Effect of hysteroscopy before starting in-vitro fertilization for women with recurrent implantation failure
A meta-analysis and systematic review

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Abstract

Objective: To study if hysteroscopy (HSC) before starting an in-vitro fertilization (IVF) cycle improves IVF outcomes in women with recurrent implantation failure (RIF).

Methods: The Medline, Cochrane, EMBASE, and Google Scholar databases were searched using the following keywords until March 31, 2017: in-vitro fertilization; infertility; hysteroscopy; recurrence; embryo implantation; and pregnancy. Randomized controlled trials (RCTs), two-arm prospective studies, and retrospective studies were included.

Results: Three RCTs, 3 nonrandomized prospective studies, and 2 retrospective cohort studies were included. The eligible studies included 3932 women with RIF: 1841 in the HSC group and 2091 in the control group. The clinical pregnancy rate and implantation rate was significantly higher in the HSC group compared with the control group (for clinical pregnancy rate, pooled odds ratio [OR] = 1.64, 95% confidence intervals [CI]: 1.30–2.07, $P < 0.001$; for implantation rate, pooled OR = 1.22, 95% CI: 1.02–1.45, $P = 0.025$). The live birth rate (pooled OR = 1.30, 95% CI: 0.90–1.88, $P = 0.168$) and the miscarriage rate (pooled OR = 0.94, 95% CI: 0.66–1.35, $P = 0.744$) of the 2 groups were not statistically significantly.

Conclusions: HSC improved the implantation rate and clinical pregnancy rates, but failed to improve live birth rate and did not affect the miscarriage rate in women with RIF undergoing IVF. Since HSC plays a significant role in pregnancy and birth outcomes of women with RIF, further studies are warranted.

Abbreviations: ART = assisted reproductive techniques, CI = confidence intervals, HSC = hysteroscopy, I^2 = inconsistency index, ICSI = IVF/intracytoplasmic sperm injection, IVF = in-vitro fertilization, NRS = nonrandomized study, OR = odds ratio, RCT = randomized controlled trial, RIF = recurrent implantation failure.

Keywords: hysteroscopy, in-vitro fertilization, infertility, recurrent implantation failure

1. Introduction

Among all of the difficulties that may be encountered during in-vitro fertilization (IVF), recurrent implantation failure (RIF)

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treatment remains the most challenging because the overall success rates of IVF in women with RIF is extremely low.[1,2] The probability of successful implantation of an embryo is only approximately 30%.[1] It is likely that implantation failure may be affected by different embryonic or endometrial factors. Although many studies focused on this topic, there is still no consensus on the definition for RIF.[1]

It has long been known that intrauterine pathologies can affect pregnancy rates in women undergoing IVF.[3,4] Currently, it is recommended to examine intrauterine pathologies before starting IVF/intracytoplasmic sperm injection (ICSI).[5–8] The best methods for assessing uterine abnormalities typically include some combination of transvaginal sonography, hysterosalpingography, and hysteroscopy (HSC).[9] However, hysterosalpingography has low specificity, high false-negative and false-positive rates.[10] Although transvaginal sonography is a noninvasive and reproducible technique, it is not very sensitive.[11] Outpatient HSC is the most commonly performed after IVF failure because HSC is typically performed if there is evidence of an abnormal uterine cavity from investigations.[9] HSC allows reliable visual assessment of the cervical canal and uterine cavity for intrauterine adhesions, endometrial polyps, submucous fibroids, endometritis, or uterine malformations that could interfere with implantation, and provides the opportunity to perform therapy in the same setting such as removing endometrial polyps, submucosal fibroids, or uterine neoplasms by excision or endometrial curettage.[12–14] Therefore, HSC is

currently the only direct method for observing physiological and pathological changes of endometrium as well as accurate biopsies and treatments.[14]

It has been reported that the prevalence of minor intrauterine abnormalities identified by HSC is as high as 30 to 45% under normal transvaginal sonography, and abnormalities found by HSC are significantly higher in patients with previous assisted reproductive techniques failure.[13,15,16] Two prospective and randomized controlled trials (RCTs) confirmed the value of HSC in women with RIF by demonstrating significantly increased clinical pregnancy rates.[17,18] Some studies have suggested that patients with/without RIF or with/without identifiable uterine pathology undergoing routine HSC before IVF can improve pregnancy outcomes.[6,19] In addition, a meta-analysis performed in 2008 suggested that HSC could improve the outcomes in women with RIF.[12] On the other hand, some authors have suggested there is no value for routing HSC in patients undergoing IVF assessment or in patients with RIF. A recent RCT study was designed to assess whether routine HSC before the first IVF treatment cycle could increase the rate of live births. The results demonstrated that routine HSC does not improve live birth rates in infertile women with a normal transvaginal ultrasound of the uterine cavity.[20] A retrospective study of 866 consecutive patients suggested that HSC should be used as a routine infertility examination because the diagnostic rate by HSC is high in patients with repeated IVF failure. However, comparing the clinical outcomes in patients with repeated IVF failure who had HSC with no pathology and with pathology, the authors did not find any statistical differences. Therefore, performing office HSC before IVF–embryo transfer is of no significant value in improving pregnancy outcomes.[21] A 2012 review of the literature by Surrey[22] concluded that insufficient number of prospective RCTs can clearly demonstrate that removal of uterine abnormalities by HSC can improve IVF outcomes.

