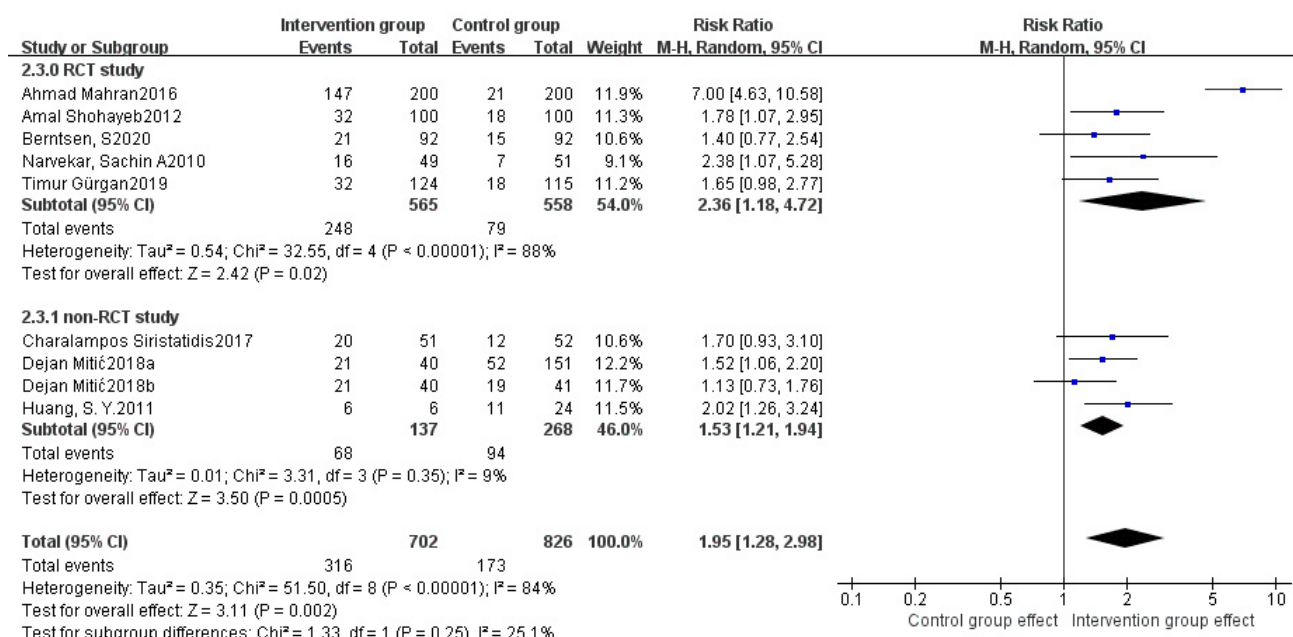
Study or Subgroup	Intervention group Events	Total	Control group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.0 RCT study						
Ahmad Mahran2016	147	200	21	200	11.9%	7.00 [4.63, 10.58]
Amal Shohayeb2012	32	100	18	100	11.3%	1.78 [1.07, 2.95]
Berntsen, S2020	21	92	15	92	10.6%	1.40 [0.77, 2.54]
Narvekar, Sachin A2010	16	49	7	51	9.1%	2.38 [1.07, 5.28]
Timur Gürgan2019	32	124	18	115	11.2%	1.65 [0.98, 2.77]
Subtotal (95% CI)		565		558	54.0%	2.36 [1.18, 4.72]
Total events	248		79			
Heterogeneity: Tau² = 0.54; Chi² = 32.55, df = 4 (P < 0.00001); I² = 88%						
Test for overall effect: Z = 2.42 (P = 0.02)						
2.3.1 non-RCT study						
Charalampos Siristatidis2017	20	51	12	52	10.6%	1.70 [0.93, 3.10]
Dejan Mitić2018a	21	40	52	151	12.2%	1.52 [1.06, 2.20]
Dejan Mitić2018b	21	40	19	41	11.7%	1.13 [0.73, 1.76]
Huang, S. Y.2011	6	6	11	24	11.5%	2.02 [1.26, 3.24]
Subtotal (95% CI)		137		268	46.0%	1.53 [1.21, 1.94]
Total events	68		94			
Heterogeneity: Tau² = 0.01; Chi² = 3.31, df = 3 (P = 0.35); I² = 9%						
Test for overall effect: Z = 3.50 (P = 0.0005)						
Total (95% CI)		702		826	100.0%	1.95 [1.28, 2.98]
Total events	316		173			
Heterogeneity: Tau² = 0.35; Chi² = 51.50, df = 8 (P < 0.00001); I² = 84%						
Test for overall effect: Z = 3.11 (P = 0.002)						
Test for subgroup differences: Chi² = 1.33. df = 1 (P = 0.25). I² = 25.1%						

