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The role of hysteroscopy in patients with recurrent implantation failure before starting in vitro fertilization: a systematic review and meta-analysis

I Gde Sastra Winata, I Wayan Agus Surya Pradnyana, Mirani Ulfa Yusrika,
I Gusti Bagus Mulia Agung Pradnyaandara, Eddy Hartono

All authors: Faculty of Medical and Health Sciences Udayana university
P.B. Sudirman Street, Dangin Puri Klod, Denpasar, Bali, Indonesia

Abstract

Objective
Recurrent Implantation Failure (RIF) remains the most challenging in-vitro fertilization (IVF) problem to treat. This is because the overall success rate is only approximately 30%. Hysteroscopy remains the gold standard for diagnosing and treating intra-uterine anomalies. This study aimed to evaluate the role of hysteroscopy (HSC) in improving pregnancy outcomes in patients with RIF.

Methods
A systematic search was performed in PubMed, ScienceDirect, Embase, and Cochrane using MeSH terms, if applicable and in accordance with the PRISMA guidelines, to determine the role of hysteroscopy compared to patients who didn't undergo hysteroscopy. The Newcastle– Ottawa scale (NOS) was used to assess the risk of bias in this analysis, and Review Manager
5.4 was used to calculate the result of 95% CI for the outcomes. The endpoints of interest were clinical pregnancy rate, live birth rate, implantation rate, and miscarriage.

Results
A total of 3 randomized controlled trials (RCT) and 5 cohort studies with 4,679 patients were included. Pooled analysis showed that patients who underwent HSC were associated with higher clinical pregnancy - [OR 1.64, 95%CI (1.32-2.03)], live birth - [OR 1.50, 95%CI (1.17-1.92)], and implantation rate [OR 1.42, 95%CI (1.02-1.98)] but no significance in miscarriage rate. Further subgroup analysis suggests HSC had a significantly greater effect on clinical pregnancy rate for patients with abnormal HSC findings [OR 1.20, 95%CI (1.01-1.42)], but no significant difference in live birth - and miscarriage rate.

Conclusion
HSC plays a significant role in improving the clinical pregnancy rate, especially in patients with abnormal HSC findings. HSC also improves implantation rate, live birth -, and clinical pregnancy rates in patients with RIF. Since the number of the study is still limited, further investigations are still needed to confirm the results.

Key words: Hysteroscopy, recurrent implantation failure, in vitro fertilization, pregnancy outcome

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Introduction:

Infertility is a major issue that affects millions of couples worldwide. In the United States, around 7.5 million couples, or 1 in 8, are affected by this condition (1). The situation is not any better in Indonesia, where a study revealed that 21.3% of couples have trouble conceiving or sustaining a pregnancy, affecting roughly one in every five couples (2). Fortunately, a solution to this problem is assisted reproductive technology (ART). Among the most frequently techniques used in ART is in vitro fertilization (IVF). Studies have shown that IVF is an excellent solution for treating infertility (3-5). It is crucial to understand that the success rate of IVF cycles resulting in live births is approximately 25-30%. Among the numerous obstacles encountered during IVF, treating recurrent implantation failure (RIF) represents the most formidable challenge due to its low success rates of around 30% for women with RIF. While ovum collection and fertilization are often successful, an inexplicable discrepancy exists between the number of embryo transfers and the number of ongoing pregnancies lasting over 12 weeks (6). The reason for this failure to implant is not yet fully comprehended, although it appears to be influenced by both the embryo itself and the uterine cavity (7,8). Some abnormalities in the uterine cavity, such as polyps, myoma, adhesions, and sometimes endometriosis, are thought to be associated with impaired implantation and reduced chance of pregnancy (9). Several studies have reported the influence of intrauterine pathologies on pregnancy rates in women who will undergo IVF (10). Therefore, it is advisable to perform an examination for intrauterine pathologies before starting IVF (11,12). Since hysteroscopy (HSC) can give a good view of the uterine cavity, it is regarded as the reference standard for detecting these uterine abnormalities (13,14). HSC are reported to significantly find more abnormalities in patients with a history of ART failure (15-17). Two randomized controlled trials (RCT) confirmed the value of HSC in women with RIF by showing an increase in clinical pregnancy rate as high as 13%. In clinical practice, hysteroscopy is often performed on infertile women scheduled for the first IVF cycle. However, several studies have shown no significant effect of routine HSC on live birth rates (17-19). Due to conflicting findings regarding the use of HSC in patients with RIF, this study was aimed to determine if HSC before starting an IVF cycle in women with RIF may improve the clinical pregnancy rate, implantation rate, and live birth rate, this study was also aimed to see whether HSC reduces the miscarriage rate in IVF patients.

Materials and Methods

Systematic Reviews and Meta-Analyses (PRISMA) (20). This research collects and uses previously published studies. Therefore, there is no need for ethical approval. The submitted protocol was registered on the International prospective register of systematic reviews-PROSPERO (www.crd.york.ac.uk/prospero).

Search Strategy and Selection Criteria

Medical Literature Analysis and Retrieval System Online (MEDLINE) via PubMed, EMBASE (Excerpta Medical Database), Science Direct and the Cochrane Library were searched without any language restriction from January 2002 until February 2023, using the following keywords: 'in vitro fertilization' or 'in-vitro fertilization' and 'infertility' and 'hysteroscopy' and 'recurrent implantation failure' or 'embryo implantation' or 'treatment failure' and 'uterine disease' and 'pregnancy'. Citation tracking was performed to identify additional publications. Our study searching protocols are presented in Supplementary Table S1.

All identified studies were screened by title and abstract. The inclusion criteria in this study were randomized controlled trial studies, non-randomized two-arm prospective studies, and two-arm retrospective studies. The study population was women with normal ultrasound examination of the uterine cavity and women who had recurrent implantation failure, defined in this study with at least 2 failed IVF embryo transfer attempts. Before starting IVF cycles, patients underwent HSC diagnostic. Meanwhile, the control population did not have a HSC before starting IVF. On the other hand, the exclusion criteria in this study were one-arm studies, article reviews, case reports, proceedings, and personal comments, studies with no data of outcome interest, and studies that aimed to assess the efficacy of HSC-associated scratching, biopsy, or treatment were also excluded. Two investigators independently identified studies that met the inclusion criteria, and the third investigator was consulted on whether any disagreements or to resolve any differences. A discussion was conducted to make the final decision.

Data Extraction; Quality Assessment

Data extraction and quality assessment were carried out independently by two investigators. Standard forms were used to extract the

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following information from each study: the study authors; study design and methodology; total and mean age of the patients; intervention used for the patients; IVF cycles failed; definition of RIF; clinical pregnancy rate; live birth rate; miscarriage rate; and implantation rate. In cases of missing data in the main results or something unclear, the authors of the original publication were contacted via email.