Thus, the objective of this study was to perform an updated meta-analysis of clinical studies (RCTs, nonrandomized prospective studies, and retrospective studies) to determine if HSC before starting an IVF cycle in women with RIF can improve the implantation rate, clinical pregnancy rate, and live birth rate, and reduce miscarriage rate.

2. Methods

2.1. Literature search and study selection

The study was performed in accordance with the PRISMA guidelines.[23] Medline, Cochrane, EMBASE, and Google Scholar databases were searched until March 31, 2017 using the keywords: in-vitro fertilization; infertility; hysteroscopy; recurrence; embryo implantation; treatment failure; uterine diseases; and pregnancy. References of potentially relevant studies were also searched. The inclusion criteria in this study were: RCTs, nonrandomized 2-arm prospective studies, and 2-arm retrospective study; women with normal ultrasound examination of the uterine cavity and women with at least 2 failed IVF–embryo transfer attempts; patients received a diagnostic HSC before starting an IVF cycle; control group received no HSC; and quantitative data of the outcomes of interest were provided. Study exclusion criteria were: one-arm studies, letters, comments, editorials, case reports, proceedings, personal communications, and non-English publications; the patients in the studies were first received their first IVF trial; studies designed for assessing the efficacy of HSC-

associated scratching, biopsy, or treatment; and no data of the outcomes of interest. The search was performed by 2 independent reviewers, and the third reviewer was consulted to resolve any differences and to make a final decision by consensus.

2.2. Data extraction

The information and data were extracted from included studies that met the following inclusion criteria: the name of the first author, year of publication, study design, number of participants in each group, participants' age and sex, number of previous failed IVF cycles, cause(s) of infertility, and outcome data. The outcomes of the meta-analysis were clinical pregnancy rate, live birth rate, miscarriage rate, and implantation rate.

2.3. Quality assessment

For RCTs, the Cochrane Risk of Bias tool was utilized to assess the included studies.[24] All RCTs were reviewed and assigned a value of "low risk," "high risk," or "unclear" as follows: random sequence generation; allocation concealment; blinding of patients and personnel; blinding of outcome assessment; adequate assessment of each outcome; avoidance of a selective outcome report; and presence or absence of an intention-to-treat analysis. In addition, for nonrandomized studies (NRS), ACROBAT-NRSI tool[25] was used to evaluate the risk of bias. Briefly, the tool assessed 7 domains (confounding, selection of participants, measurement of interventions, departures from intended interventions, missing data, measurement of outcomes, and selection of the reported results). Quality assessment was performed by 2 reviewers, and a third reviewer was consulted to resolve any disagreements.

2.4. Statistical analysis

Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for binary outcomes between women with RIF who received HSC before the IVF cycle (HSC group) and those that did not receive a HSC before the IVF cycle (control group). A χ^2-based test of homogeneity was performed and the inconsistency index (I^2) and Q statistics were determined. Heterogeneity determined using the I^2 statistic was defined as follows: 0 to 24% = no heterogeneity; 25 to 49% = moderate heterogeneity; 50 to 74% = large heterogeneity; and 75 to 100% = extreme heterogeneity.[26] When the number of studies included in a meta-analysis is small, heterogeneity tests have low statistical power.[27] When tests for heterogeneity are underpowered, random effects models of analysis are routinely used.[28] In addition, the National Research Council 1992 report Combining Information: Statistical Issues and Opportunities for Research recommends the use of random-effects approaches for meta-analysis, and the exploration of sources of variation in study results.[29] Pooled effects were calculated, and a 2-sided P value < 0.05 was considered to indicate statistical significance. In addition, subgroup analysis was performed according to study design (randomized vs. nonrandomized). Sensitivity analysis was carried out using the leave one-out approach. If there were <10 studies, publication bias analysis was not performed because ≥10 studies are needed to detect funnel plot asymmetry.[30] All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ).

2.5. Ethics

Meta-analysis did not involve human subjects and does not require an institutional review board.

3. Results

3.1. Literature search

A flow diagram of study selection is shown in Figure 1. A total of 116 articles (records identified through database searching and other sources) were identified via the database searches and other sources. After removing the duplicates, 87 articles were screened by title and abstract, and 62 articles that did not meet the inclusion criteria were excluded. The remaining 25 full-text articles were reviewed, and 17 articles were excluded due to the different objective and study design (n = 5), studied first IVF cycle instead of recurrent IVF failure (n = 3); single-arm study (n = 4); non-English articles (n = 3), and duplicate in study population (n = 2) (Fig. 1). Thus, 8 studies were included in the meta-analysis.[14,17,18,31–35]

