Ultrasound-assessed endometrial receptivity measures for the prediction of *in vitro* fertilization-embryo transfer clinical pregnancy outcomes: A meta-analysis and systematic review

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Received February 1, 2023; Accepted July 17, 2023

DOI: 10.3892/etm.2023.12152

Abstract. At present, there are currently no reliable and consistent conclusions regarding transvaginal ultrasound assessment of endometrial receptivity in predicting clinical pregnancy outcomes of *in vitro* fertilization-embryo transfer (IVF-ET). Thus, in the present study, a meta-analysis was performed on multiple endometrial receptivity indices detected by vaginal ultrasound, aiming to provide a diagnostic basis for clinical practice. PubMed, Embase, and Cochrane Library databases were searched for studies published between the establishment of the databases through to January 2023. Studies that reported infertile women undergoing IVF-ET and undergoing vaginal ultrasound were included, but repeat publication, studies where the full text was not obtainable, studies where there was incomplete information provided or data extraction was not possible, studies on animals, case reports, reviews, and systematic reviews were excluded. STATA 15.1 was used to analyze the data. The pooled results showed that the endometrial thickness [Weighted mean difference (WMD)=0.03, 95% CI: 0.00-0.06; P=0.022] and endometrial volume (WMD=0.41, 95% CI: 0.07-0.74; P=0.017) of the pregnancy group after receiving IVF-ET were all significantly higher than that of the non-pregnancy group. The pooled results also showed that the vascularization index (VI) (WMD=0.79, 95% CI: 0.56-1.03; P=0.000), flow index (FI) (WMD=1.82, 95% CI: 0.83-2.81; P=0.000) and vascularization flow index (VFI) (WMD=1.58, 95% CI: 0.91-2.24; P=0.000) of the pregnancy group after receiving IVF-ET was significantly higher than that of the non-pregnancy group. Systolic/diastolic (S/D) (WMD=-4.92, 95%CI: -8.28- -1.56; P=0.004) of the uterine artery of the pregnancy group after receiving IVF-ET was significantly lower than that of the non-pregnancy group. However, the differences between the resistance index (RI) and pulsatility index (PI) in the pregnancy group vs. the non-pregnancy group after receiving IVF-ET were not statistically significant. Vaginal ultrasound can be used to predict the outcomes of pregnancy in infertile women undergoing IVF-ET by measuring the thickness and volume of the endometrium, combined with the S/D, VI, FI, and VFI of the uterine artery.

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Key words: ultrasound, endometrial receptivity, *in vitro* fertilization-embryo transfer, pregnancy outcomes

Introduction

In recent years, the incidence of infertility has been increasing, with the World Health Organization reporting a global prevalence of ~15% (1). *In vitro* fertilization-embryo transfer (IVF-ET) is currently the most commonly used assisted reproductive technique, but embryo implantation rates are low (2), with evidence suggesting that up to two-thirds of embryo implantation failures can be attributed to poor endometrial reception and the remaining one-third due to quality defects in embryos (3). Good endometrial receptivity (ER) and embryo quality are necessary for successful implantation. ER refers to the ability of the endometrium (the inner lining of the uterus) to support embryo implantation during the menstrual cycle. It is influenced by various physiological factors and mechanisms, including hormonal regulation (4), endometrial gene expression (5), endometrial morphological changes (6), immune system modulation (7), and endometrial vascularization (8). Considering the mechanisms, first, once progesterone and estrogen signaling is disrupted, it leads to progesterone resistance and estrogen dominance. This hormone imbalance leads to increased inflammation, reducing the endometrium's receptivity to embryo implantation (4). Secondly, the upregulation of certain genes, such as Eps15 homology domain-containing 1 (EHD1) (9) and ICAM1 (10), were found to be associated with reduced ER. Third, changes in endometrial morphology, manifesting as disruption of the endometrial epithelial cells, have been shown to lead to impaired ER (6). Recently, it has been found that endometrial microbiota disturbance can cause immune microenvironment remodeling (activation of uterine NK cells and changes in specific subpopulations of T cells), which negatively impacts ER (7). Finally, adequate blood flow and angiogenesis are critical for endometrial receptivity. Blood vessels supply oxygen, nutrients, and signaling molecules necessary for embryo development and implantation. Abnormalities in endometrial vascularization can compromise implantation (8).