The risk of bias assessment for the included studies was conducted based on the study type. The randomized control trial study (RCT) was assessed using the Cochrane Risk of Bias tool (RoB) (21). The RoB consists of seven domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Other sources of bias included potential bias related to the specific study design, stopped early due to some data-dependent process, and extreme baseline imbalance. The information extracted from the paper was judged on the possible risk of bias in each domain and was rated as "low risk," "unclear," or "high risk." For non-randomized studies, the risk of bias was analyzed by the Modified Newcastle-Ottawa Scale for Cohort Studies (22). The scale contains eight items within three domains. The possible total point for domain selection is 4 points, 2 points for comparability, and 3 points for outcome domain. The quality of the study was classified as "good" if the total was 7-9, "moderate" if the total score was 4-6, and otherwise as "poor." Two reviewers independently conducted the risk bias assessment, and any disagreement was resolved by discussion with the third reviewer. The overall quality of the non-randomized studies was good and presented in Table 1 as the risk of bias individually. The summary of RCTs quality is shown in Figure 1.

Outcome Measurement:

This study aimed to see whether there is any role for hysteroscopy in patients with recurrent implantation failure before starting in vitro fertilization considering clinical pregnancy rate, live birth rate, implantation rate, and miscarriage rate. Clinical pregnancy was defined as thirty-five days after embryo transfer and ultrasound examination showing a gestational sac, live birth rate was defined as the number of deliveries that resulted in a live-born neonate, and implantation rate was defined as the number of gestational sacs determined by ultrasound by the number of embryos transferred.

Data Synthesis and Analysis Quality Assessment

The meta-analysis was performed using Review Manager 5.4. The risks in terms of the outcomes of interest were computed and will be processed using Review Manager 5.4 and will later be presented with odds ratios (ORs) with 95% confidence intervals (CIs). Heterogeneity analysis between study populations was calculated using the I^2 statistic. The I^2 statistic was defined as follows: 0-24% as no heterogeneity, 25%-49% as moderate heterogeneity, 50-74% as considerable heterogeneity, and 75%-100% as extreme heterogeneity (23). Data are summarized across groups using the Mantel-Haenszel (M-H) risk ratio (RR) fixed effect model if $I^2 < 25\%$. The random effect model is used if $I^2 > 25\%$ (24). Funnel plots were used to evaluate publication bias. Analysis was carried out using Review Manager 5.4.

Results

Literature Search:

The flow diagram of the study selection process is shown in Figure 2. A total of 1039 studies were found during the initial screening through database searching and other sources. Two hundred ninety-three studies were removed due to duplicates, leaving 746 studies. These were scrutinized further for title and abstract and 673 studies that did not meet the inclusion criteria were excluded. The remaining 73 full-text articles were finally reviewed. As many as 65 studies were excluded due to different objectives and study designs (n=15), review articles (n=16), not a recurrent IVF but rather the first IVF cycle studies (n=17); no endpoints or different outcomes of interest (n=8); and case report studies (n=9). Finally, only eight studies were included in the meta- analysis (25 – 32)

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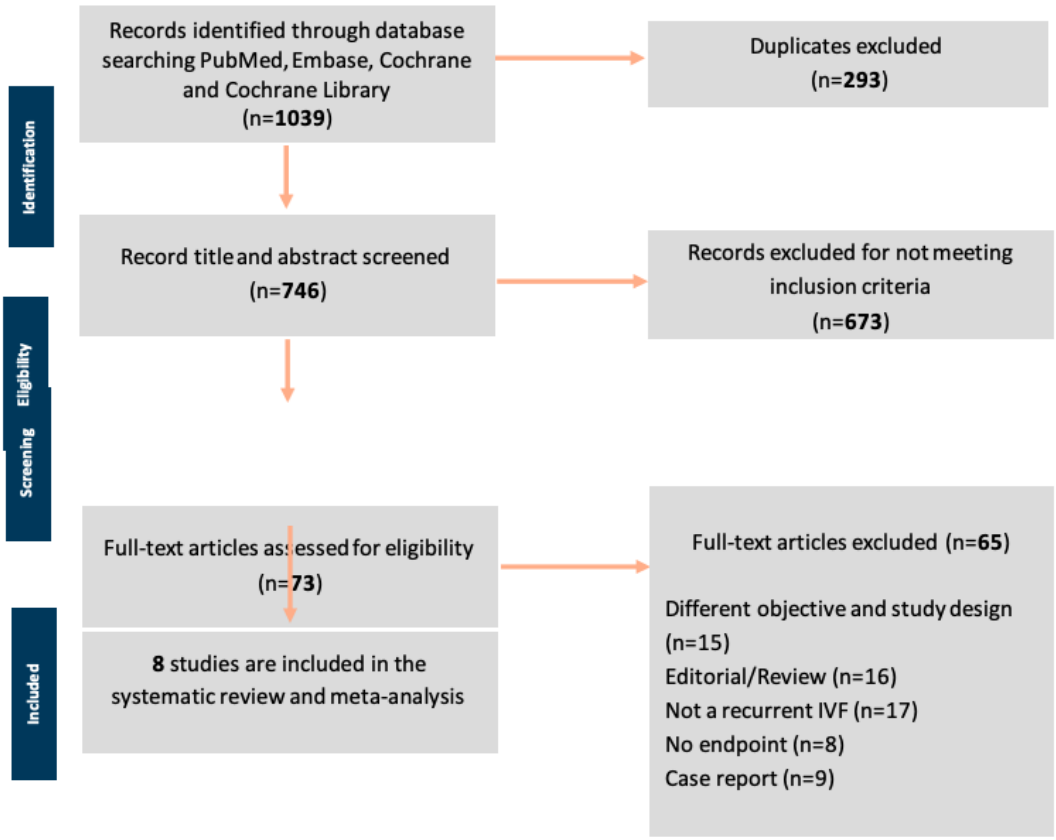

Figure 2. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.

Characteristics of Included Studies

In this meta-analysis, eight studies met the predetermined inclusion criteria comprising three RCT studies, two retrospective studies, and three cohort studies. The basic summary of study characteristics included in this review, study design, the total of patients and the percentage of patients forming the population of each intervention, mean age, mean failed IVF cycles, the definition of RIF, and clinical pregnancy definition from each of the studies are represented in Table 2.

The basic summary data concerning the hysteroscopic examination procedure, ovarian stimulation procedure, and embryo transfer procedure is available in Table 3.

There are three studies with a RCT design. All of the studies did use computer- generated randomized systems, therefore these are rated as studies having a low risk of bias. Tarek et al., and Raju et al., needed clarification about the blinding outcome assessment domain because there was no statement about blinding the assessor. Similarly, in the study by Raju et al. and Demirol et al., there is insufficient data for the blinding participant and personnel domain to declare the risk of bias. As bias due to allocation concealment, all studies were considered high risk. The hysteroscopic procedure was explicitly unconcealed, which cannot be masked between the control and experiment groups. Tarek et al. published a study protocol that explained clearly the study outcome, thus getting a low risk of selective reporting. Meanwhile, the study protocol for the rest of the studies were unavailable.

