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Review

The Effect of Hysteroscopy on the Reproductive Outcomes of Infertile Women Without Intrauterine Pathologies: A Systematic Review and Meta-Analysis

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Abstract: (1) Background: The aim of this work was to systematically review existing studies on whether hysteroscopy improves the reproductive outcomes of women with infertility even in the absence of intrauterine pathologies when compared to women who did not receive a hysteroscopy. (2) Methods: We established the Participant-Intervention-Comparison-Outcome strategy and used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement to conduct a systematic review of 11 studies which were retrieved from 3 electronic databases: Ovid-Medline, Ovid-Embase, and the Cochrane Library. Two independent investigators extracted the data from the included studies and used the Cochrane risk-of-bias tool to assess their quality. (3) Results: The primary outcome measures were the clinical pregnancy rates (CPRs) and live birth rates (LBRs) in the in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) cycles. Hysteroscopy in infertile women without intrauterine pathologies showed higher CPRs and LBRs than those in the same population who did not receive hysteroscopy in cases of recurrent implantation failure and IVF (odds ratio: 1.79 and 1.46, 95% confidence interval: 1.46-2.30 and 1.08-1.97 for CPR and LBR, respectively); however, the degree of significance was not as high for LBR. (4) Conclusions: Hysteroscopy before IVF/ICSI in infertile women without intrauterine pathologies may potentially be effective in improving the CPRs and LBRs in patients with RIF. Robust and high-quality randomized trials are warranted to confirm this finding.

Keywords: Infertile women; Hysteroscopy; Clinical pregnancy rate; Live birth rate; No Intrauterine pathology; endometrial stimulation; Systematic review

1. Introduction

Infertility is a disease that is characterized by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or that is due to an impairment of an individual's capacity to reproduce either alone or with their partner [1]. Infertility is a clinical problem that affects 13-15% of couples worldwide [2]. According to a recent paper confirming the prevalence of infertility in 195 countries from 1990 to 2017, there is an increasing trend of infertility worldwide, from 1366.85 cases per 100,000 in 1990 to 1571.35 cases per 100,000 in 2017 (a 14.962% increase) [3].

Assisted reproductive technology (ART) has been developed and distributed worldwide to help infertile couples, but, despite the high cost, its success rate remains low [4, 5]. According to a report from the Centers for Disease Control and Prevention, the rate of successful embryo implantation and

birth is only about 34% (43%, 35.8%, and 24.9% in patients who are 35-37, 38-40, and 41-42 years old, respectively) [6].

There are various reasons for implantation failure, including embryo quality and endometrial receptivity, but in many cases, the cause is unknown [7-9]. The pregnancy rate can be improved by methods such as improvement of embryo transfer and culture conditions or selection of blastocysts, but there is a limit that cannot be increased by more than 40-50% with these method [10]. It is well known that intrauterine pathology can affect the pregnancy rates in women who are using ART (in vitro fertilization/intracytoplasmic sperm injection [IVF/ICSI]), therefore it is necessary to check the intrauterine environment in order to maximize the implantation rate of quality embryos [11-13].

Hysteroscopy is the gold standard test for assessing the intrauterine condition [14]. Hysteroscopy can directly and accurately diagnose abnormalities such as intrauterine adhesions, endometrial polyps, submucosal fibroids, endometritis, or uterine structural abnormalities through visualization of the cervical and intrauterine conditions as well as through concurrent therapeutic intervention when necessary. In addition, hysteroscopy is advantageous as it can be used to perform a biopsy [15-19].

There are articles and systematic reviews that explore how confirming and treating intrauterine pathologies through hysteroscopy prior to the use of ART can have a positive effect on reproductive outcomes, as intrauterine lesions can negatively affect implantation rates [20-27]. Even in the absence of intrauterine pathological findings, there is literature that examines how performing a hysteroscopy can help improve pregnancy rates through relaxation of the cervix, the triggering of an inflammatory reaction in the endometrium, and the secretion of cytokines [23]. However, no previous systematic review has confirmed whether hysteroscopy is helpful in improving the clinical pregnancy and live birth rates, even in the absence of intrauterine pathology.

This systematic review included infertile women who did and did not undergo hysteroscopy to confirm whether it improves reproductive outcomes [24, 26-28]. A previous systematic review analyzed infertile women without intrauterine lesions who underwent hysteroscopy, but only compared them with women who were diagnosed with intrauterine pathologies after hysteroscopy was performed [24, 26]. No systematic review has been performed to confirm an improvement in the reproductive outcomes by comparing infertile women who did not undergo hysteroscopy to those who were not diagnosed with intrauterine lesions after hysteroscopy.

This systematic review was performed to provide guidance on whether routine hysteroscopy, or stimulation of the endometrium during hysteroscopy, that is performed prior to IVF improves the reproductive outcomes of infertile women without intrauterine pathology.

2. Materials and Methods

2.1. Search strategy

On January 28, 2020, all of the relevant articles regarding hysteroscopy in infertile women were searched for in the following databases: OVID-MEDLINE (1946 to January 2020), OVID-EMBASE (1974 to January 2020), and Cochrane library (the Cochrane review and trials database).

Combinations of the following Medical Subject Heading keywords were used for the searches: “hysteroscopy”, “minihysteroscopy”, “infertility”, “subfertility”, “intrauterine insemination”, “assisted conception”, “ICSI”, “fertilization in vitro or IVF”, “embryo transfer (ET)", "conception", "miscarriage or abortion", and "IVF-ET".

2.2. Inclusion and exclusion criteria

Two reviewers (S. Y. Y. and S. H. L.) independently screened the titles and abstracts of the studies extracted from the databases. The full text was subsequently reviewed for potentially relevant articles. Studies were selected regardless of whether they reported on experiences of repetitive implantation failure (RIF), and we included both randomized controlled and non-randomized studies. Studies that reported on the following were included: (a) infertility in women; (b) infertile women who were scheduled to use ART (IVF/ICSI) for the treatment of their infertility; (c)

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hysteroscopy in infertile women; and (d) the clinical pregnancy rate (CPR) or live birth rate (LBR) in infertile women without intrauterine pathologies who underwent hysteroscopy. The following types of studies were excluded: (a) animal studies; (b) articles not in English; (c) those whose content was not appropriate (conference posters, study protocols, review articles, cost-effectiveness analysis studies, and abstracts).

We defined the outcomes of interest before the systematic review. The primary outcome measures were the CPR and LBR, and the secondary outcome measures were the implantation and abortion rates, and adverse events relating to hysteroscopy.

In cases of disagreement between the reviewers, discussions were had and resolutions were made, and in cases where a consensus was not reached between the 2 reviewers, the principle of an intervening third reviewer was set, but all conflicts were resolved without the intervention of a third reviewer.

2.3. Quality assessment

Two reviewers (S. Y. Y. and S. H. L.) independently conducted quality assessments using the Risk of Bias tool (RoB 2; August 22, 2019 version) for randomized controlled trials. For non-randomized studies, the quality assessments were performed using the Risk of Bias in Non-randomized Studies of Interventions tool (ROBINS-I; August 1, 2016 version).

The RoB 2 tool includes 5 domains: bias arising from the randomization process, bias due to deviations from the intended intervention, bias due to missing outcome data, bias due to outcome measurement, and bias due to the selection of the reported results. Each criterion for the RoB 2 tool was evaluated as either “low risk”, “some concerns” or “high risk”. The ROBINS-I tool includes 7 domains: bias due to confounding, bias due to the selection of the participants, bias in the classification of the interventions, bias due to deviations from the intended interventions, and bias due to missing data. Each item was graded as “low risk”, “moderate risk”, “serious risk”, “critical risk” or “no information”. Disagreements regarding the quality assessments between the reviewers were resolved through a discussion.

2.4. Data extraction and statistical analysis

Two reviewers (S. Y. Y. and S. H. L.) independently extracted data from the studies selected according to the selection criteria. Disagreements between the reviewers were resolved through discussions. The following data were extracted for each of the 11 selected studies: author; year of publication; title; country in which the study was conducted; study design, setting, and group; number and ages of the patients; experiences of RIF; previous investigations (diagnostic tests performed before participation in the study such as transvaginal ultrasounds [TVS] or hysterosalpingography [HSG]); descriptions of the participants (inclusion and exclusion criteria, type of infertility); details of the intervention (hysteroscopy or no hysteroscopy); whether endometrial irritation was performed; method for attempting pregnancy; aim of the study; author's conclusion; main outcome measures; intergroup differences; and adverse events of hysteroscopy.