3.2. Study characteristics

The 8 studies comprised 3 RCTs, 2 retrospective cohort studies, and 3 nonrandomized prospective studies, and study characteristics were summarized in Table 1. The studies included a total of 3932 women with RIF: 1841 were in the HSC group and 2091 were in the control group (without hysteroscopic evaluation before ovarian stimulation for IVF treatment). Patients ranged in age from 26.7 to 38 years, and the mean number of previous failed IVF cycles ranged from 2 to 3.1.
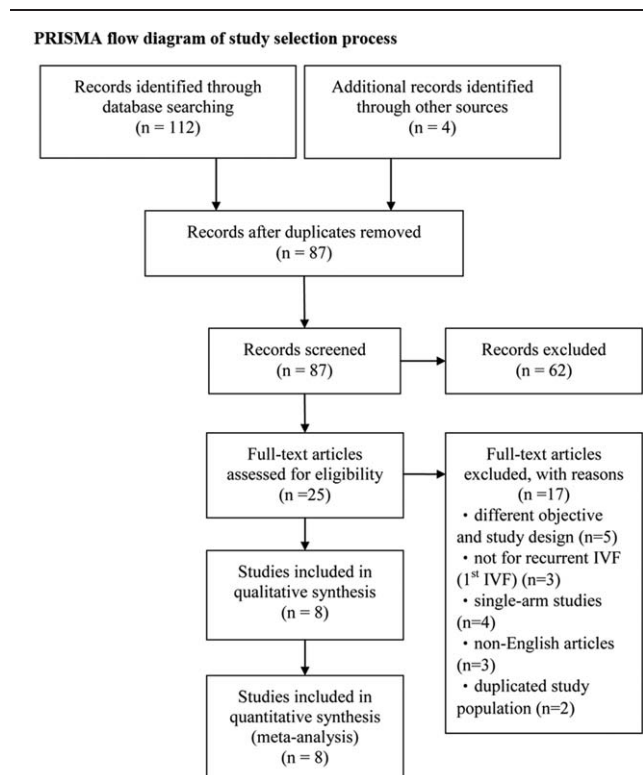

Figure 1. PRISMA flow diagram of study selection process. IVF = in-vitro fertilization.

3.3. Meta-analysis

3.3.1. Clinical pregnancy rate. Seven studies provided clinical pregnancy rate data and were included in the meta-analysis.[14,17,18,31,33–35] (Table 2) Moderate heterogeneity was found among the 6 studies (Q = 13.185, I^2 = 54.49%). The overall analysis revealed that the clinical pregnancy rate was significantly higher in the HSC group compared with the control group (pooled OR = 1.64, 95% CI: 1.30–2.07, P < 0.001) (Fig. 2A). Subgroup analysis was performed based on study design. Analysis of NRS revealed that the clinical pregnancy rate was significantly higher in the HSC group (pooled OR = 1.77, 95% CI: 1.29–2.43, P < 0.001). Analysis of RCTs also showed the clinical pregnancy rate was significantly higher in the HSC group (pooled OR = 1.50, 95% CI: 1.06–2.12, P = 0.021) (Fig. 2A).

3.3.2. Live birth rate. Only 5 studies provided live birth rate data, and were included in the analysis (2 were RCTs and 3 were NRS).[14,18,32–34] Moderate heterogeneity was noted among the 5 studies (Q = 6.007, I^2 = 55.59%). Pooled results from 5 studies showed there was no statistical significance in live birth rate (pooled OR = 1.30, 95% CI: 0.90–1.88, P = 0.168) (Fig. 2B). Subgroup analysis of the 2 RCTs and the 3 NRS both showed no significant difference in the live birth rate between the 2 groups (Fig. 2B).

3.3.3. Miscarriage rate. Only 4 studies provided miscarriage rate data, and were included in the analysis (2 were RCTs and 2 were NRS).[18,31–33] No heterogeneity was noted among the 4 studies (Q = 0.343, I^2 = 0%). Pooled results revealed no significant difference in the miscarriage rate between the 2 groups (pooled OR = 0.94, 95% CI: 0.66–1.35, P = 0.744) (Fig. 2C). Subgroup analysis of the 2 RCTs and the 2 NRS both showed no significant difference in the miscarriage rate between the 2 groups (Fig. 2C).

3.3.4. Implantation rate. Only 4 studies provided implantation rate data and were included in the meta-analysis.[14,31–33] No heterogeneity was found among the 4 studies (Q = 2.980, I^2 = 0%). The overall analysis revealed that the implantation rate was significantly higher in the HSC group compared with the control group (pooled OR = 1.22, 95% CI: 1.02–1.45, P = 0.025) (Fig. 2D). Subgroup of NRS revealed that the clinical pregnancy rate was significantly higher in the HSC group (pooled OR = 1.36, 95% CI: 1.10–1.69, P = 0.005). However, no subgroup analysis of RCT was performed because only 1 study provided implantation rate data in the subgroup of RCT (Fig. 2D).

3.4. Quality assessment

In this meta-analysis, ACROBAT-NRSI was used to evaluate the quality of the 5 NRS and Cochrane Risk of Bias tool was used to assess the risk of bias in 3 RCTs (Fig. 3). The 3 NRS had low risks of confounding, patient selection, measurement of interventions, missing data, outcome, and reported result (Fig. 3A and B). Overall, the quality of the 5 NRS was good. For the 3 RCTs, the random sequence and allocation concealment were appropriate but both performance bias and detection bias were high or unclear (Fig. 3C and D). Only one study mentioned that personnel and participants were unaware of the treatment.[27] All RCTs were at a low risk of attrition and reporting bias.