All cohort studies were of quality, with a score of 7-9. The analysis by Hosseini et al. made no point in selecting a non-exposed cohort due to the fact of using an historical cohort as control compared to the present cohort, which means that the control cohort group did not resort from the same population The excellent quality in the selection domain must consist of inclusion and exclusion criteria to ascertain the representativeness of the cohort, pick the non-exposed group from the same cohort, have a good record of exposure, and ensure no outcome is present at the start of the study. Except for Hosseini et al., the rest of the studies fulfilled those criteria. The comparability domain examined the baseline data of exposure and control group, which expect to have no significant difference. The research by Makraris et al. was rated 2 points due to matching the control and exposure group. Of a population of

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1475 in this study, only 828 were included in the analysis because only 828 patients have been compared between the hysteroscopy and non-hysteroscopy groups. In contrast, the rest of the studies showed comparability of the cohort in their characteristic table. All included studies had a good outcome domain. The assessment of the outcome and length of follow-up of the study was described clearly in the method. The adequacy of the follow-up cohort from all studies was fulfilled due to no reporting attrition in the study of more than 10% of the participants.

Overall, the eight studies included 4679 patients with RIF, 1869 patients underwent hysteroscopy before starting IVF, and 2163 patients were allocated in the control group (patients without hysteroscopic evaluation before starting ovarian stimulation for IVF treatment). In this population, the average age of patients ranged from 25.39 to 38 years, with an average number of previous failed IVF cycles ranging from 2.4 to 4.04. The broad definition of RIF in each study protocol were patients who underwent two or more failed IVF cycles with a good-quality embryo, and clinical pregnancy was determined by using an ultrasound examination with hearth beating. During hysteroscopic examination, generally a rigid hysteroscope is generally used with a sheath diameter of 4 to 5 mm and a fore oblique lens of 22-30 degrees.

Seven of the eight studies, included in this meta-analysis, reported clinical pregnancy rate data (25-31). In the forest plot, the results of this analysis have a considerable heterogeneity between the seven studies included (Chi^2=12.61, I^2=52%), overall, this pooled analysis shows that the clinical pregnancy rate is significantly higher in patients who underwent hysteroscopy (HSC) when compared to the control group, which in this case is composed of patients with RIF who got IVF treatment without prior HSC examination [OR 1.64, 95% CI (1.32-2.03) p<0.001, (figure 3). Here we can also see the included results of the subgroup analysis of the non-randomized trial studies. The subgroup analysis shows that patients undergoing HSC have a higher clinical pregnancy rate [OR 1.67, 95% CI (1.31-2.13) p<0.0001]. The same was seen in the results of the RCT research analysis here also the clinical pregnancy rate was significantly higher in the HSC group [OR 1.60, 95% CI (1.03-2.49) p=0.04]. Both these results are presented in Figure 3.

We also did analyze further a subgroup between patients with normal and abnormal hysteroscopy findings to see if there is any difference in clinical pregnancy outcome. Five studies were included in the analysis, with no heterogeneity noted (Chi^2 = 1.03, I^2 = 0%). This analysis did find that patients with abnormal hysteroscopy findings and treated accordingly have a marginally significantly higher clinical pregnancy rate [OR 1.20, 95% CI (1.01-1.42) p=0.04]. The forest plot is presented in Figure 4.

Data Synthesis

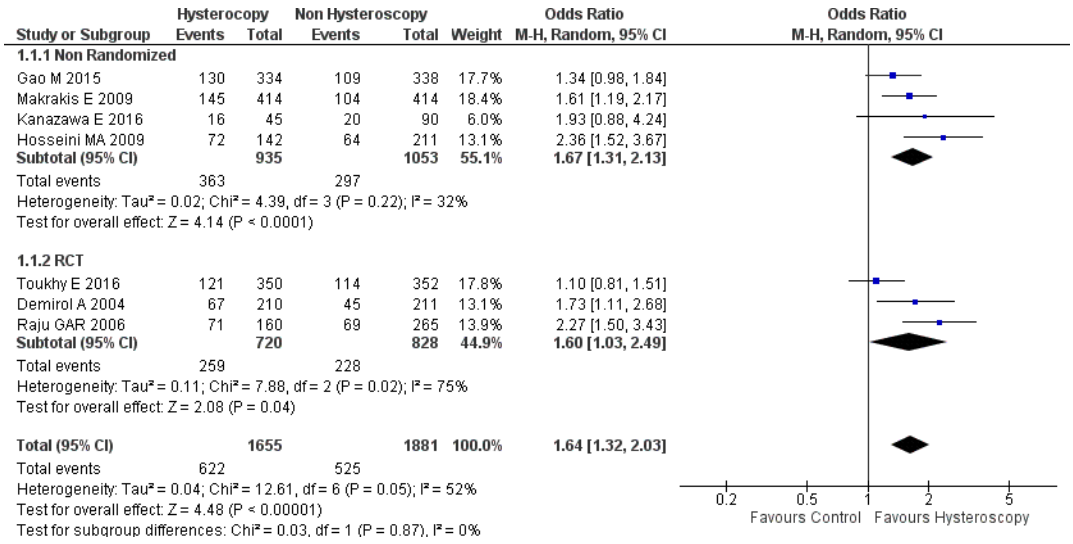

Figure 3. Forest plot of clinical pregnancy rate. Odd ratio of clinical pregnancy rate between

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patients with RIF who underwent hysteroscopy before IVF and did not undergo hysteroscopy before IVF. Test for overall effect: Z = 4.48 (p<0.0001) heterogeneity: I^2 = 52%. CI, confidence interval; RCT, randomized clinical trial.

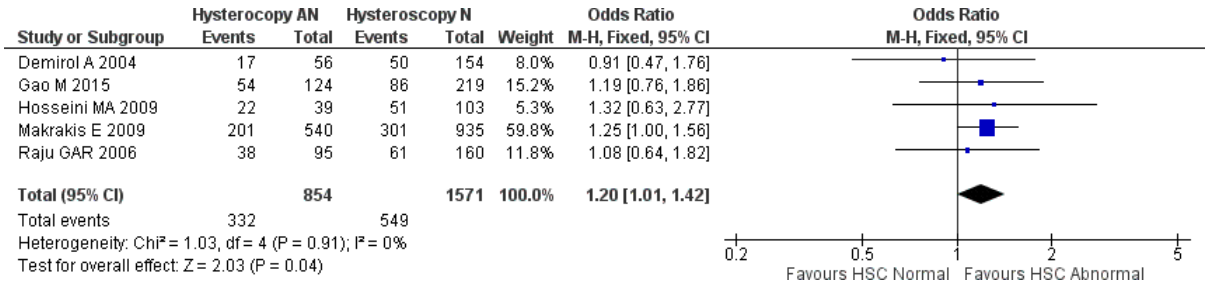

Figure 4. Forest plot of clinical pregnancy rate between normal and abnormal hysteroscopy findings in patients with RIF who underwent hysteroscopy before IVF. Test for overall effect: Z = 2.03 p=0.04 heterogeneity: I^2 = 0%. HSC: hysteroscopy.