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

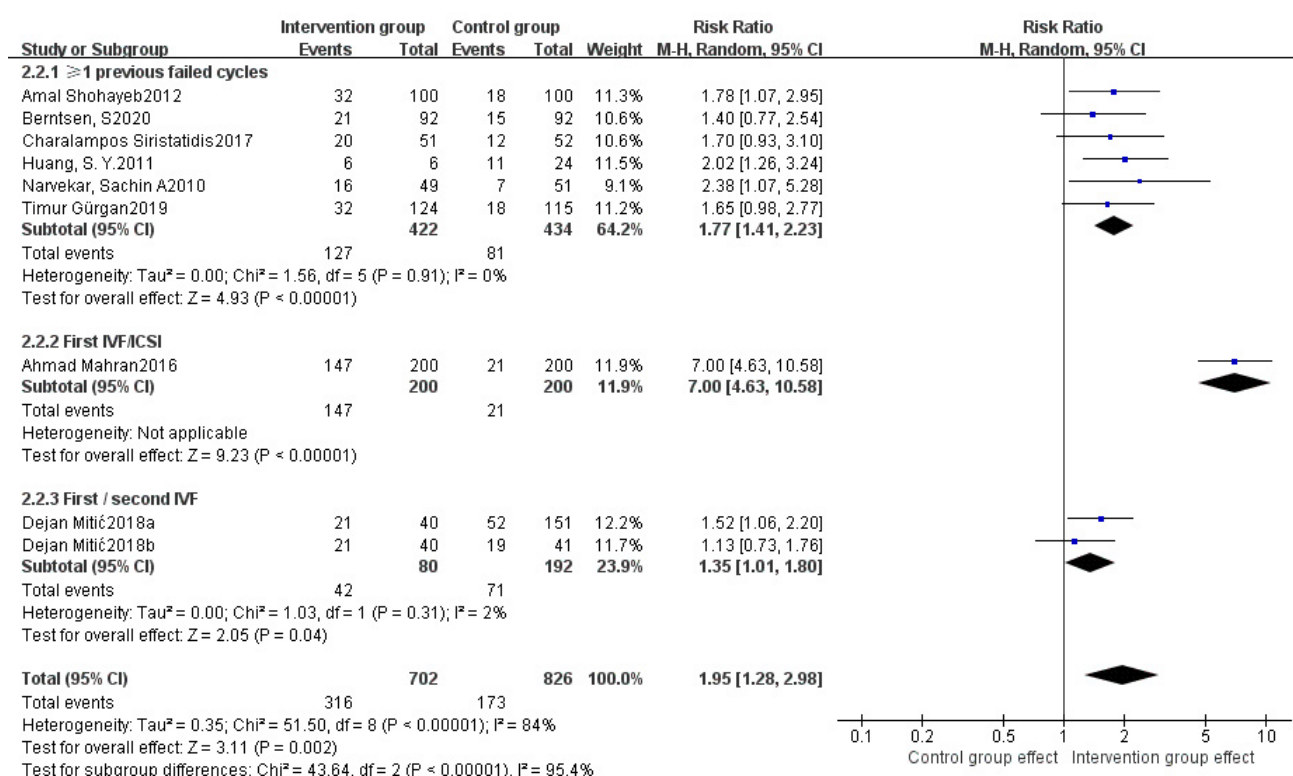| Study or Subgroup	Intervention group Events	Total	Control group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 ≥1 previous failed cycles						
Amal Shohayeb2012	32	100	18	100	11.3%	1.78 [1.07, 2.95]
Berntsen, S2020	21	92	15	92	10.6%	1.40 [0.77, 2.54]
Charalampos Siristatidis2017	20	51	12	52	10.6%	1.70 [0.93, 3.10]
Huang, S. Y.2011	6	6	11	24	11.5%	2.02 [1.26, 3.24]
Narvekar, Sachin A2010	16	49	7	51	9.1%	2.38 [1.07, 5.28]
Timur Gürgan2019	32	124	18	115	11.2%	1.65 [0.98, 2.77]
Subtotal (95% CI)		422		434	64.2%	1.77 [1.41, 2.23]
Total events	127		81			
Heterogeneity: Tau² = 0.00; Chi² = 1.56, df = 5 (P = 0.91); I² = 0%						
Test for overall effect: Z = 4.93 (P < 0.00001)						
2.2.2 First IVF/ICSI						
Ahmad Mahran2016	147	200	21	200	11.9%	7.00 [4.63, 10.58]
Subtotal (95% CI)		200		200	11.9%	7.00 [4.63, 10.58]
Total events	147		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 9.23 (P < 0.00001)						
2.2.3 First / second IVF						
Dejan Mitić2018a	21	40	52	151	12.2%	1.52 [1.06, 2.20]
Dejan Mitić2018b	21	40	19	41	11.7%	1.13 [0.73, 1.76]
Subtotal (95% CI)		80		192	23.9%	1.35 [1.01, 1.80]
Total events	42		71			
Heterogeneity: Tau² = 0.00; Chi² = 1.03, df = 1 (P = 0.31); I² = 2%						
Test for overall effect: Z = 2.05 (P = 0.04)						
Total (95% CI)		702		826	100.0%	1.95 [1.28, 2.98]
Total events	316		173			
Heterogeneity: Tau² = 0.35; Chi² = 51.50, df = 8 (P < 0.00001); I² = 84%						
Test for overall effect: Z = 3.11 (P = 0.002)						
Test for subgroup differences: Chi² = 43.64. df = 2 (P < 0.00001). I² = 95.4%						