3.5. Sensitivity analysis

Sensitivity analyses were performed using the leave-one-out approach in which the meta-analysis of outcomes was performed

Table 1

Characteristics of studies included in the meta-analysis.

References	Study design	Intervention	Number of patients	Age (years)	Number of previous failed IVF cycles	Cause of infertility	Definition of RIF
[31]	Retrospective cohort study	Hysteroscopy	45	38 (35.0–39.5)	2 times: 30 (66.7%) ≥3 times: 15 (33.3%)	N/A	Women who failed implantation after repeating fair and/or good embryo transfer more than twice
		Control	90	37 (35.8–39.0)	2 times: 39 (43.3%) ≥3 times: 51 (56.7%)	N/A	
[32]	Retrospective cohort study	Hysteroscopy	119	30.7 ± 5.3	4.04 ± 1.5	N/A	Two or more unsuccessful ART/embryo transfer cycles despite the availability of good quality embryos
		Control	244	31.9 ± 4.4	4.06 ± 1.2	N/A	
[33]	RCT	Hysteroscopy	322	33 (31–35)*	2.7 ± 0.9	Male factor: 49%; tubal factor: 19%; anovulation: 7%; endometriosis: 12%; combined: 6%; unexplained: 16%	Women were reported previously having 2, 3, or 4 fresh or frozen IVF treatment cycles ending in an embryo transfer but no pregnancy
		Control	318	33 (31–35)*	2.7 ± 1.0	Male factor: 50%; tubal factor: 17%; anovulation: 8%; endometriosis: 8%; combined: 8%; unexplained: 19%	
[14]	Prospective study	Hysteroscopy	334	31.7 ± 3.6	N/A	Female: 26%; male: 37%; both: 37%	Women had more than 2 consecutive IVF–embryo transfer failures with at least 1 good-quality cleavage embryos on day 3 in each embryo transfer
		Control	338	31.7 ± 4.1	N/A	Female: 25%; male: 40%; both: 35%	
[34]	Prospective study	Hysteroscopy	142	32.6 ± 4.2	N/A	Female: 23%; male: 18%; unexplained: 59%	Women had ≥2 assisted reproductive technology cycles with fresh and good quality and quantity (at least 8) embryos transferred
		Control	211	32.7 ± 4.3	N/A	Female: 26%; male: 19%; unexplained: 53%	
[35]	Prospective study	Hysteroscopy	414	35.4 ± 4.0	N/A	N/A	Patient had history of 2 consecutive implantation failures despite the transfer of at least 1 good-quality embryo derived from fresh IVF cycles or from 1 fresh IVF
		Control	414	35.4 ± 4.0	N/A	N/A	
[18]	RCT	Hysteroscopy normal finding	160	27.4 ± 0.6	2.8 ± 0.3	Ovulatory: 45%; endometriosis: 39%; tubal factor: 16%	Patients who had undergone 2 or more failed IVF cycles, in which 2 or more good-quality embryos transferred
		Hysteroscopy abnormal finding	95	29.1 ± 0.9	2.4 ± 0.4	Ovulatory: 46%; endometriosis: 39%; tubal factor: 16%	
		Control	265	26.7 ± 0.5	2.6 ± 0.1	Ovulatory: 46%; endometriosis: 36%; tubal factor: 18%	
[17]	RCT	Hysteroscopy normal finding	154	35.4 ± 0.6	2.6 ± 0.4	Ovulatory: 33%; male: 31%; idiopathic: 36%	Patients who had undergone 2 or more failed IVF cycles, in which 2 or more good-quality embryos transferred
		Hysteroscopy abnormal finding	56	36.2 ± 0.1	3.1 ± 0.1	Ovulatory: 29%; male: 27%; idiopathic: 44%	
		Control	211	34.3 ± 0.8	2.8 ± 0.2	Ovulatory: 35%; male: 24%; idiopathic: 41%	

ART = assisted reproductive techniques, IVF = in-vitro fertilization, N/A = not available, RCT = randomized controlled trial, RIF = recurrent implantation failure.

* Data reported as mean (range).

with each study removed in turn (Table 3). The direction and magnitude of the combined estimates of clinical pregnancy rate and miscarriage rate did not vary markedly with the removal of any one study, indicating that the meta-analysis was robust and the results were not overly influenced by any study. However, after removing the data from the study published by Hosseini et al,[34] the pooled ORs of live birth rate in the HSC group became marginally significant ($P = 0.043$) compared with the control group. In addition, after the removal of study by the Gao et al,[14] the overall analysis showed no significant difference in implantation rate between HSC and control groups (pooled OR = 1.10, 95% CI: 0.86–1.40, $P = 0.440$), indicating that the pooled estimate of live birth rate and implantation rate might be overly influenced by the study of Hosseini et al[33] and Gao et al,[14] respectively.