Five studies provided data regarding the live birth rate; three were non-randomized trials, and two were RCTs (27-29,31,32). Overall, a moderate heterogeneity was found between the five studies (Tau^2 = 0.03, Chi2 = 7.04, I^2=43%). The pooled forest plot analysis showed that patients with RIF who underwent HSC before starting IVF have a higher live birth rate [OR 1.50, 95% CI (1.17-1.92) p=0.001]. Subgroup analysis of the non-randomized trials showed the same result, patients in the HSC group have higher live birth rates [OR 1.52, 95% CI (1.20-1.94) p=0.0007). But for the RCTs, the result showed no significant difference with OR 1.49, 95% CI (0.75-2.94), p=0.25. All the results are presented in Figure 5.

We further subgroup analysis between patients with abnormal and normal hysteroscopy findings to see whether there is any live birth rate difference. The analysis included three studies with no heterogeneity (Chi^2 = 0.73, I^2 = 0%). The forest plot found no significant difference between normal and treated abnormal hysteroscopy findings for live birth rate [OR 0.90, 95% CI (0.65-1.25) p = 0.53). The results are presented in Figure 6.

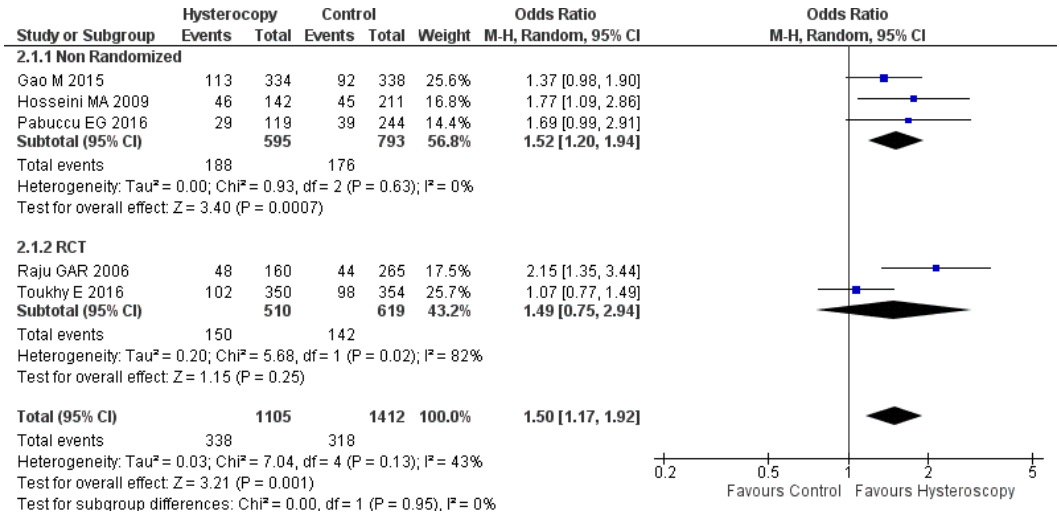

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Figure 5. Forest plot of live birth rate. Odd ratio of live birth rate between patients with RIF who underwent hysteroscopy prior to IVF and the patients who did not undergo hysteroscopy prior to IVF. Test for overall effect: Z = 3.21 (p=0.001) heterogeneity: I^2 = 43%. CI, confidence interval; RCT, randomized clinical trial.

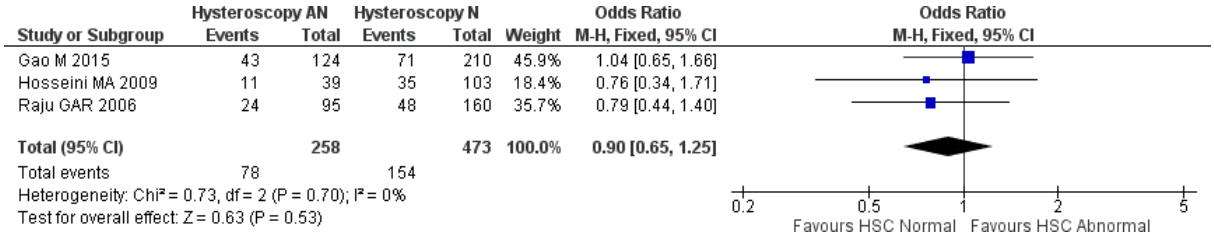

Figure 6. Forest plot of live birth rate between normal and abnormal hysteroscopy findings in patients with RIF who underwent hysteroscopy prior to IVF. Test for overall effect: Z = 0.63 p=0.53 heterogeneity: I^2 = 0%. HSC: hysteroscopy.

A total of four studies reported data related to the implantation rate, where 3 were non-randomized trials, and 1 was an RCT (28-31). This analysis shows considerable heterogeneity (Tau^2 = 0.06, Chi^2 = 6.91, I^2 = 57%). In the forest plot provided in Figure 7, it can be seen that RIF patients who underwent HSC before IVF had a higher implantation rate [OR 1.42, 95% CI (1.02-1.98) p = 0.04]. The definition of implantation in this study is the number of gestational sacs divided by the number of embryos transferred. A subgroup analysis from a non-randomized trial also showed a higher implantation rate in patients undergoing HSC [OR 1.64, 95% CI (1.11-2.42) p=0.0005). Unfortunately, no RCT subgroup analysis can be done. because only one study provided data regarding implantation rate.

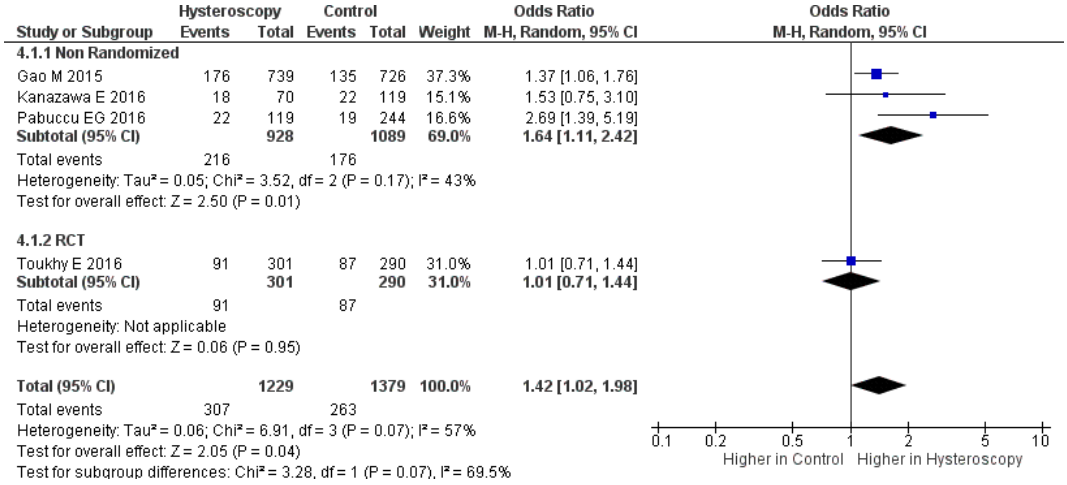

Figure 7. Forest plot of implantation rate. Odd ratio of implantation rate between patients with RIF who underwent hysteroscopy prior to IVF and the patients who did not undergo hysteroscopy prior to IVF. Test for overall effect: Z = 2.05 (p=0.04) heterogeneity: I^2 = 57%. CI, confidence interval; RCT, randomized clinical trial.