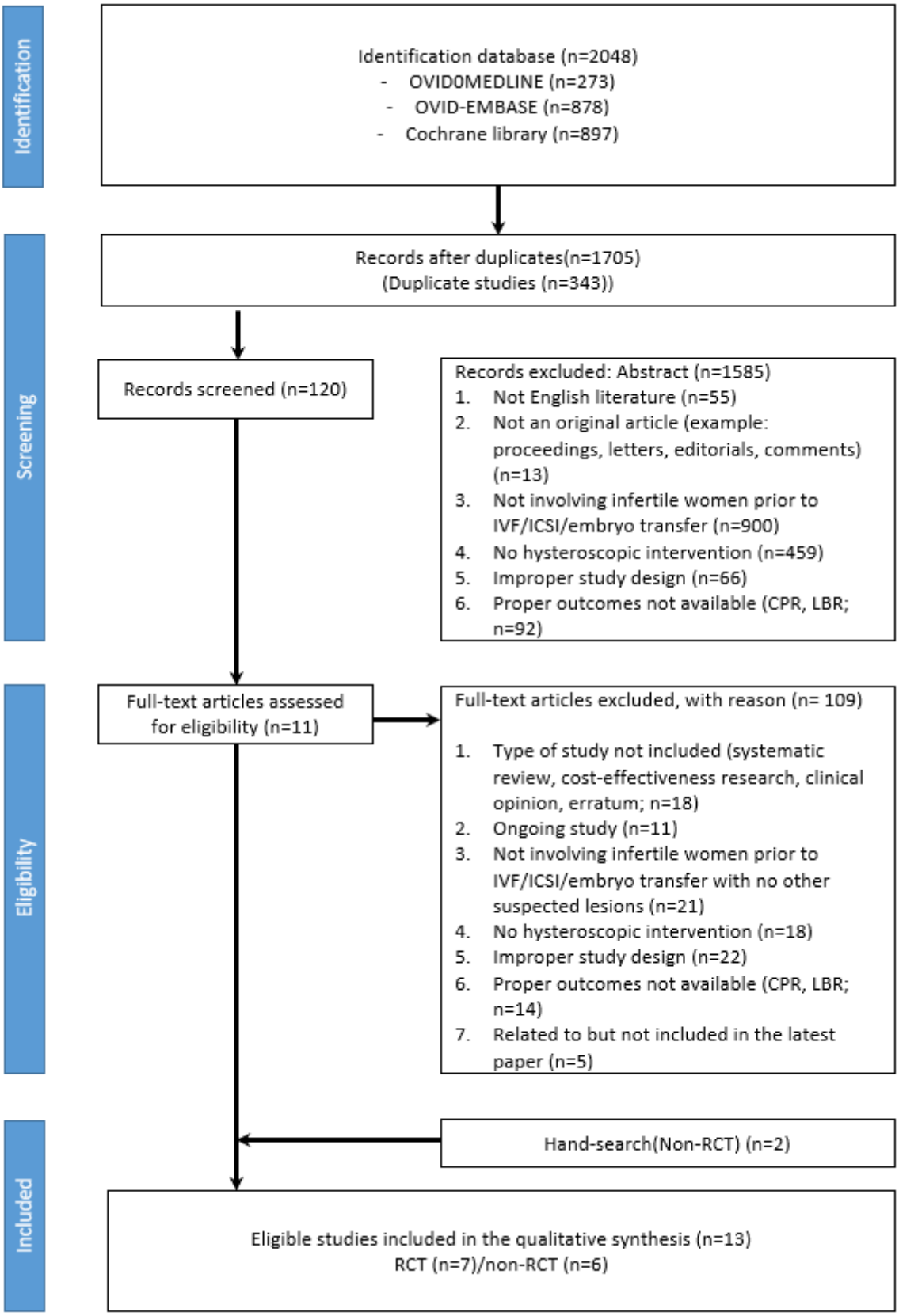
The authors of the selected studies were contacted to provide missing or unclear information on the trial methods or data. We used the Meta-analyses Of Observational Studies in Epidemiology reporting guidelines [29].

The pooled odds ratio (OR) was extracted for categorical data. Meta-analysis was undertaken where there were 2 or more studies. From each study, binary data were extracted in 2 × 2 tables and the results were pooled and expressed as OR with 95% confidence intervals (CIs) using a random-effects model, as appropriate [30]. Heterogeneity analyses were performed using forest plots, and I^2 statistics were used to quantify the heterogeneity between studies [31]. All statistical analyses were performed using RevMan version 5.4 software (Cochrane, London, United Kingdom).

3. Results

3.1. Study characteristics

142 The process of study selection is summarized in Figure 1.



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144 **Figure 1.** Study Flow Chart

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A total of 2,048 studies were initially identified. After excluding duplicates, 1,705 studies remained. A total of 120 studies were selected upon initial screening. After the full text review, 111 studies were excluded and 9 studies were included, and 2 studies were included by hand search (March 10, 2020). Ultimately, a total of 11 studies were included [23, 32-41]. The basic characteristics of the included studies are shown in Table 1. Six and 5 randomized and non-randomized controlled trials [32, 33, 35, 37, 39, 40],[23, 34, 36, 38, 41], respectively, were selected that investigated the CPRs or LBRs in infertile women without intrauterine lesions after hysteroscopy. Of the 11 studies that were included, 4 (36.4%) were conducted in Turkey [32, 36, 38, 41] and 2 (18.2%) in Iran [23, 40], while others were conducted in Egypt [35], Greece [34], India [33], the Netherlands [39], and Europe (n=1 for all) [37]. All of the subjects included in the studies were diagnosed with infertility and planning to use ART (IVF/ICSI). Six (54.5%) studies included infertile women who had experienced RIF [23, 32-34, 37, 38], and 3 (27.3%) included infertile patients who were undergoing IVF for the first time [39-41]. Two studies (18.2%) did not separately define whether the patients experienced RIF or were undergoing IVF for the first time [35, 36]. IVF/ICSI was performed after hysteroscopy in all of the studies who had a normal TVS or HSG assessment of the uterine cavity.

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First author (year)	Country	Study design	Setting	Groups/ n (PP population)		Age (m ± SD)	RIF history	Previous investigations	Method of pregnancy attempt	Description of participants
Demirol et al. (2004) [32]	Turkey	RCT	Single center 2000-2003	Hysteroscopy · Normal finding · Abnormal finding No hysteroscopy	210 154 56 211	- 35.4 ± 0.6 36.2 ± 0.1 34.3 ± 0.8	RIF	HSG normal	IVF	· Inclusion criteria: Women with primary infertility; Normal HSG; Age: 24-40
Raju et al. (2006) [33]	India	RCT	Single center 2002-2005	Hysteroscopy · Normal finding · Abnormal finding No hysteroscopy	255 160 95 265	- 27.40 ± 0.60 29.04 ± 0.92 26.72 ± 0.46	RIF	HSG normal	IVF	· Inclusion criteria: Women with primary infertility; Normal HSG; Age: 26-30
Shawki et al. (2012) [35]	Egypt	RCT	Single center 2007-2010	Hysteroscopy · Normal finding · Abnormal finding No hysteroscopy	120 (105) 35 70 120	33 ± 11.14 - - 31 ± 12.324	Unselected	HSG, TVS normal	ICSI	· Inclusion criteria: Women with primary or secondary infertility · Exclusion criteria: Uterine factor of infertility; Abnormal HSG or TVS; Previous intrauterine surgery; Contraindication for hysteroscopy
El-Toukhy et al. (2016). [37]	UK, Belgium, Italy, and Czech Republic	RCT	Multi center 2010-2013	Hysteroscopy · Normal finding · Abnormal finding No hysteroscopy	350 (323) 238 85 352 (348)	33.0 - - 33.0	RIF	TVS normal	IVF	· Inclusion criteria: Age <38 years · Exclusion criteria: <2 or >4 failed IVF cycles ending in an ET; Hysteroscopy: < 2 months before randomization; submucous or intramural uterine fibroids