Clinically, endometrial receptivity is usually evaluated from endometrial morphology, ultrasound imaging, biochemistry, and other aspects (11). Among them, transvaginal ultrasound assessment of endometrial receptivity is non-invasive and highly repeatable and thus has been widely used in clinical practice (12). However, due to the use of ultrasound to measure the relevant indicators of endometrial receptivity, it is affected to a certain extent by the subjective factors of the examiner and the objective factors that differ between different ultrasound machines and equipment (13). Therefore, there are currently no reliable and consistent conclusions regarding transvaginal ultrasound assessment of endometrial receptivity in predicting clinical pregnancy outcomes in IVF-ET. In the present meta-analysis multiple endometrial receptivity indices that can be used to predict the outcomes of IVF-ET clinical pregnancy, such as transvaginal ultrasound measurement of endometrial thickness, endometrial volume, peak uterine systolic blood flow velocity to end-diastolic blood flow velocity ratio (systolic/diastolic S/D), pulsatility index (PI), resistance index (RI), vascularization index (VI), flow index (FI), and vascularization flow index (VFI), were assessed, with the aim of providing a diagnostic basis for clinical practice.

Materials and methods

Literature inclusion and exclusion criteria. The inclusion criteria for the meta-analysis were: i) Study object, infertile women undergoing IVF-ET and undergoing vaginal ultrasound; ii) intervention measures, whether the pregnancy was successful after receiving IVF-ET; iii) outcome indicators, endometrial thickness (cm), endometrial volume (cm^3), resistive index (RI) of the uterine artery, pulsatility index (PI) of the uterine artery, systolic/diastolic (S/D), vascularization index (VI), flow index (FI) and vascularization flow index (VFI); and iv) study design, case-control or cohort studies.

The exclusion criteria were: Repeat publications, studies where the full text was not available, studies where data could not be extracted, studies using animal experiments, reviews, meta-analyses, and systematic reviews.

Search strategy. For this meta-analysis, PubMed (https://pubmed.ncbi.nlm.nih.gov), Embase (https://www.embase.com/), and Cochrane Library (https://www.cochranelibrary.com/) databases were searched from establishment of the database to January 2023. The search terms were: (((((((((((((((('Ultrasonography'[Mesh]) OR (Diagnostic Ultrasound[Title/Abstract])) OR (Diagnostic Ultrasounds[Title/Abstract])) OR (Ultrasound Imaging[Title/Abstract])) OR (Echotomography[Title/Abstract])) OR (Ultrasonic Imaging[Title/Abstract])) OR (Medical Sonography[Title/Abstract])) OR (Ultrasonographic Imaging[Title/Abstract])) OR (Ultrasonographic Imagings[Title/Abstract])) OR (Echography[Title/Abstract])) OR (Ultrasonic Diagnoses[Title/Abstract])) OR (Ultrasonic Diagnosis[Title/Abstract])) OR (Computer Echotomography[Title/Abstract])) OR (Ultrasonic Tomography[Title/Abstract])) OR (Ultrasound[Title/Abstract])) AND (((((('Embryo Transfer'[Mesh]) OR (Embryo Transfers[Title/Abstract])) OR (Blastocyst Transfer[Title/Abstract])) OR (Tubal Embryo Transfer[Title/Abstract])) OR (Tubal Embryo Stage Transfer[Title/Abstract])) OR (((((((((('Fertilization *in Vitro*'[Mesh]) OR (*In Vitro* Fertilization[Title/Abstract])) OR (*In Vitro* Fertilizations[Title/Abstract])) OR (Test-Tube Fertilization[Title/Abstract])) OR (Test Tube Fertilization [Title/Abstract])) OR (Test Tube Fertilizations[Title/Abstract])) OR (Fertilizations *in Vitro*[Title/Abstract])) OR (Test-Tube Babies[Title/Abstract])) OR (Test Tube Babies[Title/Abstract])) OR (Test-Tube Baby[Title/Abstract])))) AND ((pregnancy outcome[Title/Abstract]) OR (pregnancy outcomes[Title/Abstract]))) AND ((((('Infertility'[Mesh]) OR (Sterility[Title/Abstract])) OR (Reproductive Sterilit[Title/Abstract])) OR (Subfertility[Title/Abstract])) OR (Sub-Fertility[Title/Abstract])).