Seven studies reported miscarriage rate data; four were non-randomized, and the other three were RCTs. From the forest plot, the analysis had no significant heterogeneity among the studies (Chi2 = 7.84, I2=23%) (25,27,32). Pooled analysis showed that patients with RIF who underwent HSC before starting IVF had no significant miscarriage rate compared to patients with RIF who did not undergo HSC [OR 1.27, 95% CI (0.97-1.65) p=0.08]. Still, when we see the forest plot, the miscarriage rate does shift towards the control side, indicating that the miscarriage rate may be higher in the control group, but it is not statistically significant. The subgroup analysis of the non-randomized trial and RCT group also showed no significant difference [OR 1.45, 95% CI (1.00-2.12) p=0.05] and [OR 1.10, 95% CI

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(0.75- 1.61) p=0.64] respectively. All the results are provided in Figure 8. We also did further analyze the subgroup between normal and abnormal hysteroscopy findings. Three studies provided data regarding the difference between normal and abnormal hysteroscopy findings for miscarriage rate. No significant heterogeneity was found between the three studies. Pooled analysis shows no significant difference between normal and abnormal hysteroscopy findings for miscarriage rate [OR 0.91, 95% CI (0.52-1.59) p=0.75]. The results are provided in Figure 9.

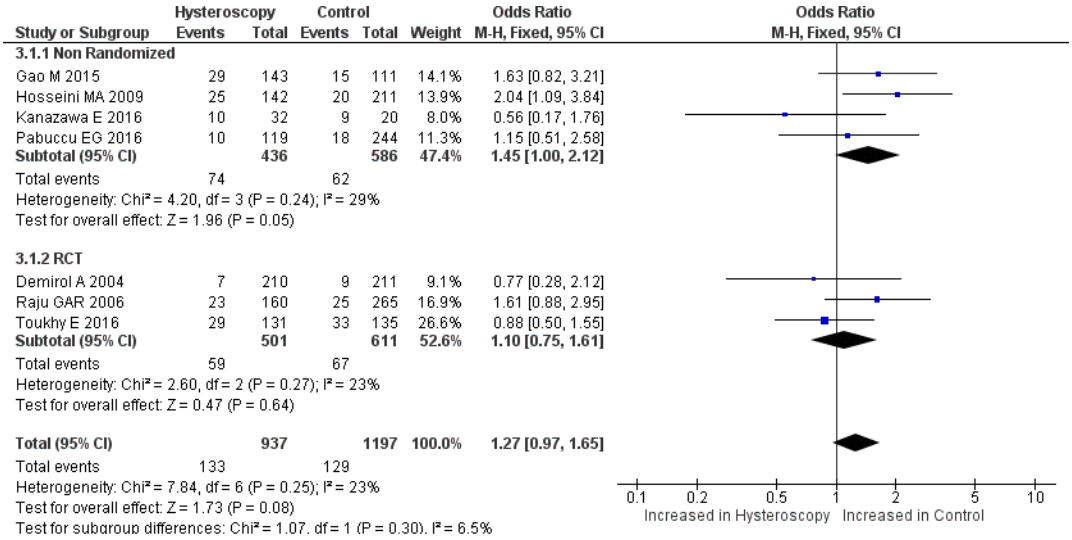

Figure 8. Forest plot of miscarriage rate. Odd ratio of miscarriage rate between patients with RIF who underwent hysteroscopy prior to IVF and the patients who did not undergo hysteroscopy prior to IVF. Test for overall effect: Z = 1.73 (p=0.08) heterogeneity: I^2 = 23%. CI, confidence interval; RCT, randomized clinical trial.

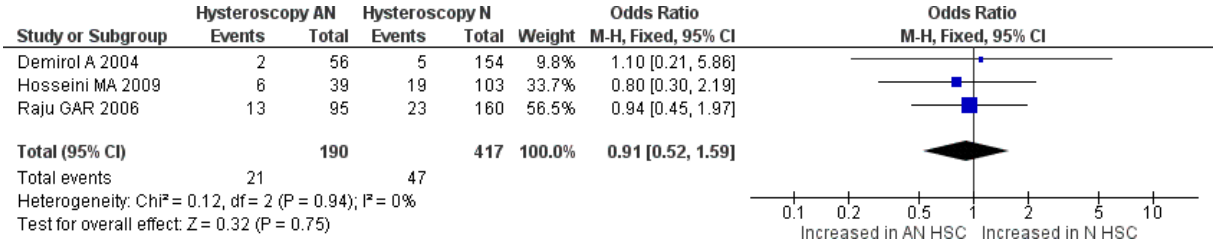

Figure 9. Forest plot of miscarriage rate between normal and abnormal hysteroscopy findings in patients with RIF who underwent hysteroscopy prior to IVF. Test for overall effect: Z = 0.32 p=0.75 heterogeneity: I^2 = 0%. HSC: hysteroscopy.

Discussion

There are two main findings of this meta-analysis study. First, patients with RIF who underwent HSC prior to the IVF procedure were associated with improved clinical pregnancy -, live birth -, and implantation rate. Second, the subgroup analysis of patients with normal vs. abnormal HSC findings suggests that HSC had a significantly greater effect on the clinical pregnancy rate for patients with abnormal HSC findings. The broadly used RIF definition of the studies included patients who had two or more failed IVF cycles with good-quality embryos, with an average number of previous failed IVF cycles ranging from 2.4 to 4.04. Overall, our results demonstrate that HSC has a role in improving pregnancy outcomes in patients with RIF.

IVF has widely known as the most common ART procedure performed worldwide (33). In the late 70s, the first successful IVF treatment in humans was performed in England, with a laparoscopic retrieval of a single oocyte from the ovary. The oocyte was fertilized in vitro and transferred into her uterus as an embryo (34). Since then, IVF technology has advanced and become more widely available. In most cases, ART is used to treat infertility. Infertility is

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frequently correlated with anatomical and physiological abnormalities of the ovaries, fallopian tubes, and uterus. Based on the intrauterine pathologies, IVF can be performed by bypassing the affected area. For example, IVF bypasses the fallopian tubes directly in patients with tubal factor infertility (33-36). Thus, evaluating the intrauterine pathologies for IVF success is crucial.

Repeated or recurrent implantation failure (RIF) is a problem that has baffled many experts for quite a long time in the IVF environment and has been attributed to embryo quality and decreased endometrial receptivity. One of the suspected causes of RIF is specific issues in the uterine cavity, such as the inadequacy of endometrial thickness, adhesions, and anatomical abnormalities. Endometrial and uterine pathologies such as endometrial hyperplasia, polyps, leiomyoma, and endometriosis have been reported to occur in 18%-50% of women with RIF (17,36,37). Because of this, it is recommended to examine intrauterine pathologies before starting IVF. Several options that are often performed and are not invasive are a combination of transvaginal sonography, hysterosalpingography and hysteroscopy. But unfortunately, hysterosalpingography has low specificity, high false-negative, and high false-positive rates. Although transvaginal sonography is a noninvasive option, the results are less sensitive (6,10,38,39).