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

chanical 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 mechan-

ical 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
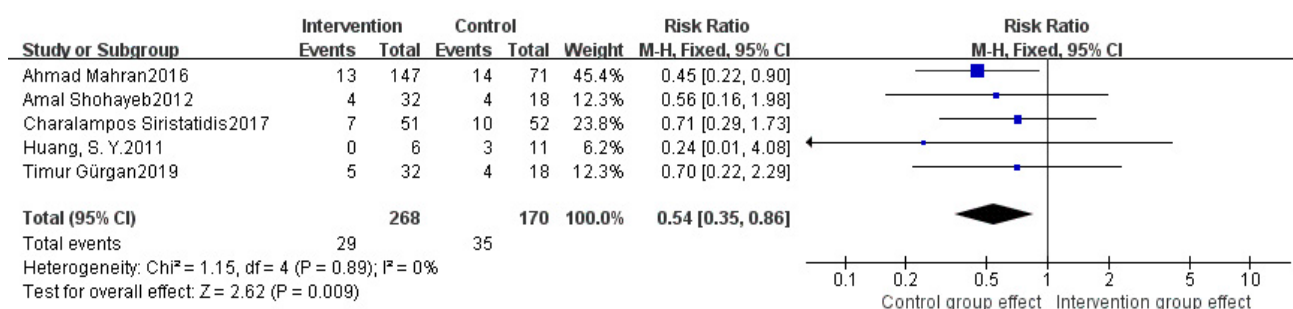