4. Discussion

The purpose of this meta-analysis was to determine if HSC before an IVF cycle in patients with RIF improved pregnancy outcomes. The results indicated that HSC clearly improved the implantation rate and clinical pregnancy rate, but did not improve the live birth rate and reduce rate of miscarriage. The preponderance of studies has suggested that HSC before IVF improves outcomes in patients undergoing their first IVF cycle and in patients with RIF.[6,7,15,36] Previous studies reported a higher rate of uterine abnormalities in patients with RIF than in the general IVF population.[6,13,15,16,37] Another study[22] indicated that HSC can identify uterine pathologies that previously determined to be normal by transvaginal ultrasound, and that this correction can improve the pregnancy rate and live birth rates. For example, Dalal et al[7] studied 248 women with a variable number of failed IVF cycles
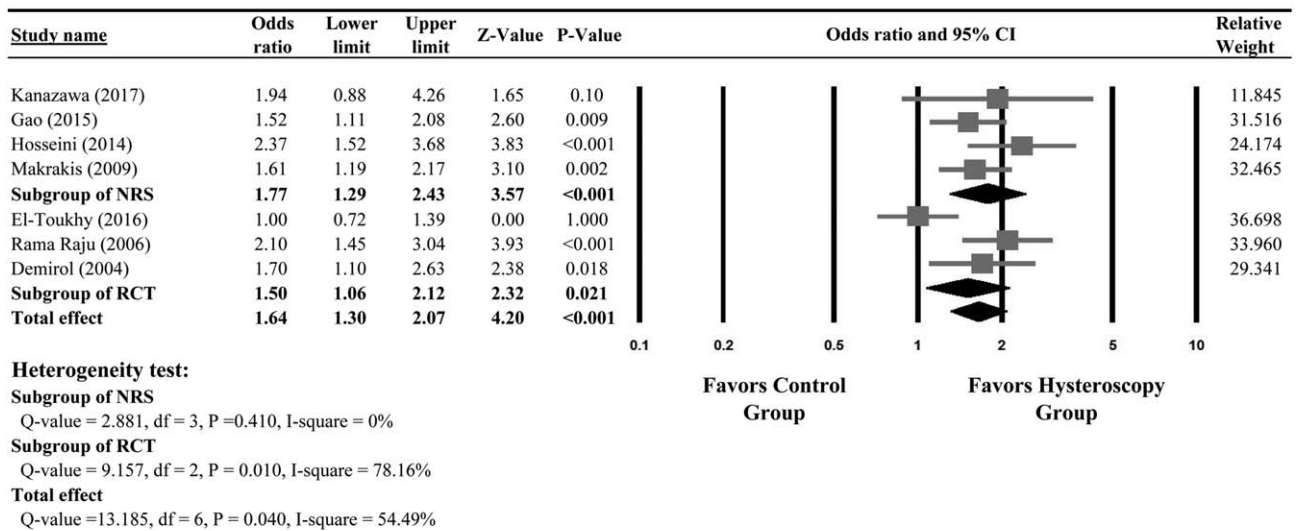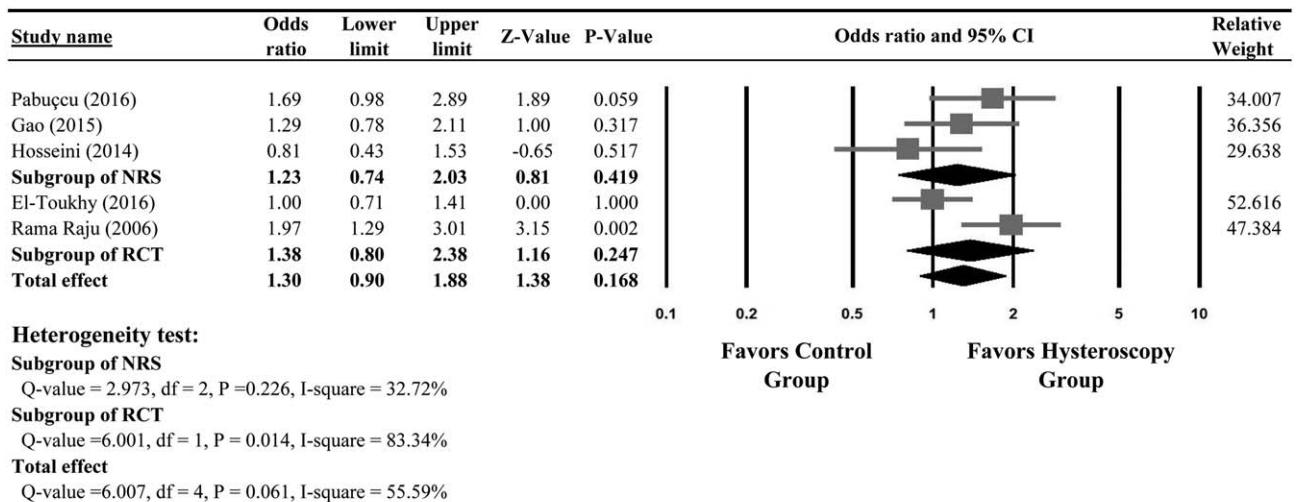
Figure 2. Meta-analysis forest plot for odds ratio of (A) clinical pregnancy rate; (B) live birth rate; (C) miscarriage rate; and (D) implantation rate, including subgroup analysis (RCTs and nonrandomized studies). CI = confidence intervals, NRS = nonrandomized study, RCT = randomized controlled trial.