A more effective method for simultaneously evaluating the uterine cavity and providing treatment is hysteroscopy (40). As a result, HSC is the gold standard for evaluating the uterine cavity (13,14). In women with unsuccessful IVF treatments, HSC examination of the uterus is beneficial. A recent study reported that in patients whose transvaginal sonography examination results were normal, it turned out that during HSC examination, there were minor intrauterine abnormalities as high as 30%-45%, and abnormalities found during HSC were significantly higher in patients who had a history of ART failure (15,17). This explains why many specialists perform HSC as the initial routine exam on patients with infertility despite the guideline recommendation (41).

A continuous process, starting with a successful implantation, establishing a clinical pregnancy, and ending with the delivery of a live baby, demonstrates the success of IVF. In our analysis, RIF patients that previously underwent HSC examination had higher clinical pregnancy rates [OR 1.64, 95% CI (1.32-2.03) p<0.001]. Subgroup analysis also did reveal that patients with abnormal hysteroscopy and had been treated for the latter did have higher pregnancy rate and a higher live birth rate [OR 1.50, 95% CI (1.17-1.92) p=0.001] but no significant difference could be demonstrated between patients with abnormal hysteroscopy findings compared patients with normal hysteroscopic findings.

The RIF patients who did undergo HSC before IVF also had a higher implantation rate [OR 1.42 (95% CI 1.02-1.98, p = 0.04]. These results align with a study conducted by Gao M, where it was found that RIF patients who underwent HSC had a significantly higher implantation rate (28). Uniquely, the study did not find a significant difference in the implantation rate in patients between abnormal and abnormal HSC findings. This can be caused because HSC can see minor lesions such as endometrial dysfunction and hyperplasi, polyps and adhesions that may occur due to ovarian stimulation and repeated intrauterine operations; this procedure can cause minor tissue damage (26). Besides that, HSC is said to be able to favor subsequent pregnancy outcomes. During HSC, cervical dilatation occurs, which allows the correction of cervical stenosis and facilitates the ET process, and uterine distention fluid can help flush the uterine cavity. The absence of a significant increase in the implantation rate in patients with abnormal HSC findings could be due to immune factors or poor embryo development (42).

The conclusion is that hysteroscopy has a fertility-enhancing effect, which is also thought to occur independently of the correction of intrauterine abnormalities. Hysteroscopy is also believed to improve ART outcomes through an endometrial injury that helps embryo implantation (42).

Strengths and Limitations

The strengths of our analysis were that we did include RCT studies with a high level of evidence; we also included two-arm cohorts and retrospective studies, of an overall good quality. Our results were generally consistent across the studies when we saw the primary endpoints, which ensured consistency in each study. This meta-analysis has several limitations, apart from the relatively small number of studies that could be included. Important is to note that patient demographics and procedure differences, that should have been accounted for in this analysis, may influence the outcome and which may also increase heterogeneity. It should also be remembered that some of the results of this study have considerable heterogeneity; this is quite difficult to correct in a meta-analysis study because we cannot control every population in each study. Therefore, there is a possibility of bias that we

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cannot control.

Conclusion

Overall, this meta-analysis shows that hysteroscopic examination in patients with RIF before IVF significantly improved clinical pregnancy -, implantation-, and live birth rates. Also, to our knowledge, this meta-analysis is the first to look at differences in patients with abnormal and normal hysteroscopic findings, but unfortunately, no significant differences could be brought to evidence. Although many studies have been related to the role of hysteroscopy in patients with RIF before starting IVF treatment, additional studies are still needed, especially large-scale RCT studies.

Table 1. Modified Newcastle-Ottawa Scale for Cohort Study

No	Author, years	Selection				Comparability	Outcome			Overall score	Quality of study
		Representativeness of the exposed cohort	Selection of non-exposed cohort	Ascertainment of the exposure	Outcome was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Enough follow up time	Adequacy of follow up of cohorts		
1	Makrakis E, 2009	1	1	1	1	2	1	1	1	9	Good
2	Hosseini, 2014	1	0	1	1	1	1	1	1	7	Good
3	Gao M, 2015	1	1	1	1	1	1	1	1	8	Good
4	Kanazawa E, 2016	1	1	1	1	1	1	1	1	8	Good
5	Pabuccu EG, 2016	1	1	1	1	1	1	1	1	8	Good

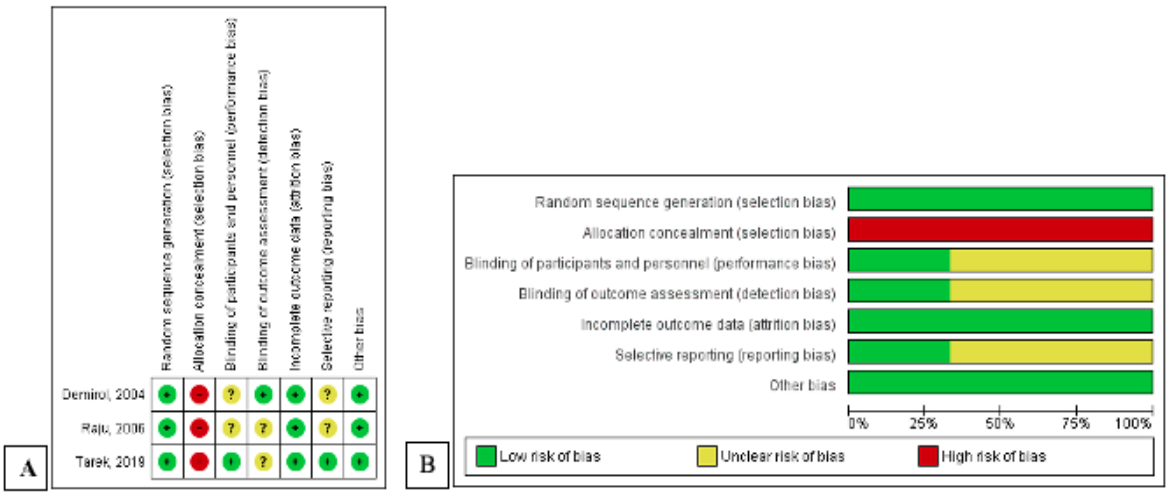

Figure 1. Quality assessment of RCT. (A) Risk of potential bias of individual RCT studies. (B) Risk of bias summary of all RCT studies. RCT: Randomized controlled trial.