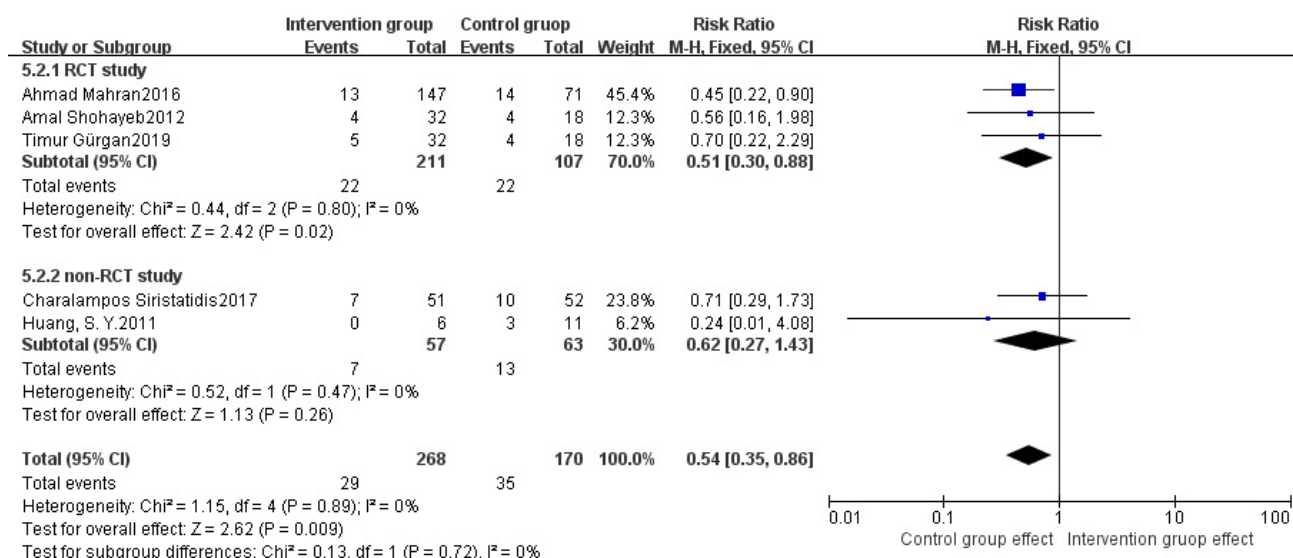**Fig. 10. Comparison of abortion rate between intervention group and control group.**

Fig. 11. Subgroup analysis of abortion rate between intervention group and control group stratified by RCT vs non-RCT.
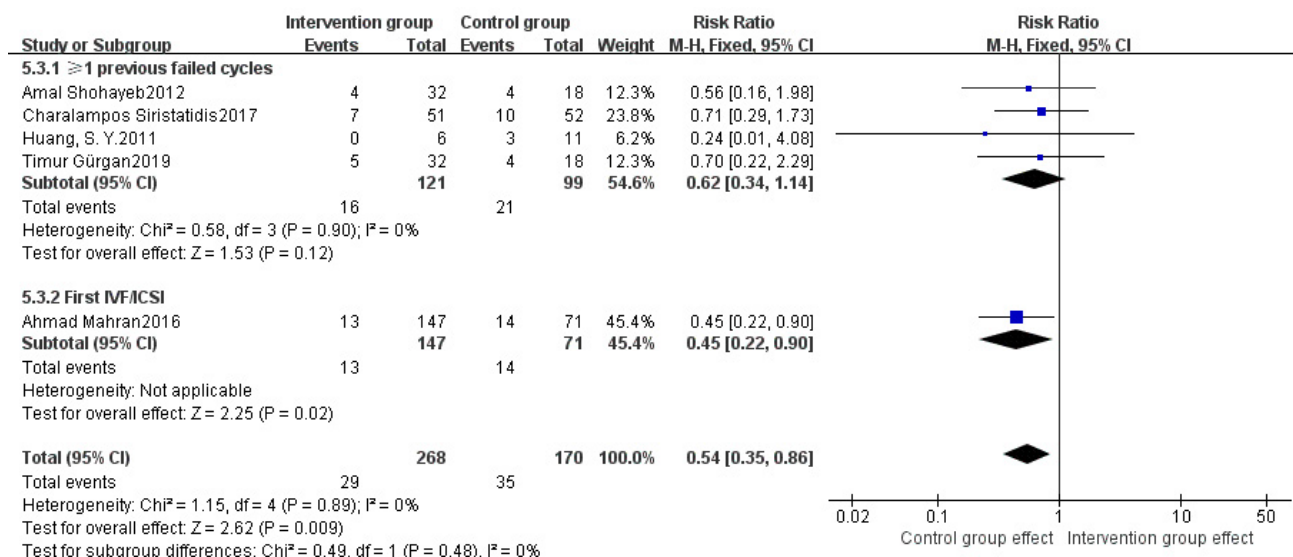