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First author (year)	Country	Study design	Setting	Groups/ n (PP population)		Age (m ± SD)	RIF history	Previous investigations	Method of pregnancy attempt	Description of participants
										diagnosed; Untreated tubal hydrosalpinges; BMI >35 kg/m²;
Smit et al. (2016) [39]	Netherlands	RCT	Multi center 2011-2013	Hysteroscopy · Normal finding · Abnormal finding No hysteroscopy	369 (325) 288 37 373 (364)	33 ± 4.4 - - 33 ± 4.5	First	TVS normal	IVF/ICSI	· Inclusion criteria: Infertile women; No visible intracavitary pathology · Exclusion criteria: History of 2 or more miscarriages; Intermenstrual bleeding; Undergone hysteroscopy previously
Alleyassin et al. (2017) [40]	Iran	RCT	Single center 2014-2015	Hysteroscopy · Normal finding · Abnormal finding No hysteroscopy	110 85 25 110	29.55 ± 3.85 - - 29.14 ± 4.34	First	HSG, TVS, semen analysis, hormonal profile normal	ICSI	· Exclusion criteria: Recurrent miscarriages; History of hysteroscopy treatment
Makrakis et al. (2009) [34]	Greece	Prospective observational and matched case-control study	Single center 2002-2008	Hysteroscopy · Normal finding · Abnormal finding No hysteroscopy	1475 935 540 414	35.38 ± 3.96 35.8 ± 4.3 36.2 ± 4.6 35.39 ± 3.95	RIF	HSG normal	IVF/ICSI	· Inclusion criteria: Infertility; Age ≤ 42 years; Completion of a new IVF cycle with ET performed

First author (year)	Country	Study design	Setting	Groups/ n (PP population)		Age (m ± SD)	RIF history	Previous investigations	Method of pregnancy attempt	Description of participants
Kilic et al. (2013) [36]	Turkey	Prospective cohort study	Single center 2008-2010	Hysteroscopy · Normal finding · Abnormal finding No hysteroscopy	100 59 41 398	31.9 ± 3.4 - - 31.4 ± 3.2	Unselected	HSG, TVS normal	IVF	· Inclusion criteria: Diagnosis of infertility due to male factor, unexplained factor and female factors (including ovulatory and/or tubal) or multi factor; Age ≤ 39 years; BMI ≤30 kg/m^2
Hosseini et al. (2014) [23]	Iran	Prospective cohort study	Single center 2010-2011	Hysteroscopy · Normal finding · Abnormal finding No hysteroscopy	142 103 39 211	32.6 ± 4.2 - - 32.7 ± 4.3	RIF	HSG, TVS normal	ART IVF/ET	· Exclusion criteria: Age: >38 years of age; BMI <35 kg/m^2; Apparent uterine and tubal pathology; Hypothalamic amenorrhea; History of hysteroscopy in the last 3 months; Couples requiring testicular sperm extraction and aspiration for sperm recovery and gamete or embryo donations; Couples with abnormal karyotypes; Women positive for thrombophilia
Pabuccu et al. (2016) [38]	Turkey	Retrospective cohort study	Single center 2007-2014	Hysteroscopy · Normal finding · Abnormal finding No hysteroscopy	119 58 61 244	30.7 ± 5.3 - - 31.93 ± 4.4	RIF	HSG, TVS normal	IVF/ICSI	· Inclusion criteria: Age: 18-40 years; FSH levels of <15 IU/mL · Exclusion criteria:

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First author (year)	Country	Study design	Setting	Groups/ n (PP population)		Age (m ± SD)	RIF history	Previous investigations	Method of pregnancy attempt	Description of participants
										Poor ovarian response according to the Bologna criteria or Premature ovarian failure; Male subject with severe oligozoospermia, oligoasthenozoospermia, azoospermia; Preimplantation genetic screening, and cryopreserved/thawed ET cycles; Women with confirmed endometriosis; Women with hypothalamic amenorrhea; underwent OH more than 6 months prior to a new cycle
Tanakan et al. (2019) [41]	Turkey	Retrospective cohort study	Single center 2010-2014	Hysteroscopy · Normal finding · Abnormal finding No hysteroscopy	48 42 6 282	29.9 ± 4.3 - - 30.3 ± 4.2	First	HSG, TVS normal	IVF	· Inclusion criteria: Primary infertility; female age <40 years; BMI 19-35 kg/m^2; couple with unexplained tubal factor or mild/moderate male factor infertility · Exclusion criteria: History of operative hysteroscopy; azoospermia; diminished ovarian reserve (antral follicle count <5 at transvaginal ultrasound)

First author (year)	Country	Study design	Setting	Groups/ n (PP population)	Age (m ± SD)	RIF history	Previous investigations	Method of pregnancy attempt	Description of participants

Notes - n: number of participants; PP: per protocol; m: mean, SD: standard deviation; RIF: recurrent implantation failure; RCT: randomized controlled trial; HSG: hysterosalpingography; IVF: in vitro fertilization; TVS: transvaginal sonography; BMI: body mass index; ET: embryo transfer; ICSI: intracytoplasmic sperm injection; ART: artificial reproductive technologies; OH: office hysteroscopy; FSH: follicle stimulating hormone.

161 **Table 1.** The characteristics of the included studies

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3.2. *Characteristics of intervention*

Of the 11 studies included in our systematic review, 2 (18.2%) performed endometrial stimulation during the hysteroscopy [33, 35]. In 1 of the 2 studies, sampling of the endometrium by aspiration using a 4 mm cannula was performed at the end of the procedure, and the samples were sent for histological evaluation [33] In the other, the endometrial biopsy was performed using biopsy forceps under direct visualization [35]. In the hysteroscopy intervention group, hysteroscopy was performed in the early proliferative phase, then the use of ART (IVF/ICSI) was attempted. In the control group, the attempt to use assisted reproductive technology was made immediately.

A 2.9-5.5 mm diameter hysteroscope was used for the intervention group. Four and 3 cases (36.4% and 27.3%, respectively) used a 4 mm and 5 mm diameter hysteroscope, respectively [23, 32, 33, 36, 38-40]. One study (15.4%) did not mention the diameter of the hysteroscope used [41]. The characteristics of the hysteroscopies are summarized in Table 2.

Study	Intervention		Comparator	Endometrial irritation (I Only)	Method of pregnancy attempt (Both I and C)	Embryo / Day of ET	Author's conclusion	Main outcome measures	Intergroup differences	Adverse events of the hysteroscopy
	Timing	Hysteroscope								
Demirol et al. (2004) [32]	The early proliferative phase before controlled ovarian stimulation for IVF treatment (2-6 months after the last failed IVF cycles)	5mm continuous flow, lens diameter 2.9 mm, 30° view, 5mm diameter sheath, Bettocchi, size 5 [Karl Storz GmbH and Co., Tuttlingen, Germany]	Immediate controlled ovarian stimulation for IVF treatment	No scratching	IVF	Fresh embryo / Day 3	Patients with normal HSG but recurrent IVF-ET failure should be evaluated prior to commencing IVF-ET cycles to improve the clinical PR"	(1) Number of clinical pregnancies (2) Number of first trimester abortions	(1) <0.05 (2) NS	Mild pain resembling menstrual cramps
Raju et al. (2006) [33]	The early proliferative phase before controlled ovarian stimulation for IVF treatment	5 mm diameter, 1.9 mm miniature, 30°view, 3 mm Bettochi continuous flow sheath with an incorporated 5 Fr working channel [Karl Storz GmbH and Co., Tuttlingen, Germany]	Immediate controlled ovarian stimulation for IVF treatment	Endometrial biopsy	IVF	Fresh embryo / Day 3	Patients with recurrent IVF-ET failures after normal HSG should also be reevaluated using hysteroscopy prior to commencing IVF-ET cycles in order to enhance the CPR	(1) CPR (2) Miscarriage rate (3) LBR	(1) <0.05 (2) NS (3) <0.05	No further complications
Shawki et al. (2012) [35]	The early postmenstrual period before controlled ovarian stimulation for ICSI	3.5 mm with a 0° grade [Versascope; Gynecare, Ethicon, Sommerville, NJ, USA])	Immediate controlled ovarian stimulation for ICSI	Endometrial biopsy	ICSI	Fresh embryo / Not specified	Improvement in implantation and CPR were observed after OH prior to ICSI Routine OH should be an essential step of the infertility workup before ART even in	(1) CPR (2) Implantation rate	(1) <0.05 (2) <0.05	Not specified