Miscarriage rate

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	P-Value	Odds ratio and 95% CI	Relative Weight
Kanazawa (2017)	0.95	0.25	3.58	-0.07	0.943		27.134
Pabuçcu (2016)	1.16	0.52	2.61	0.37	0.712		72.866
Subgroup of NRS	**1.10**	**0.55**	**2.20**	**0.28**	**0.781**		
El-Toukhy (2016)	0.89	0.51	1.58	-0.39	0.697		55.386
Rama Raju (2006)	0.88	0.47	1.66	-0.40	0.692		44.614
Subgroup of RCT	**0.89**	**0.58**	**1.35**	**-0.55**	**0.579**		
Total effect	**0.94**	**0.66**	**1.35**	**-0.33**	**0.744**		

Favors Control Group — Favors Hysteroscopy Group

Heterogeneity test:
Subgroup of NRS
  Q-value =0.065, df = 1, P =0.800, I-square = 0%
Subgroup of RCT
  Q-value =0.001, df = 1, P = 0.973, I-square = 0%
Total effect
  Q-value =0.343, df = 3, P = 0952, I-square = 0%

C

Implantation rate

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	P-Value	Odds ratio and 95% CI	Relative Weight
Kanazawa (2017)	1.53	0.75	3.11	1.18	0.238		
Pabuçcu (2016)	1.25	0.73	2.15	0.83	0.408		34.007
Gao (2015)	1.37	1.06	1.76	2.43	0.015		36.356
Subgroup of NRS	**1.36**	**1.10**	**1.69**	**2.79**	**0.005**		
El-Toukhy (2016)	1.00	0.75	1.34	0.00	1.000		52.616
Subgroup of RCT	**1.00**	**0.75**	**1.34**	**0.00**	**1.000**		
Total effect	**1.22**	**1.02**	**1.45**	**2.24**	**0.025**		

Favors Control Group — Favors Hysteroscopy Group

Heterogeneity test:
Subgroup of NRS
  Q-value = 0.196, df = 2, P =0.907, I-square = 0%
Total effect
  Q-value =2.980, df = 3, P = 0.395, I-square = 0%

D

Figure 2. (Continued).

and showed that HSC identified 25% of female intrauterine pathologies. When the abnormality was identified, the pregnancy rate after IVF was significantly increased. On the other hand, the study by Chung et al[38] reported that HSC improved the live birth rate in women with RIF, regardless of uterine abnormalities. Taken together, these data suggest that HSC should be mandatory in the evaluation of patients with RIF.

While it appears clear that HSC is useful in patients with RIF, other authors have examined whether routine HSC before the first IVF cycle is valuable. A RTC study reported by Shawki et al[6] randomized 240 patients with normal hysterosalpingo-grams and/or normal transvaginal sonography to receive HSC before ICSI. A significantly higher pregnancy rate was observed in the HSC group compared to the non-HSC group. Similarly, Elsetohy et al[36] divided patients with normal transvaginal ultrasonography into 2 groups. One group received HSC before ICSI and the other group did not. HSC detected abnormalities in about 50% of patients who diagnosed as normal by normal ultrasound, and HSC significantly improved the pregnancy rate with an OR=2.77. Two prior meta-analyses have examined the

value of HSC before IVF. In 2008, the meta-analysis by El-Toukhy et al[12] included 2 RCTs and 3 NRS with a total of 1691 patients. The overall analysis showed that HSC improved the pregnancy rate in the subsequent cycle in patients undergoing their first IVF cycle, and in patients with prior failed cycles (RIF). The authors postulated that the improvement of pregnancy rate was the identification and subsequent treatment of uterine abnormalities, but cautioned that more high-quality trials were needed to confirm the effect of HSC in patients undergoing IVF. The meta-analysis in 2014 included 1 RCT and 5 NRS and concluded that HSC in asymptomatic women before their first IVF cycle improved outcomes.[39] Both meta-analyses were not specifically designed for women with RIF.