Literature screening and data extraction. Two researchers independently performed the literature search, screening, and data extraction. When a question or dispute arose, a consensus was reached after discussion. The data extraction included: Author, article publication year, country, study design, sample size, age, BMI, anti-Mullerian Hormone (pmol/l), and the outcome indicators.

Assessment of the quality of the literature. Two researchers independently conducted literature quality evaluations using the Newcastle-Ottawa Scale (NOS) for cohort studies (14). NOS includes 4 items (4 points) for 'Research Subject Selection', 1 item (2 points) for 'Comparability between Groups' and 3 items (3 points) for 'Result Measurement', with a full score of 9 points, where a score ≥7 is regarded as high-quality literature, and <7 is divided into lower-quality literature. When the scores differed between the two researchers, it was decided through discussion or consultation with a third person. The present meta-analysis was performed based on the related items of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (15).

Data synthesis and statistical analysis. Data were analyzed using STATA version 15.1 (StataCorp LLC). Weighted mean differences (WMDs) were used to assess differences in continuous variables. I^2 and Q tests were used to evaluate heterogeneity. If the heterogeneity test was $P\geq0.1$ and $I^2\leq50\%$, there was homogeneity amongst the studies; if they were $P<0.1$ and $I^2>50\%$, there was heterogeneity, and a sensitivity analysis was performed to identify the source. A random effects model was used for combining effects in the present meta-analysis. Funnel plots and Egger's tests were used to analyse publication bias.

Results

Literature search results. In the present study, 168 studies were retrieved from the database. After eliminating duplicate studies, 95 studies were included. After browsing the titles and abstracts, 59 studies were identified. Finally, 14 articles were included in the meta-analysis (Fig. 1).

Baseline characteristics and quality assessment of the included studies. In total, 14 cohort studies were included in the present meta-analysis (16-29). The combined patient sample size was 4,842. The mean age distribution of the pregnancy group was 30.3-34.4 years, while the mean age distribution of the non-pregnancy group was between 31.5-35.8 years,