Study	Intervention		Comparator	Endometrial irritation (I Only)	Method of pregnancy attempt (Both I and C)	Embryo / Day of ET	Author's conclusion	Main outcome measures	Intergroup differences	Adverse events of the hysteroscopy
	Timing	Hysteroscope								
		Optic Illumination (250-W Xenon light source)					patients with normal HSG and/or TVS"			
El-Toukhy et al. (2016) [37]	Before controlled ovarian stimulation for IVF -within 14 days of menstruation	2.9 mm diameter, rigid 30° view, with an atraumatic tip [TROPHY scope; Karl Storz, Tuttlingen, Germany]	Immediate controlled ovarian stimulation for IVF/ICSI	No scratching	IVF (with or without ICSI)	Fresh embryo / When it is considered top quality (Day 2 or Days 3-4 or Days 5-6)	Routine OH does not improve IVF outcomes in women with RIF who have a normal uterine ultrasound scan	(1) Pregnancy rate (2) CPR (3) LBR (after 1 cycle of IVF)	(1) 0.86 (2) 0.65 (3) 0.96	No hysteroscopy-related adverse events
Smit et al. (2016) [39]	In the early-mid follicular phase of a menstrual cycle (days 3–12) 1–3 months before the start of IVF treatment.	5 mm outer-diameter continuous flow hysteroscope with a 5 Fr working channel and a 30° direction of view	Immediate start of IVF	No scratching	IVF	Fresh embryo / Not specified	Routine OH before the first IVF or ICSI treatment cycle does not improve fertility prospects in infertile women with a normal TVS of the uterine cavity who have not had a previous hysteroscopy	(1) Implantation rate (2) CPR (3) OPR (4) LBR	(1) 0.23 (2) 0.71 (3) 0.69 (4) 0.75	One (<1%) woman: endometritis after hysteroscopy.
Alleyassin et al. (2017) [40]	Between the 18th and 22nd day of their menstrual cycles (mid-luteal phase) before ICSI cycles	4 mm diameter diagnostic sheath, continuous flow, rigid, 30° view [Karl Storz Endoscopy, Tuttlingen, Germany])	Did not undergo OH before ICSI cycles	No scratching	ICSI	Fresh embryo / Day 3	Routine OH before ICSI cycles provides direct evaluation of uterine cavity CPR improves after correction of endometrial cavity abnormalities	(1) CPR (2) Miscarriage rate	(1) 0.004 (2) NS	Not specified

Study	Intervention		Comparator	Endometrial irritation (I Only)	Method of pregnancy attempt (Both I and C)	Embryo / Day of ET	Author's conclusion	Main outcome measures	Intergroup differences	Adverse events of the hysteroscopy
	Timing	Hysteroscope								
Makrakis et al. (2009) [34]	Less than 12 months before the first IVF attempts Shortly after cessation of menses	2.9 mm, 30degree angle, external sheath of 5.5-mm diameter providing inflow and outflow [Karl Storz, Tuttlingen, Germany]	Matched control (No hysteroscopy before IVF cycles)	No scratching	IVF	Fresh or frozen embryo / Day 3-5	Hysteroscopy could be seen as a positive prognostic factor for achieving a subsequent IVF pregnancy in women with a history of 2 consecutive implantation failures	(1) CPR (2) OPR	(1) 0.04 (2) 0.06	Not specified
Kilic et al. (2013) [36]	Assessed prior to IVF Follicular phase (days 5–7 of menstrual cycle)	4 mm [Karl-Storz GmbH & Co. KG, Tuttlingen, Germany]	Underwent IVF without OH evaluation	No scratching	IVF	Not specified	OH before IVF can detect and treat intrauterine pathologies, which has a positive effect on pregnancy outcome.	(1) LBR	(1) <0.05	Not specified
Hosseini et al. (2014) [23]	In the menstrual cycle just before ovarian stimulation or endometrial preparation	4 mm rigid, continuous flow, 30° forward, and oblique view	Hysteroscopy was not performed	No scratching	ART IVF/ET	Fresh or frozen embryo / Day 3	OH before fresh cycles and frozen thawed cycles in women experiencing RIF with apparently normal uterine cavity significantly increases the pregnancy rates, respectively	(1) CPR (2) CPR (3) Delivery rate	(1) <0.001 (2) 0.001 (3) 0.026	Not specified
Pabuçcu et al. (2016) [38]	In early follicular phase (1–6 months before the beginning of a new cycle)	4 mm outer diameter, rigid, continuous flow; 30° forward and oblique view	Immediately started a new ART cycle	No scratching	IVF/ICSI	Fresh embryo / day 3 or Day 5	Unrecognized intrauterine pathologies can be easily detected and concurrently treated	(1) Implantation rate (2) Chemical	(1) 0.38 (2) 0.08 (3) 0.06	Not specified

Study	Intervention		Comparator	Endometrial irritation (I Only)	Method of pregnancy attempt (Both I and C)	Embryo / Day of ET	Author's conclusion	Main outcome measures	Intergroup differences	Adverse events of the hysteroscopy
	Timing	Hysteroscope								
							during the OH procedure with high success rates. The overall beneficial impact in terms of reproductive outcomes seems to depend on the extent of the pathology	pregnancy rate (3) LBR (4) Miscarriage rate	(4) 0.26	
Tanacan et al. (2019) [41]	In the early to midfollicular phase of the menstrual cycle (1–3 months before the start of IVF)	Not specified	Without diagnostic hysteroscopy prior to the first IVF cycle	No scratching	IVF	Fresh embryo / Day 3 or Day 5	OH before the first IVF treatment cycle did not improve fertility outcomes in patients without previously detected pathology of the uterine cavity Routine usage of hysteroscopy should not be offered to patients their first IVF cycles	(1) Implantation rate (2) CPR (3) LBR	(1) 0.840 (2) 0.541 (3) 0.420	Not specified

Notes - I: intervention; C: control; IVF: in vitro fertilization; ET: embryo transfer; HSG: hysterosalpingography; TVS: transvaginal sonography; NS: not significant; ART: artificial reproductive technology; ICSI: intracytoplasmic sperm injection; TVS: transvaginal sonography; OH: office hysteroscopy; RIF: recurrent implantation failure; Fr: French; CPR: clinical pregnancy rate; OPR: ongoing pregnancy rate; PR: pregnancy rate; LBR: live birth rate.

175 **Table 2.** The characteristics and effectiveness of the reviewed interventions

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3.3. *Study quality*

We performed a quality assessment of 6 and 5 randomized and non-randomized controlled studies, respectively, that confirmed the reproductive outcomes when the use of ART was attempted in a group who did not have hysteroscopies performed and in whom no intrauterine pathologies were identified after hysteroscopy.

Of the 6 randomized studies, 3 [32, 33, 40] were graded as "some concerns" in the selection bias (bias arising from the randomization process) category because the allocation concealment information could not be confirmed, but the imbalances at baseline did not suggest any problems. The selection bias for the other 3 studies [35, 37, 39] was graded as "low risk". In all 6 randomized studies [32, 33, 35, 37, 39, 40], performance bias (bias due to deviations from the intended intervention) and detection bias (bias in measurement of the outcome) were both graded as "low risk".

In the evaluation of attrition bias (bias due to missing outcome data), 1 [35] out of 6 studies were evaluated as having "some concern" because an intention-to-treat analysis was not conducted, and 5 studies [32, 33, 37, 39, 40] were evaluated as "low risk". The reporting bias (bias in selection of the reported result) was rated as "low risk" in 2 studies [37, 39], while 4 studies were rated as "some concern" because they did not report selected results, and there was no information as to whether the analysis was performed according to a predefined plan [32, 33, 35, 40].

Of the 5 non-randomized studies, 4 [23, 34, 38, 41] were classified as "moderate risk" for bias due to confounding (the pre-intervention domain in confounding) because the confounding variables were properly measured and controlled, and the measurement of the important domains was sufficiently reliable and valid. In 1 study [36], even though IVF was performed, the confounding variables for whether the patients experienced RIF were not identified, therefore it was graded as "serious risk". Biases due to deviations from the intended interventions (the post-intervention domain in confounding) were graded as "low risk" in all 5 studies [23, 34, 36, 38, 41].

For bias in selection of participants into the study (the pre-intervention domain in selection bias), 3 studies [34, 38, 41] were rated as "moderate risk". One [34] out of the 3 selected as moderate was included because selection of the patients for the study may have been related to the intervention (hysteroscopy) but this was adjusted for. The remaining 2 [38, 41] were selected based on the inclusion/exclusion criteria regardless of the interventions or outcomes, but, as they were retrospective studies, the start of the follow-up period and intervention did not coincide. Two studies [23, 36] were evaluated as "low risk". Biases due to missing data (the post-intervention domain in selection bias) were graded as "low risk" in all 5 studies [23, 34, 36, 38, 41].