Our study failed to demonstrate that HSC improved the live birth rate. Similarly, the inSIGHT RCT randomized 750 women with normal transvaginal ultrasound undergoing their first IVF cycle to receive or not receive HSC, and showed that there was no different in the live birth rate between the 2 groups.[20] However, sensitivity analysis of our included studies indicated that the outcome of the live birth rate analysis was overly influenced by 1
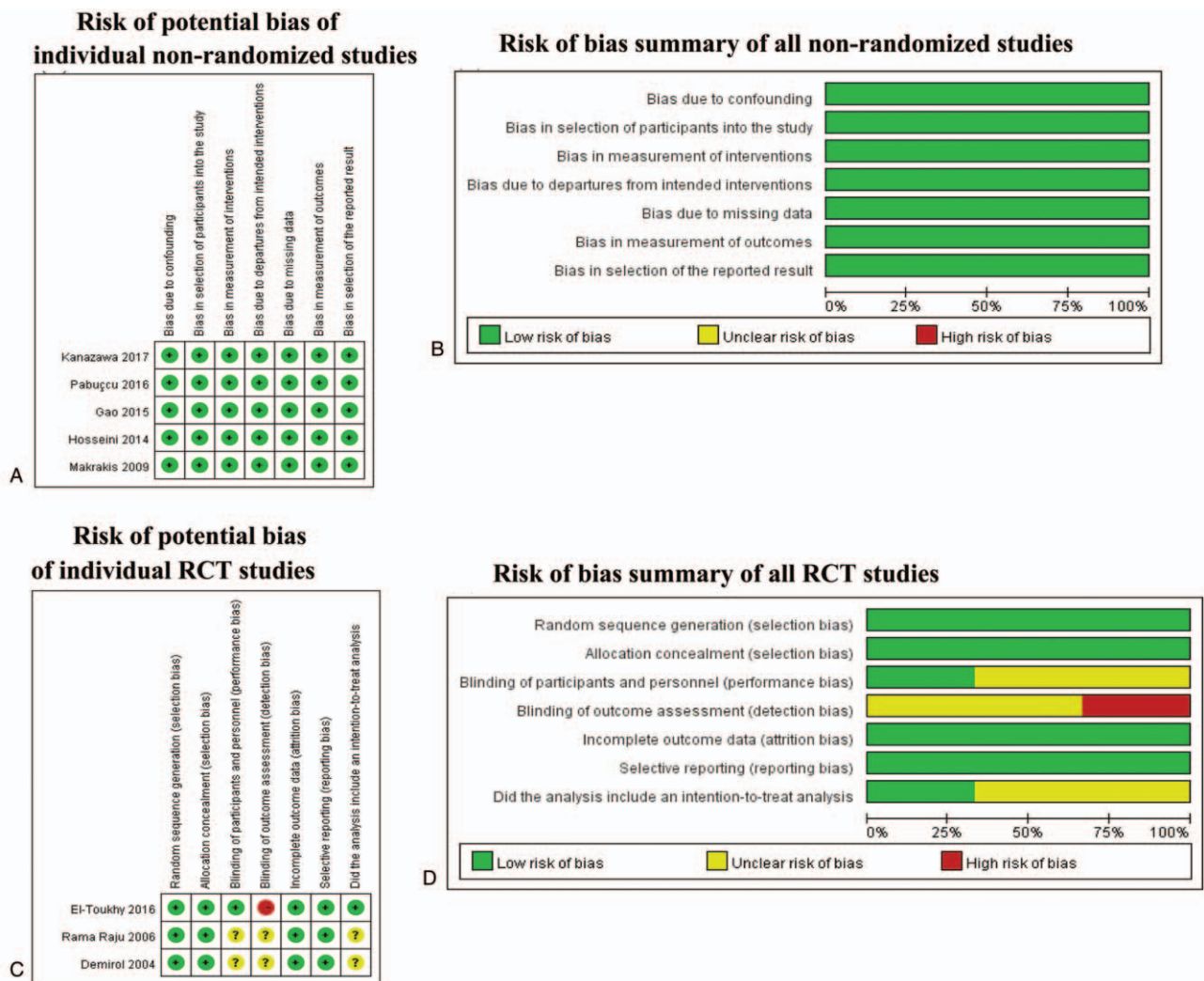
Figure 3. Quality assessment (publication bias) of nonrandomized studies (A and B) and RCTs (C and D). (A) Risk of potential bias of individual nonrandomized studies. (B) Risk of bias summary of all nonrandomized studies. (C) Risk of potential bias of individual RCT studies. (D) Risk of bias summary of all RCT studies. RCT = randomized controlled trial.

study.[34] When the study was removed, the live birth rate was statistically significantly higher in patients who received an HSC. The results, however, need to be interpreted with caution as only 5 studies were included in the analysis of live birth rate and only 2 RCTs were included. In addition, the study by Hosseini et al[34] was a nonrandomized prospective study.

The mechanism associated with improving implantation rate and clinical pregnancy rate is not clear. Rama Raju et al[18] suggested that pregnancy outcome can be improved by treating small intrauterine lesions effectively using office HSC which has a significant role in altering the uterine environment and ultimately improving the pregnancy outcome. Shohayeb et al[8] reported that a single endometrial biopsy (endometrial scratching) during HSC was associated with a significantly higher implantation rate, clinical pregnancy rate, and live birth rate after ICSI than if a biopsy was not performed. Similarly, Seval et al[40] reported that "endometrial scratching" during HSC improved the implantation and pregnancy rates in women with RIF as compared to HSC alone. Recently, a Cochrane review also recommend the beneficial effects of scratching.[3] The review postulated that

endometrial scratching or biopsy during HSC may alter the inflammatory characteristics or developmental status of the endometrium, which is more conducive for embryo implantation.[40] Because implantation and subsequent pregnancy involve an incredibly complex interplay of maternal and fetal factors as well as a delicate balance of pro-inflammatory and anti-inflammatory cytokines, all of which can affect endometrial receptivity and implantation.[5,41–43]