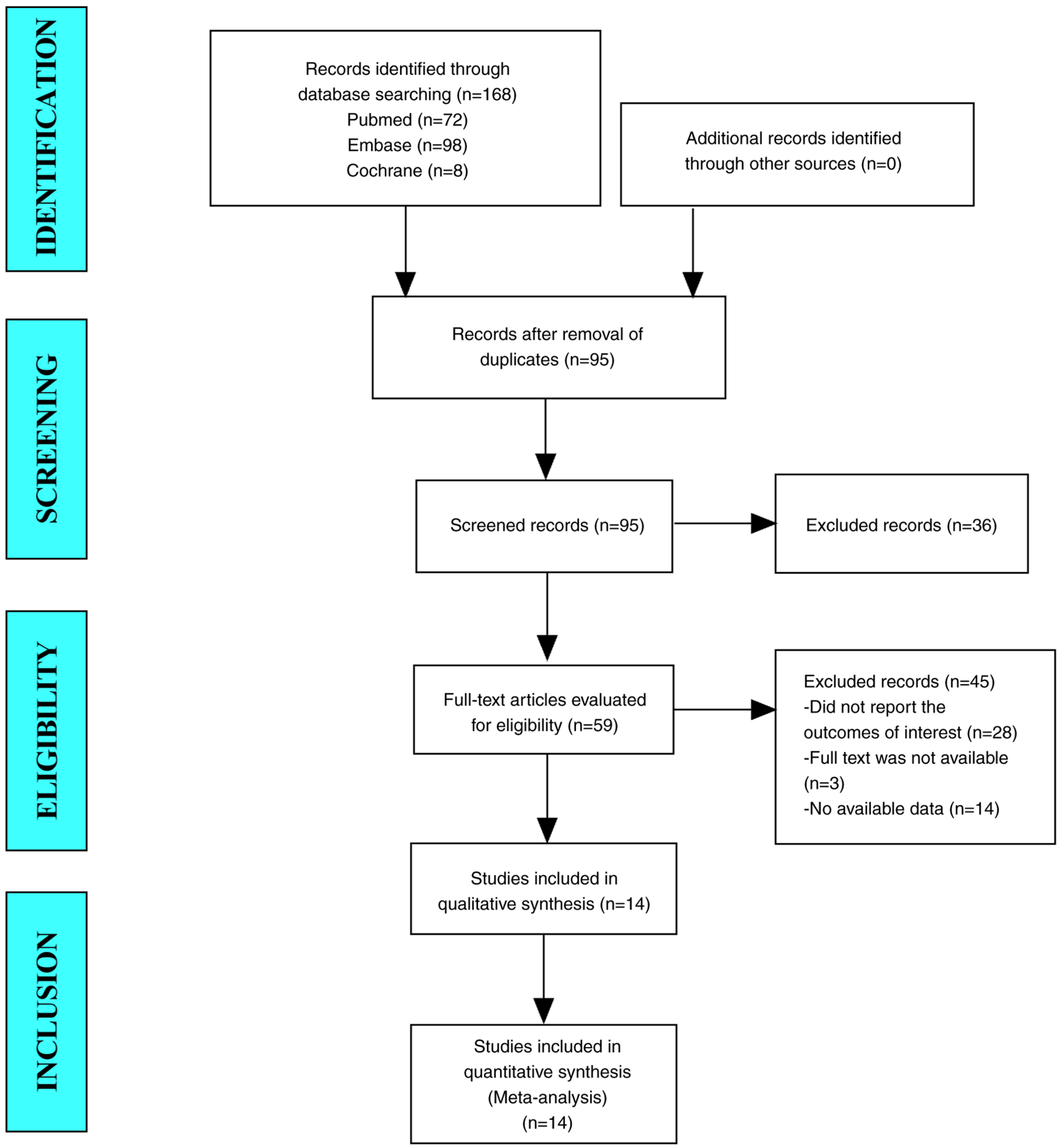

Figure 1. Flow diagram for selection of studies.

indicating that the ages of the two groups did not differ notably. In addition, the BMI distribution of the pregnancy group was 21.2-23.6, while in the non-pregnancy group, it was 21.4-23.3, indicating that the BMI of the two groups were comparable as well (Table I). The NOS scores used for quality assessment for all 14 studies were >7 (Table II).

Results of the meta-analysis

Endometrial thickness (cm). A total of 12 studies reported transvaginal ultrasound endometrial thickness in infertile women undergoing IVF-ET. There was significant heterogeneity (I^2=59.0%, P=0.005). A meta-analysis was performed using a random effects model. The pooled results showed that the endometrial thickness of the pregnancy group after receiving IVF-ET was significantly higher than that of the non-pregnancy (WMD=0.03, 95% CI: 0.00-0.06; P=0.022) (Fig. 2).

Endometrial volume (cm^3). A total of 5 studies reported transvaginal ultrasound endometrial volume in infertile women undergoing IVF-ET. There was no significant heterogeneity (I^2=0.0%, P=0.933). The pooled results of the random-effects model showed that the endometrial volume of the pregnancy group after receiving IVF-ET was significantly higher than that of the non-pregnancy group (WMD=0.41, 95% CI: 0.07-0.74; P=0.017) (Fig. 3).

Table I. Baseline characteristics and quality assessment of the included studies.