Fig. 12. Subgroup analysis of abortion rate between intervention group and control group stratified by prior history of failed cycles.

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 scis-

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, LJL and JL designed the research study. LJL and JL performed the research and collected the data. LZX provided help and advice to LJL 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.

Conflict of interest

The authors declare no conflict of interest.

References

[1] European IVF-Monitoring Consortium (EIM); European Society of Human Reproduction and Embryology (ESHRE), Kupka MS, D'Hooghe T, Ferraretti AP, de Mouzon J, *et al.* Assisted reproductive technology in Europe, 2011: results generated from European registers by ESHRE. Human Reproduction. 2016; 31: 233–248.

[2] Salamonsen LA, Evans J, Nguyen HPT, Edgell TA. The Microenvironment of Human Implantation: Determinant of Reproductive Success. American Journal of Reproductive Immunology. 2016; 75: 218–225.

[3] Mor G, Cardenas I, Abrahams V, Guller S. Inflammation and pregnancy: the role of the immune system at the implantation site. Annals of the New York Academy of Sciences. 2011; 1221: 80–87.

[4] Barash A, Dekel N, Fieldust S, Segal I, Schechtman E, Granot I. Local injury to the endometrium doubles the incidence of successful pregnancies in patients undergoing *in vitro* fertilization. Fertility and Sterility. 2003; 79: 1317–1322.

[5] Kalma Y, Granot I, Gnainsky Y, Or Y, Czernobilsky B, Dekel N, *et al.* Endometrial biopsy-induced gene modulation: first evidence for the expression of bladder-transmembranal uroplakin Ib in human endometrium. Fertility and Sterility. 2009; 91: 1042–1049.

[6] Mitic D, Basic M, Petric A, Stamenovic S. The effects of local endometrial injury made by hysteroscopy on *in vitro* fertilization outcome. Vojnosanitetski Pregled. 2018; 75: 570–575.

[7] Santamaria X, Katzorke N, Simón C. Endometrial 'scratching': what the data show. Current Opinion in Obstetrics & Gynecology. 2018; 28: 242–249.

[8] Mahran A, Ibrahim M, Bahaa H. The effect of endometrial injury on first cycle IVF/ICSI outcome: a randomized controlled trial. International Journal of Reproductive Biomedicine. 2016; 14: 193–198.

[9] Izquierdo Rodriguez A, de la Fuente Bitaine L, Spies K, Lora D, Galindo A. Endometrial Scratching Effect on Clinical Pregnancy Rates in Patients Undergoing Egg Donor *in Vitro* Fertilization Cycles: the ENDOSCRATCH Randomized Clinical Trial (NCT03108157). Reproductive Sciences. 2020; 27: 1863–1872.