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Table 2. Base Summary of Study Characteristics

No	Author	Country	Study Design	Total Patients		Intervention	Age (Years), SD	IVF Cycles Failed, SD	Definition of RIF	Clinical Pregnancy
1	Demirol A, 2004	Turkey	RCT	421	154	Hysteroscopy Normal	35.4, 0.6	2.6, 0.4	Patients who had undergone 2 or more failed IVF cycles in which two or more good-quality embryos transferred	Clinical pregnancies were confirmed by TVS at 6–7 weeks of gestation.
					56	Hysteroscopy Abnormal	36.2, 0.1	3.1, 0.1		
					211	Control	34.3, 0.8	2.8, 0.2		
2	Makrakis E, 2009	Greece	Prospective Matched Case-Control	1475	414	Hysteroscopy	35.38, 3.96	NA	History of 2 consecutive implantation failures despite the transfer of at least 1 good-quality embryo derived from fresh IVF cycles or 1 fresh IVF and its subsequent frozen/thaw cycle	NA
					414	Control	25.39, 3.95	NA		
3	Hosseini MA, 2014	Iran	2 Arms Cohort	353	142	Hysteroscopy	32.6, 4.2	2.5	≥ 2 ART cycles with fresh and good quality (according to previous ART history of the patient) and quantity (at least eight) of embryos transferred.	Each pregnant woman was followed up with an ultrasound scan until the fetal heart was documented (clinical pregnancy) and until delivery.
					211	Control	32.7, 4.3	3		
4	Gao M, 2015	China	2 Arms Cohort	672	334	Hysteroscopy	31.72, 3.55	NA	More than 2 consecutive ET failures with at least one good-quality cleavage embryo on day 3 in each ET	Clinical pregnancy was defined by TVS-confirmed intrauterine gestational sac and fetal heartbeat.
					338	Control	31.74, 4.08	NA		
5	Pabuccu EG, 2016	Turkey	2 Arms Retrospective	363	119	Hysteroscopy	30.7, 5.3	4.04, 1.5	Two or more unsuccessful ART/embryo transfer cycles despite the availability of good-quality embryos	NA
					244	Control	31.92, 4.4	3.06, 1.21		
6	Kanazawa E, 2016	Japan	2 Arms Retrospective Cohort	173	45	Hysteroscopy	38	NA	Patients who have failed implantation after repeating fair or good embryo transfer more than twice.	Clinical pregnancy was confirmed by ultrasound evidence of a gestational sac after a positive pregnancy test (urine β-human chorionic gonadotropin [β-hCG] level > 25 IU/L).
					128	Control	37	NA		
7	Toukhy E, 2019	United Kingdom	Multi Centre RCT	702	350	Hysteroscopy	32.7, 3.1	2.7, 0.9	Patients with two to four in vitro fertilization treatment cycles ending in an embryo transfer but no pregnancy and who were undergoing a further treatment cycle of in vitro fertilization	Observation of fetal cardiac activity on ultrasound scan four or more weeks after embryo transfer
					352	Control	32.7, 3.2	2.7, 1.0		
8	Raju GAR, 2006	India	RCT	520	160	Hysteroscopy Normal	27.4, 0.6	2.8, 0.3	Two or more failed IVF cycles in which two or more good-quality embryos were transferred per procedure	Clinical pregnancy was made after visualization of fetal heart pulsation four weeks later by transvaginal sonography (TVS).
					95	Hysteroscopy Abnormal	29.04, 0.92	2.4, 0.4		
					265	Control	26.72, 0.46	2.6, 0.1		

TVS: Transvaginal ultrasonography; ET: Embryo transfer; ART: Assisted reproductive technology; IVF: In vitro fertilization; hCG: Human chorionic gonadotropin; IU: International unit; RCT: Randomized controlled trial; NA: Not available

Table 3. The Base Summary of Hysteroscopy Examination Procedure, Ovarian Stimulation Procedure, and Embryo Transfer Procedure

No	Author	Hysteroscopy Examination	Ovarian Stimulation Procedure	Embryo Transfer Procedure
1	Demirol A	The hysteroscopy was performed in the early proliferative phase using a saline distention medium and a 5 mm continuous flow office hysteroscopy. The scope is based on a rod lens system with a diameter of 2.9 mm and a 30-degree view. The continuous flow sheath has an oval profile and maximum 5 mm diameter with an incorporated 5Fr working channel; the mechanical instruments used were grasping forceps with teeth and scissors. Intrauterine pressure was maintained at a constant 25/235 mmHg using an electronic pump for irrigation and aspiration. Semi-rigid operative hysteroscopic instruments such as scissors, grasping forceps, and biopsy forceps were used for the treatment.	IVF treatments were carried out on the menstrual cycles after office hysteroscopies. Patients were placed on an ovarian stimulation protocol that began with daily subcutaneous injections of leuprolide acetate 1 mg on day 21 of that cycle and continued until day 3 of the next menstrual cycle. If ovarian suppression was achieved (oestradiol < 40 pg/ml), 225 IU/day of gonadotrophin was started on day 3 or 4, and the dose arrangement was performed based on individual response. An ovulatory dose of 10,000 IU human chorionic gonadotrophins was given when at least two follicles of 18 mm diameter or more were observed.	Transvaginal ultrasonography (TVS)-guided oocyte retrieval was performed, embryo transfer was performed on day 3, and a maximum of four embryos, selected according to their quality, were transferred. Progesterone vaginal suppositories gave luteal support.
2	Makrakis E	Hysteroscopies were performed with the vaginoscopic approach under sedation using a 2.9 mm, 30-degree angle	Controlled ovarian hyperstimulation with a long protocol (mid-luteal beginning of gonadotropin-	Regarding frozen/thaw cycles, embryo thawing, and transfer were

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		hysteroscope with an external sheath of 5.5 mm diameter, providing inflow, outflow, and 5F working channels. Without introducing a speculum or tenaculum, and after vaginal and cervical disinfection, the hysteroscope was inserted in the vagina, the external cervical os was identified, and the scope was inserted through the cervical canal into the cavity with gentle movements, respecting the anatomy of the genital tract. Uterine cavity distention was achieved with normal saline installation. In patients with cavity distortion/pathology, appropriate treatment was applied simultaneously.	releasing hormone [GnRH] analog and stimulation with recombinant follicle-stimulating hormone [FSH] after confirmation of down-regulation), a short protocol (GnRH analog from cycle day 2 and recombinant FSH from cycle day 3), or a flexible antagonist protocol (recombinant FSH from cycle day 2 and addition of a GnRH antagonist when the leading follicles reached dimensions of 14–15 mm), with transvaginal ultrasound-guided oocyte retrieval 35 hours after the administration of 10 000 IU of human chorionic gonadotropin. The IVF or ICSI was performed with the respective male partner's spermatozoa, and sequential culture media were used in all cases.	synchronized according to the serum luteinizing hormone surge on a natural cycle. All ETs were performed with a Wallace catheter under ultrasound guidance. The number of transferred embryos depended on the female age and on embryo availability and quality (assessed with a 2-grade embryo score).
3	Hosseini MA	Hysteroscopy in the dorsolithotomy position and under general anesthesia was performed in the menstrual cycle just before ovarian stimulation or endometrial preparation by the attending physicians of the department. A rigid hysteroscope (continuous flow; 30° forward oblique view) with an outer diameter of 4 mm using 0.9% normal saline via a pressure pump was applied. The uterine cavity was adequately distended with the preset pressure between 80 and 100 mmHg. If there is any pathology, they were removed using mechanical instruments such as, forceps and scissors.	After complete desensitization with a long protocol using buserelin, ovarian stimulation with recombinant gonadotrophin, Gonal F, and human menopausal gonadotrophin based on age, weight, and the ovarian reserve was started. Transvaginal ultrasound was performed every 3–5 days to monitor follicular development, and final oocyte maturation was triggered with 10 000 IU human chorionic gonadotrophin (hCG). Then, oocytes were collected transvaginally 36–38 h later.	Up to four good-quality embryos were transferred transcervical 3 days later. Luteal phase support was by progesterone suppository Cyclogest. Serum β-hCG was checked 14 days after embryo transfer, and a transvaginal ultrasound scan was performed 2 weeks later to detect a gestational sac.
4	Gao M 2015	All HSC procedures were standardized, using a 6-mm outer-diameter continuous-flow rigid hysteroscope with a 22° direction of view. Normal 5% glucose or saline solutions distended the uterine cavity with a distention pressure maintained at approximately 20 kPa. A high-sensitivity cold-light-source fiber optic television camera and monitoring system collected HSC observations and image recordings. During HSC operation, all the images were observed continuously, and typical images were recorded fragmentally.	NA	Embryo transfer with either frozen or fresh embryos within 6 months after recruitment. ET was performed with at least one good-quality cleavage embryo on day 3. The criteria for good-quality cleavage embryos on day 3 were defined as being of 7 cells or more, equally sized blastomeres, less than 20% fragmentation, and no multinucleation.
5	Pabuccu EG 2016	All patients were examined during their early follicular phase, 1–6 months before starting a new ART cycle, via the	ICSI and all sperm injections were performed with fresh specimens. One ART cycle of each patient was included	During the study period, one embryo was transferred to patients aged <35,