		Sample size		Age		BMI		Anti-Mullerian Hormone, pmol/l		
First author, year	Country	Pregnancy	Non-pregnancy	Pregnancy	Non-pregnancy	Pregnancy	Non-pregnancy	Pregnancy	Non-pregnancy	(Refs.)
Zhang *et al*, 2022	China	1,167	686	32.2±3.5	33.1±3.7	23.6±3.9	23.2±3.7	29.6±22.1	26.3±22.0	(16)
Crosby *et al*, 2022	Ireland	21	29	34.4±2.1	34.7±2.2	23.4±3.0	23.3±2.5	21.8±14.9	16.3±12.8	(17)
Tong *et al*, 2020	China	36	43	31.0±4.2	32.5±4.6	21.5±2.3	22.3±2.9	36.1±23.9	37.7±31.1	(18)
Long *et al*, 2019	China	29	32	33.2±3.3	32.1±3.8	22.9±3.4	21.4±2.4	/	/	(19)
Koo *et al*, 2018	Korea	20	15	33.6±3.6	35.8±3.1	/	/	24.3±18.6	26.4±25.7	(20)
Prasad *et al*, 2017	India	76	112	31.2±3.9	31.5±4.3	/	/	/	/	(21)
Son *et al*, 2014	Korea	29	41	32.9±4.1	34.7±3.7	21.2±2.5	22.1±3.9	/	/	(22)
Zhao *et al*, 2014	China	1,010	923	30.6±4.4	31.8±4.8	21.6±2.6	21.9±3.1	/	/	(23)
Nandi *et al*, 2014	UK	7	9	/	/	/	/	/	/	(24)
Engels *et al*, 2011	Spain	9	70	33.0±3.6		/	/	/	/	(25)
Záckování *et al*, 2009	Czech Republic	15	15	31.3±1.1	31.5±1.1	22.9±1.1	23.0±0.8	/	/	(26)
Mercé *et al*, 2008	Spain	38	39	33.9±3.4	34.3±3.5	/	/	/	/	(27)
Chien *et al*, 2004	China	91	226	32.7±3.6	33.6±3.9	/	/	/	/	(28)
Wu *et al*, 2003	China	18	36	30.3±3.8	32.2±4.4	/	/	/	/	(29)

Table II. NOS quality assessment of the included studies.

	Selection				Comparability	Outcome			
First author, year	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of exposure	Based on design and analysis	Assessment of the outcome	Follow-up	Adequacy of follow-up	Overall score
Zhang *et al*, 2022	1	1	1	1	2	0	1	1	8
Crosby *et al*, 2022	1	1	1	1	2	0	1	0	7
Tong *et al*, 2020	1	1	1	1	2	0	1	1	8
Long *et al*, 2019	1	1	1	1	2	0	1	2	9
Koo *et al*, 2018	1	1	1	1	2	0	1	0	7
Prasad *et al*, 2017	1	1	1	1	1	0	1	1	7
Son *et al*, 2014	1	1	1	1	1	0	1	1	7
Zhao *et al*, 2014	1	1	1	1	2	0	1	1	8
Nandi *et al*, 2014	1	1	1	1	2	0	1	1	8
Engels *et al*, 2011	1	1	1	1	2	0	1	0	7
Zácková *et al*, 2009	1	1	1	1	2	0	1	0	7
Mercé *et al*, 2008	1	1	1	1	1	0	1	1	7
Chien *et al*, 2004	1	1	1	1	2	0	1	0	7
Wu *et al*, 2003	1	1	1	1	1	0	1	1	7

NOS, Newcastle-Ottawa Scale.