As a result of the quality assessment of the bias in the classification of the interventions (in the intervention domain in information bias), 2 and 3 studies [23, 34, 36, 38, 41] were graded as "low risk" and "moderate risk", respectively. These studies were assessed as "moderate risk" because the intervention status was well defined, however some aspects regarding the assignment of the intervention status were determined retrospectively. Bias in the measurement of outcomes (the post-intervention domain for information bias) was graded as "low risk" in all 5 studies [23, 34, 36, 38, 41] because the outcome measures such as the CPRs and LBRs involved negligible assessor judgment.

As for the bias in the selection of the reported results (reporting bias), 4 studies [23, 36, 38, 41] were evaluated as "moderate risk" because their pre-registered protocol or statistical analysis plans could not be identified. In 1 study [34], even though the study period was long enough (6 years), the LBR was not reported and this was graded as a "serious risk". The results of the quality assessment are summarized in Figure 2.

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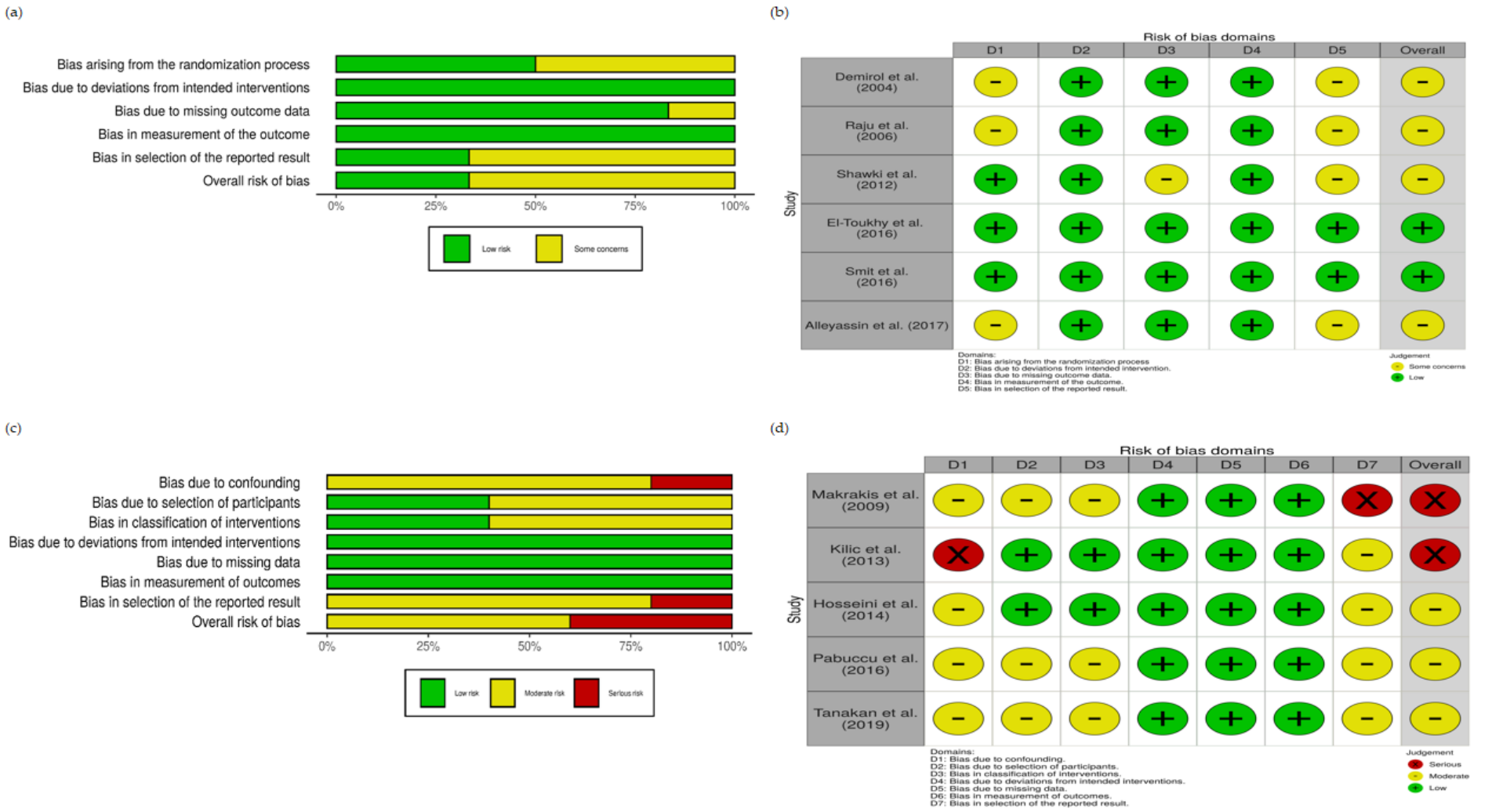

Figure 2. Quality assessment (a) Risk of Bias 2.0 graph for randomized controlled studies; (b) Risk of Bias 2.0 summary for randomized studies; (c) Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) graph for non-randomized studies; (d) ROBINS-I summary for non-randomized studies

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3.4. *Primary outcome measures: CPR and LBR*

3.4.1. Analysis based on the history of RIF

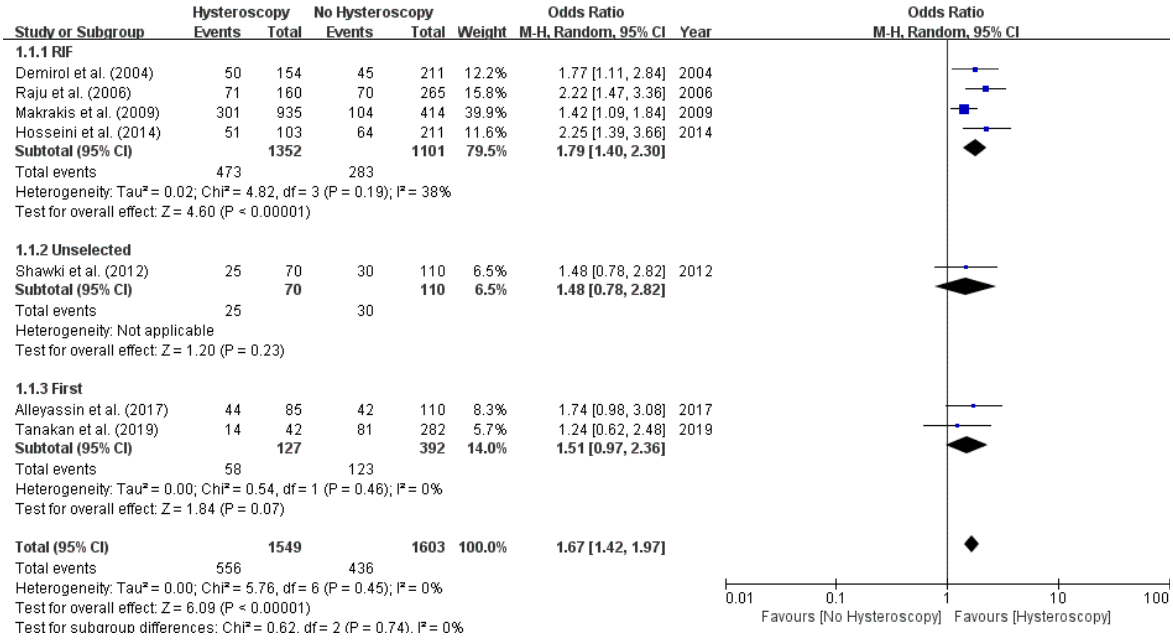
- CPR

In 7 of the 11 studies on infertile patients included in our systematic review, CPRs were reported in the groups without intrauterine pathologies who underwent hysteroscopy and were analyzed based on a history of RIF [23, 32-35, 40, 41]. The heterogeneity analyses of 4 and 3 randomized and non-randomized studies, respectively [32, 33, 35, 40] [23, 34, 41] showed low heterogeneity (total I^2=0%, RIF group I^2=38%). Therefore, an integrated analysis was conducted. In total, 3,152 infertile women were included in the 7 studies: 1,549 in the hysteroscopy group without intrauterine pathologies and 1,603 in the control group. The results of the analysis of the 7 studies showed that the RIF group before IVF/ISCI had a significant difference in the CPR (OR: 1.67, 95% CI: 1.42-1.97, I^2=0%, P=0.45).