There are several limitations in this report, beyond the limited number of studies. Moderate heterogeneity was present among the included studies. Only 3 RCTs (high level of evidence) were included in our study. The rest of studies were either nonrandomized clinical trials or retrospective studies. However, the outcomes of the meta-analysis showed no difference when only RCTs were included. The definitions of RIF were slightly different in the included studies (Table 1). Most of the studies defined RIF as the women who failed implantation after repeating fair and/or good embryo transfer more than twice. El-Toukhy et al[33] more specifically defined RIF that the women having 2, 3, or 4 fresh or frozen IVF treatment cycles ending in an embryo

Table 2

Primary outcomes of the studies included in the meta-analysis.

References	Study design	Intervention	Number of patients	Clinical pregnancy rate [*]	Live birth rate	miscarriage rate	Implantation rate
[31]	Retrospective cohort study	Hysteroscopy	45	16/45 (35.6%)	N/A	7/16 (43.8%)	18/70 (25.8%)
		Control	90	20/90 (22.2%)	N/A	9/20 (45.0%)	22/119 (18.5%)
[32]	Retrospective cohort study	Hysteroscopy	119	N/A	29/119 (24.3%)	10/119 (8.4%)	22.4%
		Control	244	N/A	39/244 (16.0%)	18/244 (7.3%)	18.7%
[33]	RCT	Hysteroscopy	322	114/301 (38%)	102/322 (29%)	29/133 (22%)	129/410 embryos (32%)
		Control	318	110/290 (38%)	102/318 (29%)	33/136 (24%)	134/423 embryos (32%)
[14]	NRS	Hysteroscopy	334	140/334 (41.9%)	114/334 (34.1%)	N/A	176/739 (23.8%)
		Control	338	109/338 (32.2%)	97/338 (28.7%)	N/A	135/726 (18.6%)
[34]	NRS	Hysteroscopy	142	72/142 (50.7%)	36/83 (43.4%)	N/A	N/A
		Control	211	64/211 (30.3%)	35/72 (48.6%)	N/A	N/A
[35]	NRS	Hysteroscopy	414	145/414 (35.0%)	N/A	N/A	N/A
		Control	414	104/414 (25.1%)	N/A	N/A	N/A
[18]	RCT	Hysteroscopy normal finding	160	71/160 (44.4%)	48/160 (30%)	23/71 (32.3%)	N/A
		Hysteroscopy abnormal finding	95	38/95 (39.6%)	24/95 (25%)	13/38 (35.1%)	N/A
		Control	265	69/265 (26.2%)	44/265 (16.6%)	25/69 (36.2%)	N/A
[17]	RCT	Hysteroscopy normal finding	154	50/154 (32.5%)	N/A	N/A	N/A
		Hysteroscopy abnormal finding	56	17/56 (30.4%)	N/A	N/A	N/A
		Control	211	45/211 (21.6%)	N/A	N/A	N/A

N/A = not available, NRS = nonrandomized study, RCT = randomized controlled trial.
[*] Data reported as number of patients (%).

transfer but no pregnancy. Furthermore, we did not examine whether or not abnormalities (adverse events) were found on HSC in the eligible studies and what effect may have had on the outcomes of IVF. We also did not examine IVF protocols, which likely varied among the studies.

In conclusion, HSC significantly improved the implantation rate and clinical pregnancy rates but it failed to improve live birth rate and affect the miscarriage rate in women with RIF undergoing IVF. In addition, the role of HSC in IVF patients with RIF should be investigated by more RCT studies.

Table 3

Sensitivity analysis.

Study name	Statistics with study removed				
	Point	Lower limit	Upper limit	Z Value	P Value
Clinical pregnancy					
[30]	1.63	1.28	2.06	4.03	<0.001
[33]	1.77	1.52	2.07	7.14	<0.001
[14]	1.68	1.28	2.20	3.76	<0.001
[34]	1.55	1.24	1.93	3.92	<0.001
[35]	1.66	1.26	2.18	3.63	<0.001
[18]	1.57	1.24	1.99	3.73	<0.001
[17]	1.64	1.27	2.11	3.80	<0.001
Live birth					
[33]	1.43	1.00	2.04	1.94	0.052
[32]	1.23	0.85	1.78	1.07	0.284
[14]	1.30	0.87	1.95	1.26	0.207
[34]	1.41	1.01	1.96	2.02	0.043
[18]	1.14	0.87	1.50	0.96	0.337
Miscarriage rate					
[31]	0.94	0.65	1.37	−0.32	0.749
[33]	0.98	0.61	1.56	−0.10	0.918
[32]	0.89	0.60	1.34	−0.55	0.582
[18]	0.97	0.63	1.51	−0.12	0.902
Implantation rate					
[31]	1.20	1.00	1.44	2.01	0.045
[33]	1.36	1.10	1.69	2.79	0.005
[32]	1.22	1.01	1.46	2.08	0.038
[14]	1.10	0.86	1.40	0.77	0.440

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