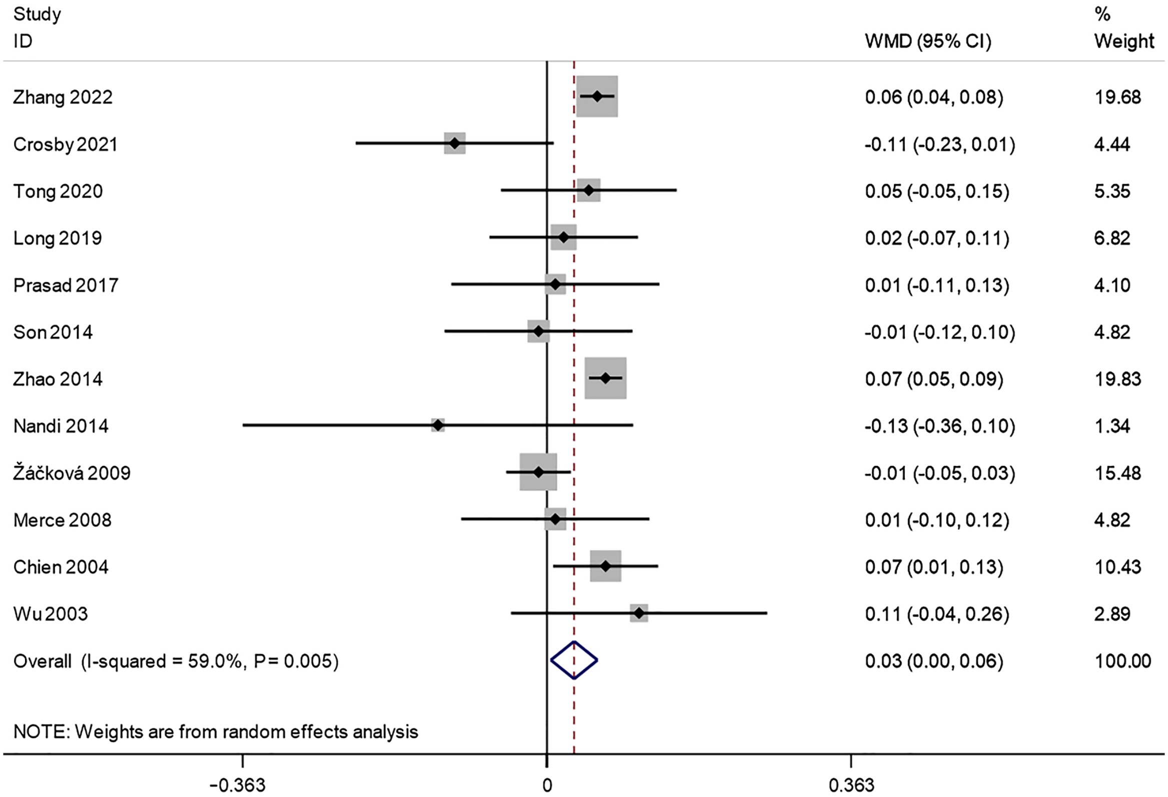

Figure 2. Endometrial thickness in infertile women undergoing IVF-ET. IVF-ET, *in vitro* fertilization-embryo transfer; WMD, weighted mean difference; CI, confidence interval.