		vaginoscopic approach as previously described. No routine pre-operative analgesia, antibiotics, sedation, or cervical preparation was used. A rigid hysteroscope (continuous flow; 30° forward oblique view) with an outer diameter of 4 mm using 0.9% normal saline was used. Following adequate distension of the uterine cavity, a systematic inspection was performed. Standard gynecologic surgical procedures were used to treat the recognized pathologies, such as removing all polyps and adhesions. A senior physician performed all the procedures.	in the study. All the OS cycles were conducted using the short antagonist protocol with recombinant or human menopausal gonadotropins (150–300 IU/day s.c.). Ovarian stimulation, oocyte retrieval, and embryo transfer procedures were performed as described elsewhere. Top-quality embryos were defined as those with ≥7 evenly sized cells and ≤10% fragmentation on day 3 and with a ≥3 AA quality of blastocyst morphology on day 5.	while two embryos were transferred to those ≥35 years following local legislation.
6	Kanazawa E 2016	Hysteroscopy was performed before the transfer cycle.	Hormone-replacement therapy in each group was our standard endometrial preparation protocol for FET cycles with transdermal estrogen patches for approximately 16 days. A transvaginal ultrasound was then performed, and if the endometrial thickness was >7.0 mm with a triple-line appearance, the patients were started on a regimen of 600 mg/day micronized progesterone, vaginally till 9 weeks of pregnancy and continued transdermal estrogen patches till eight weeks of pregnancy.	Embryo transfer with a Kitazato catheter under transvaginal ultrasound guidance was performed by four skilled doctors between 3 and 5 days later, depending on the embryo's stage of development. The embryos were classified according to Veeck's grading and Gardner's grading. Up to two embryos were transferred, including two-step embryo transfer.
7	Toukhy E 2019	Outpatient hysteroscopy was performed using a rigid 30° view 2.9 mm diameter hysteroscope with an atraumatic tip in a vaginoscopic approach. The hysteroscope could be assembled with accessory sheaths in an active or passive position. Each hysteroscopy was started with the single-flow 2·9 mm instrument to inspect the cervical canal and uterine cavity. If necessary, the accessory diagnostic (3.7 mm) or operative (4.4 mm) sheath was moved forward to establish a double-flow mode and allow operative intervention using 5 French instruments (crocodile forceps, biopsy forceps, and scissors). An isotonic solution (0.9% Normal saline or Ringer lactate) was administered via a pressure-controlled pump or simple pressure cuff system to provide the lowest pressure required to distend the uterine cavity for adequate visualization. No routine pre-operative analgesia, antibiotics, sedation, or	The in vitro fertilization treatment cycle commenced in the menstrual cycle immediately following the outpatient hysteroscopy. The ovarian stimulation protocols used for the in vitro fertilization treatment cycles were described previously. Briefly, follicle-stimulating hormone injections were started at 150-450 IU daily for multi-follicular ovarian stimulation. Final oocyte maturation was induced using 5,000-10,000 IU of human chorionic gonadotrophin when at least two 18 mm follicles were seen on ultrasound scanning. Ultrasound-guided oocyte retrieval was performed 34-38 hours following human chorionic gonadotrophin administration. Progesterone supplementation was used for luteal phase support and continued for up to eight weeks gestation if the pregnancy had occurred.	Embryo development and quality after fertilization were assessed until transfer or freezing. One and three embryos were transferred into the uterine cavity according to each participating center's protocol.

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		cervical preparation was used. A standardized protocol, data collection tool, and accurate description of possible abnormalities were provided to each participating center.		
8	Raju GAR 2006	Hysteroscopy was carried out at Krishna endoscopy on an outpatient basis without anesthesia. Midazolam 0.1 mg/kg was given intravenously as a sedative when needed. All hysteroscopies were performed in the early proliferative phase using a 1.9 mm hysteroscope, which has a 30 view with a 3 mm continuous flow sheath. The flow sheath has a maximum 5 mm diameter with an incorporated 5 Fr working channel. Associated mechanical instruments used were grasping forceps with teeth and scissors. Uterine distention was accomplished with glycine, and 80 mmHg constant intrauterine pressure was maintained using an electronic pump. At the end of the procedure, a sample of endometrium was taken for histological evaluation by aspiration using a 4 mm cannula. The patients were discharged after 15–60 min of the procedure, and no further complications were observed.	Down-regulation was initiated using an intramuscular injection of Decapeptide 3.75 mg on day 21 of the cycle. Adequacy of down-regulation was confirmed by measuring E2 (≤ 50 pg/ml) and LH levels (< 1 ng/ml). Controlled ovarian stimulation was achieved using recombinant FSH (Recagon, Organon), and the dose was adjusted based on individual response. Human chorionic gonadotropin (hCG) at 10,000 IU was given after two follicles of 18 mm or more were visualized in the ultrasound scan. Oocyte retrieval was scheduled 36 h later by transvaginal ultrasonography (TVS).	After fertilization, embryo transfer was performed on day 3, and the number of embryos transferred was kept constant in all patient groups. Progesterone vaginal suppositories gave luteal support. Two weeks after embryo transfer, serum human chorionic gonadotropin (hCG) was measured to confirm pregnancy and a diagnosis of clinical pregnancy was made.

IVF: In vitro fertilization; TVS: Transvaginal ultrasonography; ET: Embryo transfer; hCG: Human chorionic gonadotropin; IU: International unit ART: Assisted reproductive technology; GnRH: Gonadotropin-releasing hormone; FSH: Follicle-stimulating hormone; ICSI: Intracytoplasmic sperm injection; HSC: Hysteroscopy; NA: Not available

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