- LBR

In 8 of the 11 studies on infertile patients included in our systematic review , LBRs were reported in the groups without intrauterine pathologies who underwent hysteroscopy and were analyzed based on a history of RIF [23, 33, 34, 36-39, 41]. The heterogeneity analyses of 3 and 5 randomized and non-randomized studies, respectively, [23, 33, 34, 36-39, 41] did not show high levels of heterogeneity (total I^2=38%, RIF group I^2=58%). Therefore, an integrated analysis was conducted. In total, 4,372 infertile women were included in the 8 studies: 1,854 in the hysteroscopy group without intrauterine pathologies and 2,518 in the control group. The results of the analysis of the 8 studies showed significant differences in the RIF group before IVF/ISCI, but the differences in the LBRs were not significant (OR: 1.46, 95% CI: 1.08-1.97, I^2=58%, P=0.05).

(**a**)



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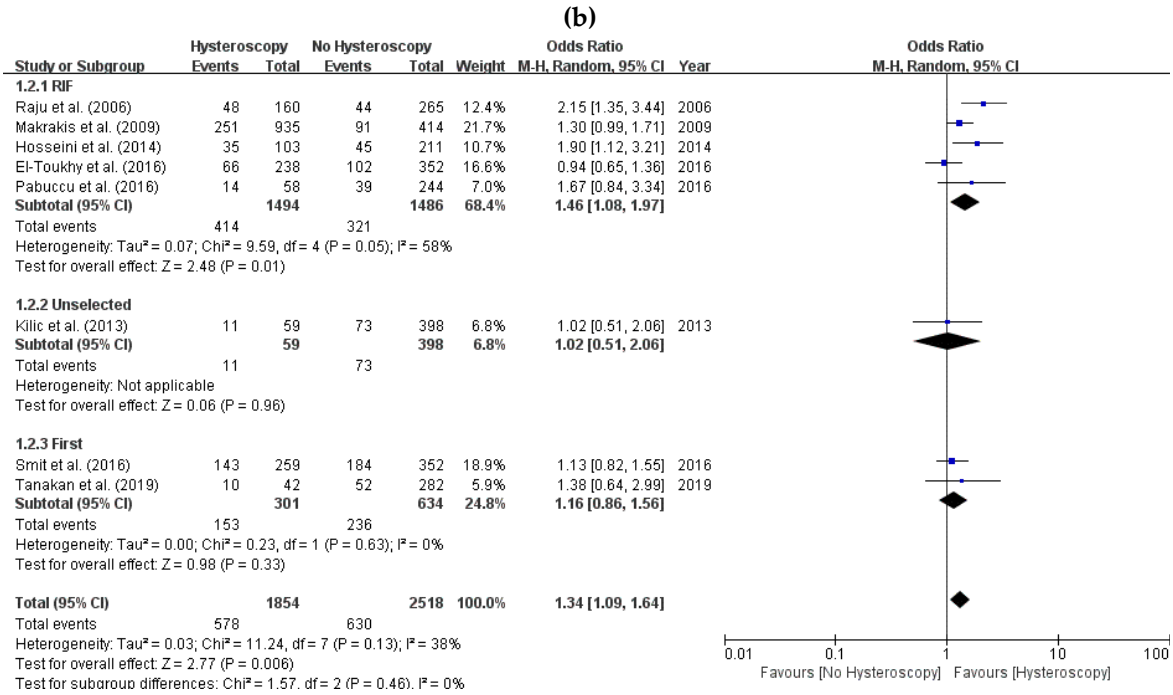

Figure 3. Meta-analysis based on history of recurrent implantation failure: (a) Clinical pregnancy rate; (b) Live birth rate. Abbreviations - MH: Mantel-Haenszel; RIF: recurrent implantation failure; CI: confidence interval.

3.4.2. Analysis based on endometrial stimulation

- CPR

In 7 studies on infertile patients, CPRs were reported in the groups without intrauterine pathologies who underwent hysteroscopy and were analyzed according to whether the patients received endometrial stimulation [23, 32-35, 40, 41]. In total, 3,152 infertile women were included in the 7 studies: 1,549 in the hysteroscopy group without intrauterine pathologies and 1,603 in the control group. The results of the 7 studies showed significant differences in the CPRs both regardless of whether they received endometrial stimulation in the hysteroscopy group without intrauterine pathologies before IVF/ICSI when compared with the control group (OR: 1.70, 95% CI: 1.44-2.00, I^2=0%, P=0.54).

- LBR

In 8 studies of infertile patients, the LBRs were reported in the group without intrauterine pathologies who underwent hysteroscopy before IVF/ICSI and analyzed according to whether the patients received endometrial stimulation [23, 33, 34, 36-39, 41]. In total, 4,372 infertile women were included in the 8 studies: 1,854 in the hysteroscopy group without intrauterine pathologies and 2,518 in the control group. The results of the 8 studies showed significant differences in the LBRs both with or without endometrial stimulation in the hysteroscopy group without intrauterine pathologies before IVF/ICSI when compared with the control group, but the degree of significance was not as high for LBR (OR: 1.34, 95% CI: 1.09-1.64, I^2=38%, P=0.13).

The difference in the statistical significance of the LBR between the hysteroscopy group without intrauterine pathologies and the group who did not undergo hysteroscopy was smaller in studies without endometrial stimulation than in the combined results of studies both with and without endometrial stimulation (OR: 1.23, 95% CI: 1.04-1.45, I^2=5%, P=0.39).

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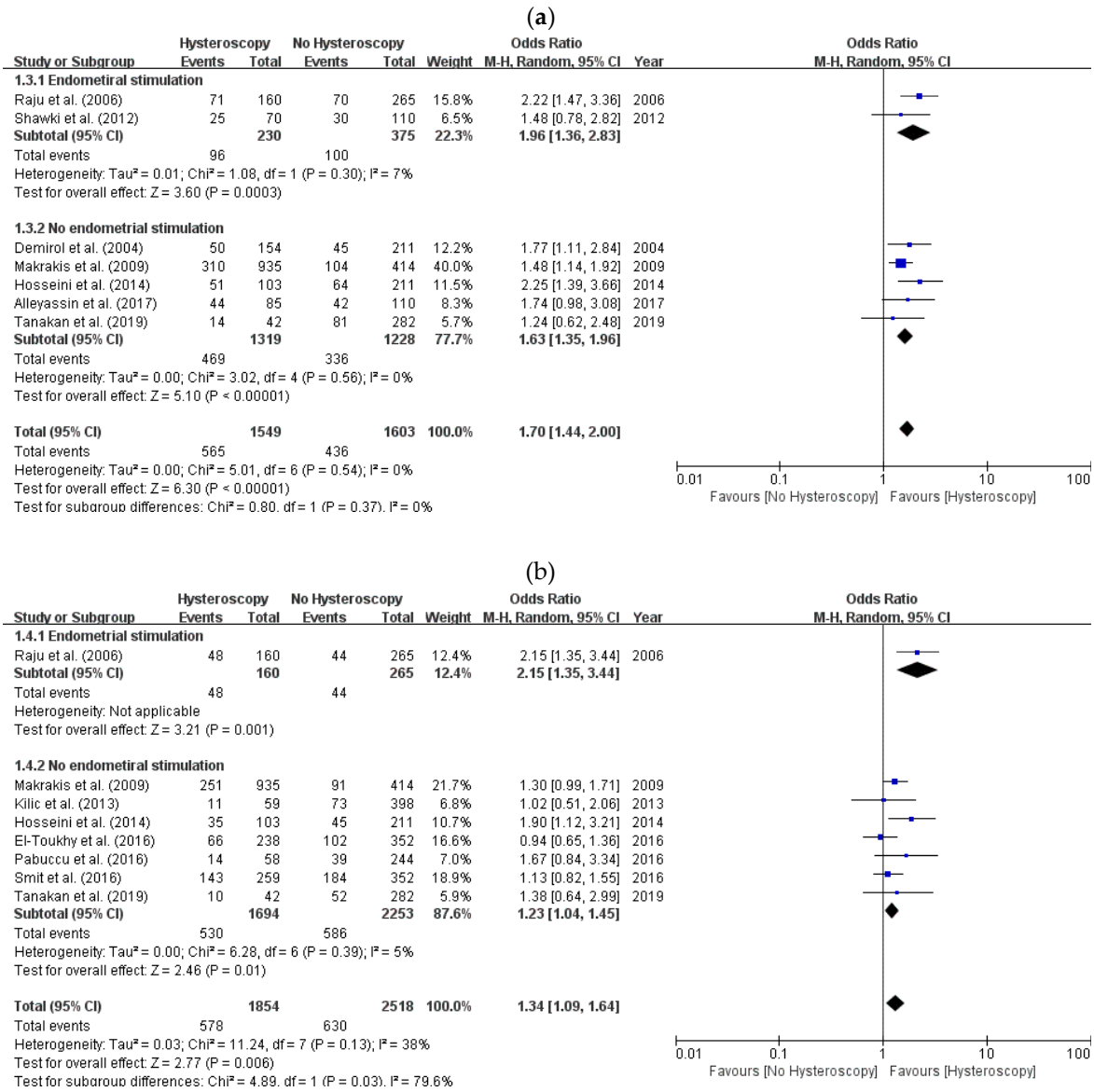