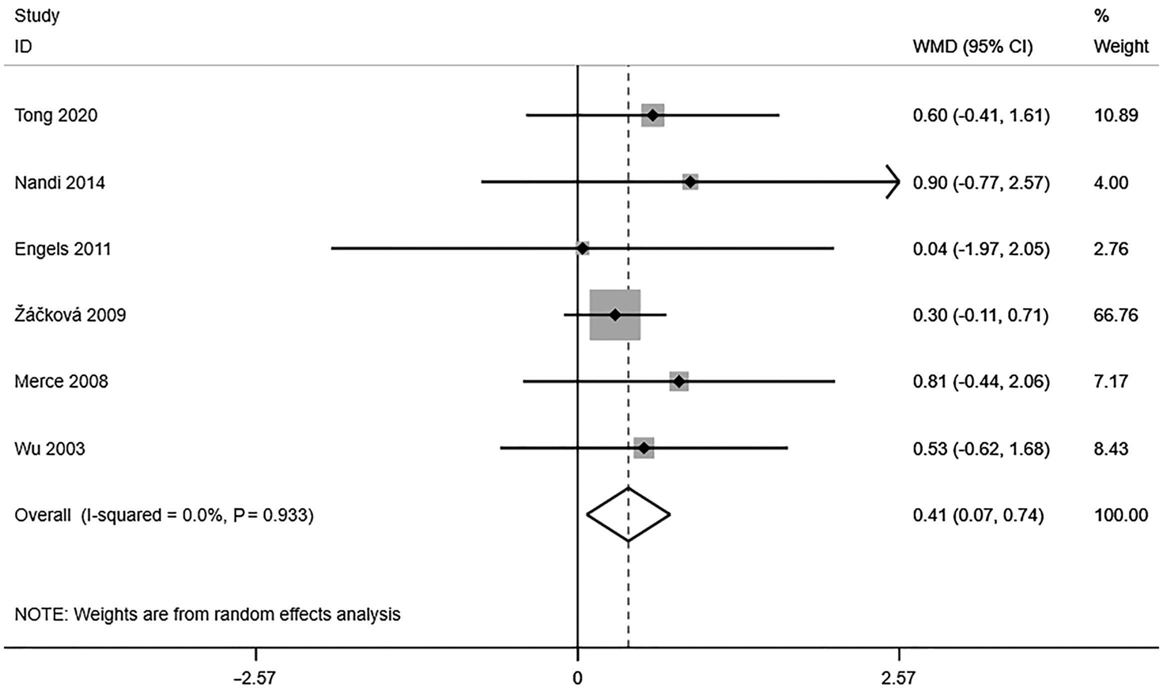

Figure 3. Endometrial volume in infertile women undergoing IVF-ET. IVF-ET, *in vitro* fertilization-embryo transfer; WMD, weighted mean difference; CI, confidence interval.

RI of the uterine artery. A total of 6 studies reported transvaginal ultrasound RI in infertile women undergoing IVF-ET. There was significant heterogeneity (I^2=78.3%, P=0.000), and a meta-analysis was performed using a random effects model. The pooled results showed that the difference between RI in the pregnancy group and the non-pregnancy group after receiving IVF-ET was not statistically significant (WMD=-0.01, 95% CI: -0.05-0.02; P=0.422) (Fig. 4).