[10] Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0 (updated March 2011). The Cochrane Collaboration. 2011. Available at: https://handbook-5-1.cochrane.org/ (Accessed: 1 October 2018)

[11] Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi

J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ Journal of Surgery. 2003; 73: 712–716.

[12] RevMan. Review Manager (RevMan) [Computer program]. Version 5.3.0. Copenhagen: The Nordic Cochrane Centre. The Cochrane Collaboration. 2014. Available at: https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman/revman-5-download (Accessed: 20 January 2019).

[13] Shohayeb A, El-Khayat W. Does a single endometrial biopsy regimen (S-EBR) improve ICSI outcome in patients with repeated implantation failure? A randomised controlled trial. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2012; 164: 176–179.

[14] Narvekar SA, Gupta N, Shetty N, Kottur A, Srinivas M, Rao KA. Does local endometrial injury in the nontransfer cycle improve the IVF-ET outcome in the subsequent cycle in patients with previous unsuccessful IVF? a randomized controlled pilot study. Journal of Human Reproductive Sciences. 2010; 3: 15–19.

[15] Siristatidis C, Kreatsa M, Koutlaki N, Galazios G, Pergialiotis V, Papantoniou N. Endometrial injury for RIF patients undergoing IVF/ICSI: a prospective nonrandomized controlled trial. Gynecological Endocrinology. 2017; 33: 297–300.

[16] Berntsen S, Hare KJ, Løssl K, Bogstad J, Palmø J, Prætorius L, *et al*. Endometrial scratch injury with office hysteroscopy before IVF/ICSI: a randomised controlled trial. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2020; 252: 112–117.

[17] Huang S, Wang C, Soong Y, Wang H, Wang M, Lin C, *et al*. Site-specific endometrial injury improves implantation and pregnancy in patients with repeated implantation failures. Reproductive Biology and Endocrinology. 2011; 9: 140.

[18] Gürgan T, Kalem Z, Kalem MN, Ruso H, Benkhalifa M, Makrigiannakis A. Systematic and standardized hysteroscopic endometrial injury for treatment of recurrent implantation failure. Reproductive BioMedicine Online. 2019; 39: 477–483.

[19] Sar-Shalom Nahshon C, Sagi-Dain L, Wiener-Megnazi Z, Dirnfeld M. The impact of intentional endometrial injury on reproductive outcomes: a systematic review and meta-analysis. Human Reproduction Update. 2019; 25: 95–113.

[20] Nahshon C, Sagi-Dain L, Dirnfeld M. The impact of endometrial injury on reproductive outcomes: results of an updated meta-analysis. Reproductive Medicine and Biology. 2020; 19: 334–349.

[21] Humphrey KW. Interactions between oestradiol 3, 17 beta and progesterone on the induction and growth of deciduomata in ovariectomized mice. Australian Journal of Biological Sciences. 1969; 22: 689–699.

[22] Gnainsky Y, Granot I, Aldo PB, Barash A, Or Y, Schechtman E, *et al*. Local injury of the endometrium induces an inflammatory response that promotes successful implantation. Fertility and Sterility. 2010; 94: 2030–2036.

[23] Kumbak B, Sahin L, Ozkan S, Atilgan R. Impact of luteal phase hysteroscopy and concurrent endometrial biopsy on subsequent IVF cycle outcome. Archives of Gynecology and Obstetrics. 2014; 290: 369–374.

[24] Cao H, You D, Yuan M, Xi M. Hysteroscopy after repeated implantation failure of assisted reproductive technology: a meta-analysis. Journal of Obstetrics and Gynaecology Research. 2018; 44: 365–373.

[25] El-Mazny A, Abou-Salem N, El-Sherbiny W, Saber W. Outpatient hysteroscopy: a routine investigation before assisted reproductive techniques? Fertility and Sterility. 2011; 95: 272–276.