Figure 4. Meta-analysis based on endometrial stimulation: (a) Clinical pregnancy rate; (b) Live birth rate. Abbreviations - MH: Mantel-Haenszel; CI: confidence interval.

3.5. Secondary outcome measures: implantation and miscarriage rates, and adverse events

3.5.1. Implantation rate

The implantation rates for the hysteroscopy groups were reported, but there was no study that separately reported the implantation rates of the infertile patients without intrauterine pathologies, so this parameter was excluded from the analysis.

3.5.2. Miscarriage rate

In 3 out of the 11 studies included in the review, the miscarriage rates of the infertile patients without intrauterine pathologies in the hysteroscopy groups were reported and analyzed according to the type of study i.e., randomized or non-randomized controlled studies [23, 32, 33]. In total, 820 infertile women were included in the 3 studies: 328 in the hysteroscopy group without intrauterine pathologies and 492 in the control group. The results of the 3 studies did not show a significant difference in the miscarriage rates in the hysteroscopy group who did not have intrauterine pathologies compared with the control group (OR: 1.22, 95% CI: 0.57-2.58, I^2=60%, P=0.08). The randomized controlled and non-randomized studies were divided, and a subgroup analysis was

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performed. There was no significant difference in the miscarriage rates in the 2 randomized studies [32, 33] (OR: 0.83, 95% CI: 0.46-1.50, I^2=0%, P=0.84).

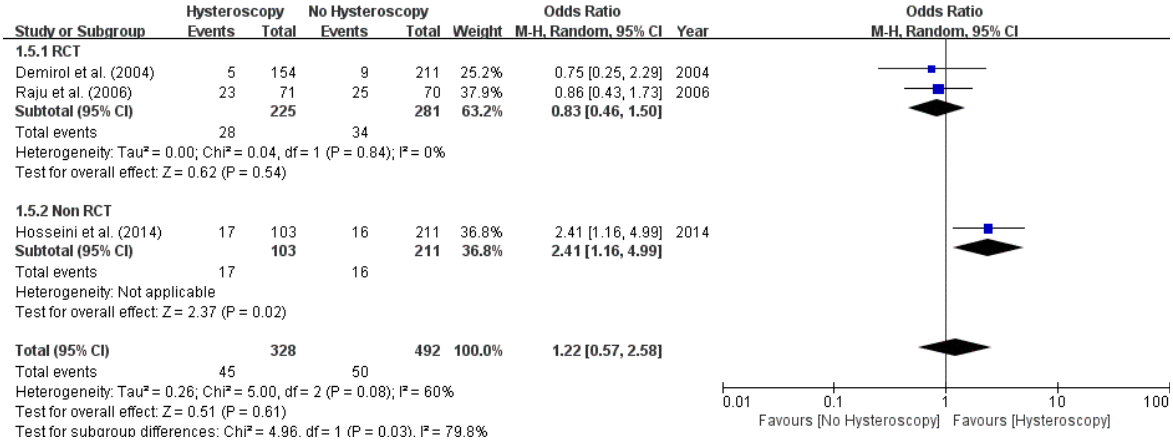


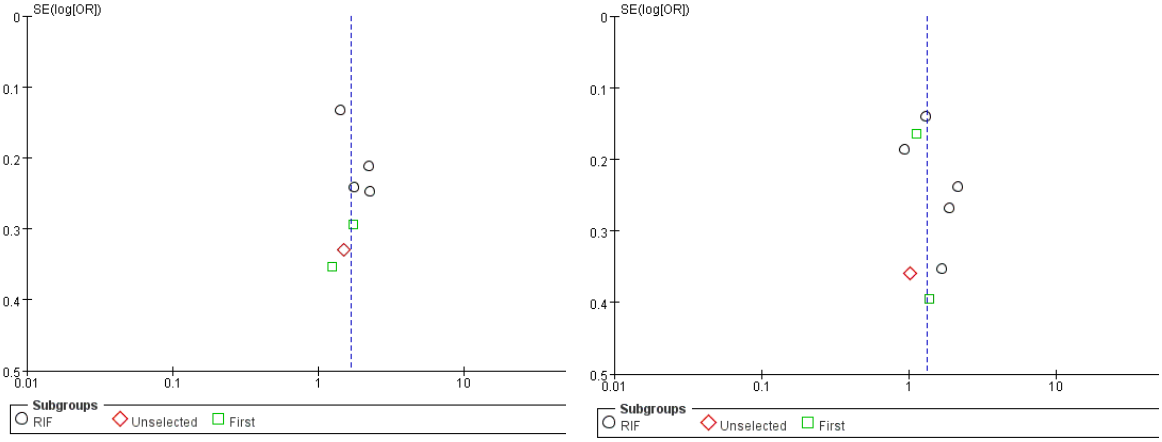
Figure 5. Meta-analysis of miscarriage rate. Abbreviations - MH: Mantel-Haenszel; CI: confidence interval.

3.5.3. Adverse events relating to hysteroscopy

Seven studies (63.6%) did not mention any adverse events relating to hysteroscopy [23, 34-36, 38, 40, 41]. Of the 11 studies included in the review, 4 reported adverse events in the hysteroscopy group, but there were no studies that separately reported on the adverse events of infertile patients without intrauterine pathologies, so this was excluded from the analysis. There were no adverse events in 2 of the studies [33, 37] and another 2 studies (15.4%) reported that the patient developed pain[32] and endometritis (1%) [39].

3.6. Publication bias

Publication bias for the CPRs and LBRs (7 and 8 studies, respectively) [23, 32-35, 40, 41] [23, 33, 34, 36-39, 41] were analyzed using funnel plots and did not suggest any evidence of bias (Figure 6).



(**a**) (**b**)

Figure 6. Funnel plot of the effects of hysteroscopy for infertile women without intrauterine pathologies (a) Clinical pregnancy rate; (b) Live birth rate

4. Discussion

This systematic review was conducted by selecting 11 studies to confirm the effect of hysteroscopy on the clinical pregnancy and live birth rates in female infertile patients who were scheduled for the use of ART (IVF/ICSI). Previous systematic reviews have compared groups who did and did not receive hysteroscopies [24, 25]; however, this study is the first to compare the reproductive outcomes of groups of infertile patients who underwent hysteroscopy and were not

diagnosed with intrauterine pathologies and groups of infertile patients who did not undergo hysteroscopy. This systematic review reflects the results of the latest research.

4.1. *The impact of a history of RIF on pregnancy*

The main findings of this systematic review are that hysteroscopy before IVF/ICSI in infertile women who have experienced RIF is more effective for the clinical pregnancy and live birth rates than not having a hysteroscopy, even without intrauterine pathologies. There were no improvements in the clinical pregnancy and live birth rates in infertile patients undergoing IVF for the first time.

El-Toukhy et al. noted in a systematic review that the benefit of a hysteroscopy before IVF was lower in infertile patients undergoing IVF for the first time than in infertile patients who experienced RIF. It has been explained that as the number of IVF failures increases, the risk of intrauterine pathology increases, which may be related to hysteroscopy's ability to reliably detect and potentially treat the intrauterine pathologies that occur during the hysteroscopy [42-44]. In this study, the same result was confirmed even though hysteroscopy was not used to correct the intrauterine pathologies. Therefore, we suspect that there may be other factors affecting the endometrial receptivity of infertile patients who have experienced RIFs that do not affect those who are receiving IVF for the first time. El-Toukhy et al. explained that the fertility-enhancing effect of hysteroscopy could also be independent of whether intrauterine pathologies are corrected and could be related to a number of other factors [44].

In their studies, El-Toukhy et al. and Pundir et al. reported on the causes that appear to be responsible for improving the reproductive outcomes when hysteroscopy is performed. The benefits may be due to hysteroscopy allowing for more accurate embryo placement and easier ET, and that the effect of the use of saline for the irrigation of harmful, anti-adhesive glycoprotein molecules on the endometrial surface leads to improved endometrial conditions and mechanically stimulates the endometrium which may enhance the endometrial receptivity beyond correcting intrauterine pathologies [24, 44-47].

However, out of the 4 studies [23, 32-34] which confirmed the CPRs of infertile patients with RIF, only 2 were randomized [32, 33] in a single institution setting, and the other 2 were non-randomized [23, 34]. Of the 5 studies that identified the LBRs [23, 33, 34, 37, 38], 2 and 3 were randomized and non-randomized, respectively [33, 37] [23, 34, 38].

It appears that the live birth and clinical pregnancy rates of infertile patients with RIF have increased with statistical significance (OR: 1.46 and 1.79, 95% CI: 1.08-1.97 and 1.40-2.30, I^2 =58% and 38%, P=0.05 and 0.19 for LBR and CPR, respectively). However, as the number of studies is still insufficient and there are few randomized studies, caution is required when interpreting the effects of hysteroscopy on the pregnancy and fertility rates, and verification of its effectiveness in a larger multicenter randomized clinical study in the future is recommended.

4.2. *Impact of endometrial stimulation*

In this study, we found that when hysteroscopy was performed prior to IVF/ICSI it had a significant effect on the improvement of the CPR in infertile patients without endometrial pathologies, regardless of whether the endometrium was stimulated or not. The results show that hysteroscopy alone may have a positive effect on IVF outcomes. Saline used during hysteroscopy mechanically removes harmful anti-adhesive glycoprotein molecules involved in endometrial receptivity from the endometrial surface (cyclooxygenase-2, mucin-I, integrin $\alpha V\beta 3$) [45]. Mechanical endometrial injury may enhance endometrial receptivity by modulating the expression of gene encoding factors required for implantation, such as glycodelin A, laminin alpha-4, integrin alpha-6, and matrix metalloproteinase-I [46, 47]. One study reported that when an endometrial biopsy was performed repeatedly, Cx43 (a gap junction protein), which could be a possible parameter for successful implantation that may predict implantation competence, was expressed; and that this could help improve the reproductive outcomes and pregnancy rates [48].

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Both of the studies that stimulated the endometrium during hysteroscopy were randomized [33, 35], and 3 of 5 studies that did not stimulate the endometrium were non-randomized, while the remaining 2 studies were randomized [32, 40].

In addition, the LBR when the endometrium was not stimulated during hysteroscopy was analyzed in 2 and 5 randomized and non-randomized studies, respectively [37, 39] [23, 34, 36, 38, 41]. The results of the meta-analysis of all 7 studies showed that the improvement in the LBR was significant (OR: 1.23, 95% CI: 1.04-1.45, I^2=5%, P=0.39). However, it was found that the analysis was not significant when only 2 multi-center randomized controlled studies were analyzed. It seems that not stimulating the endometrium does not help to improve the LBR given the high-quality research results of the studies [OR: 1.04, 95% CI: 0.83-1.32, I^2 =0%, P=0.47].

Kamath et al. did not present patients without pathologies separately, but reported that there was no benefit in performing hysteroscopy without endometrial stimulation [28, 33, 35]. In this study, 2 studies [37, 39] with low risks for bias found that there is no benefit to hysteroscopy without endometrial stimulation, confirming the same results. Shohayeb et al. did not report on infertile women without intrauterine pathologies separately but showed similar results to those found in this study, which found that the group that had the endometrium stimulated (single endometrial biopsy regimen) when the hysteroscopy was performed prior to implementing ICSI for infertile women who experienced RIFs had significantly improved CPRs and LBRs over those who only had hysteroscopy performed [34, 49].

There are various mechanisms proposed in support of endometrial scratch injury, which may improve the endometrial receptivity. Most recently hypothesized is the "backward development hypothesis" which states that endometrial scratch injury may delay endometrial maturation, minimizing the negative effects of ovarian stimulation and implantation [50-52]. Another hypothesis is that injury may trigger the massive secretion of growth factors and cytokines which may be beneficial for embryo implantation [53, 54]. The last hypothesis is based on animal models, in which injury may induce rapid growth of the endometrial cells in a similar fashion to that of the decidual cells in humans [50, 51, 53-56].

The birth rates in cases where the endometrium was stimulated during hysteroscopy were not integrated into this study because only 1 study existed [33], but, in this study, endometrial stimulation appeared to be effective [OR: 2.15, 95% CI: 1.35-3.44]. Further research is needed to determine whether stimulation of the endometrium during hysteroscopy for patients with infertility who are scheduled for IVF/ICSI will help improve the LBR even if there are no uterine pathologies.

4.3. Limitations and Strengths

The limitation of this systematic review was, while the number of infertile women without intrauterine pathologies in the hysteroscopy group was confirmed, there was a study that did not investigate the CPR, LBR, and implantation and miscarriage rates separately. We tried to contact the author and include it, but no response was received, so we could not include all of the data on infertile women without intrauterine pathologies who underwent hysteroscopy before ART in our study.

In order to see the effect of hysteroscopy alone, subjects without intrauterine pathologies should be included in both the hysteroscopy and non-hysteroscopy groups, however it is difficult to determine the presence of intrauterine lesions until hysteroscopy is performed.

In order to see the effect of hysteroscopy only, hysteroscopy should be conducted in patients with infertility who do not have uterine pathologies which may be identified through 3D TVS in the future [39].

Despite these limitations, this study is meaningful as it is the first systematic review that measures the effect of the use of hysteroscopy on the clinical pregnancy and live birth rates in infertile women without intrauterine pathologies.

Large-scale, multicenter, randomized controlled trials are needed in the future to verify the findings of this systematic review that hysteroscopy may be regarded as effective for infertile women without intrauterine pathologies. Furthermore, studies that confirm the effect of only performing hysteroscopy or the effect of hysteroscopy with endometrial stimulation compared with no

hysteroscopy before IVF/ICSI in women with infertility without intrauterine pathologies on the implantation, pregnancy, miscarriage, and live birth rates are required.

5. Conclusions

In conclusion, a systematic review and meta-analysis of the published studies showed that even if there are no intrauterine pathologies in infertile women who experienced RIF, performing a hysteroscopy before IVF/ICSI may improve the CPRs and LBRs as opposed to not performing it. In addition, stimulation of the endometrium during hysteroscopy seems to be effective in increasing the CPR. Large-scale randomized studies are needed to provide strong evidence in the future.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1; Figure 1 Study Flow Chart, Table 1. The characteristics of the included studies, Table 2. The characteristics and effectiveness of the reviewed interventions, Figure 2. Quality assessment (a) Risk of Bias 2.0 graph for randomized controlled studies; (b) Risk of Bias 2.0 summary for randomized studies; (c) Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) graph for non-randomized studies; (d) ROBINS-I summary for non-randomized studies, Figure 3. Meta-analysis based on history of recurrent implantation failure: (a) Clinical pregnancy rate; (b) Live birth rate, Figure 4. Meta-analysis based on endometrial stimulation: (a) Clinical pregnancy rate; (b) Live birth rate, Figure 5. Meta-analysis of miscarriage rate, Figure 6. Funnel plot of the effects of hysteroscopy for infertile women without intrauterine pathologies (a) Clinical pregnancy rate; (b) Live birth rate

Author Contributions: Conceptualization, S. Y. Y.; methodology, S. Y. Y.; software, S. Y. Y.; validation, S.Y.Y, S. H. L, and S.J.C; formal analysis, S.Y.Y, S. H. L; writing—original draft preparation, S.Y.Y, S. H. L; writing—review and editing S.Y.Y, S. H. L and S.J.C; visualization, S.Y.Y; supervision, S. H. L. All authors have read and agreed to the published version of the manuscript.

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