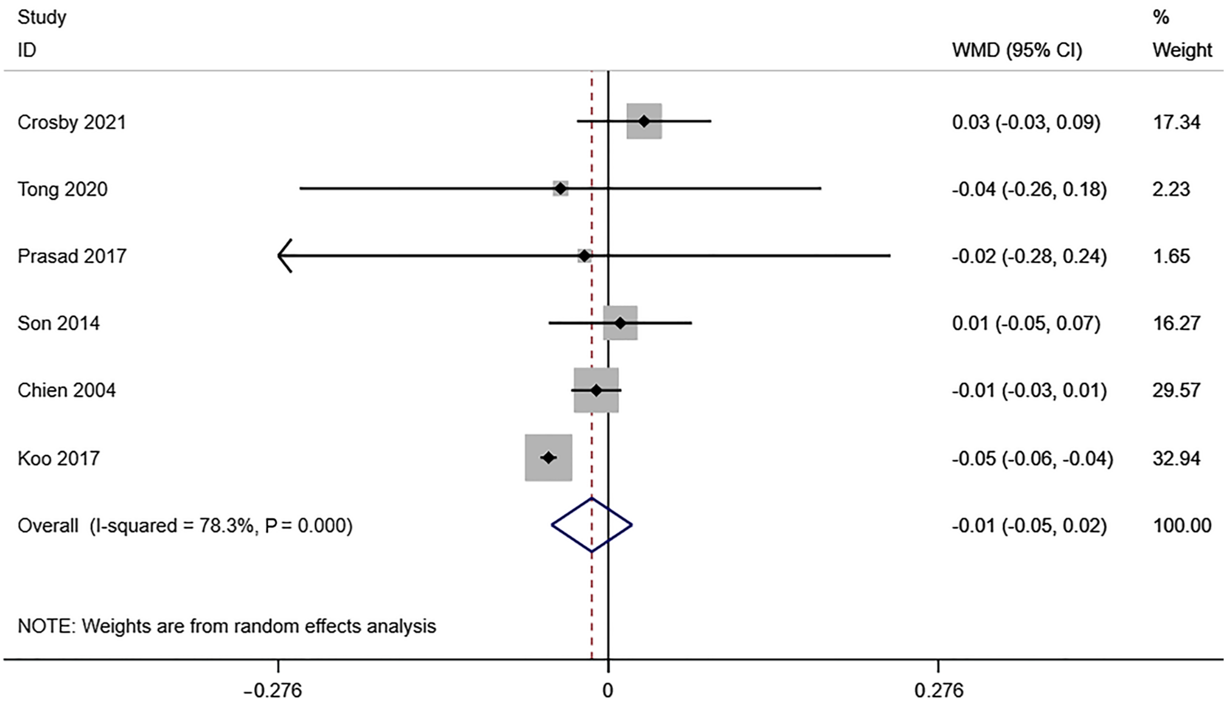

Figure 4. RI of the uterine artery in infertile women undergoing IVF-ET. IVF-ET, *in vitro* fertilization-embryo transfer; WMD, weighted mean difference; CI, confidence interval.

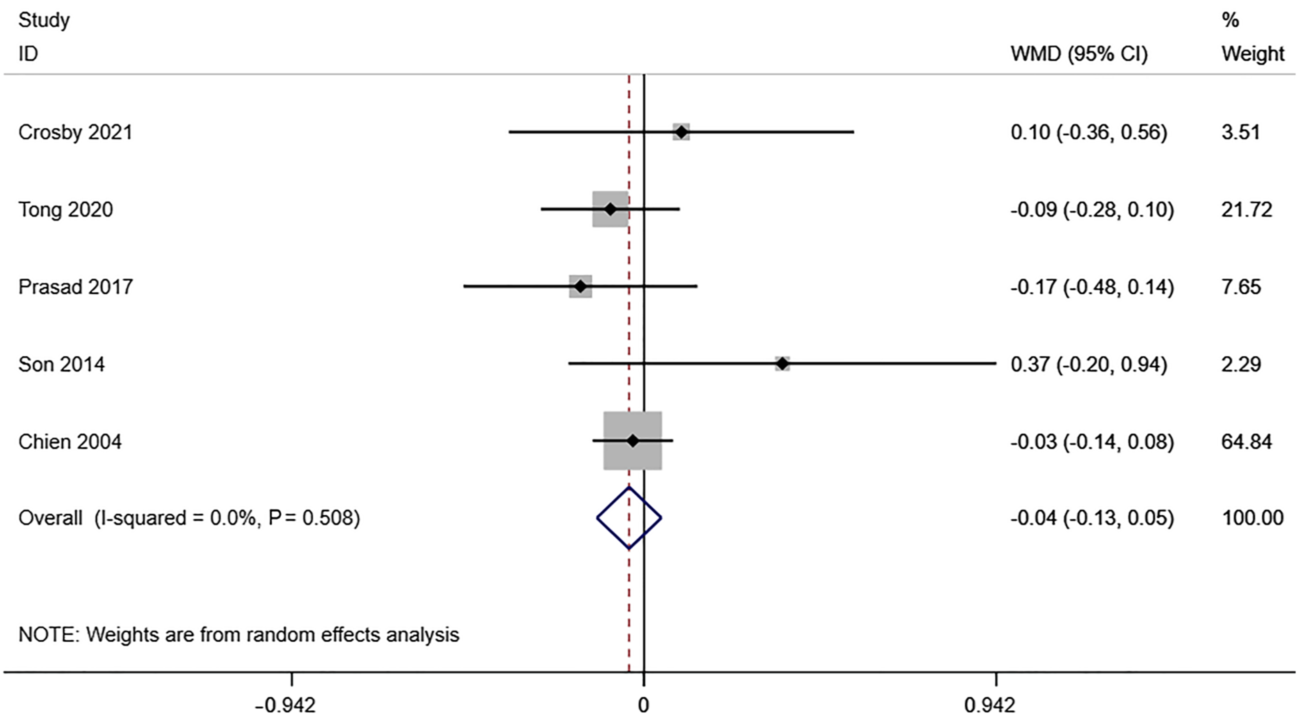

Figure 5. PI of the uterine artery in infertile women undergoing IVF-ET. IVF-ET, *in vitro* fertilization-embryo transfer; WMD, weighted mean difference; CI, confidence interval.

PI of the uterine artery. A total of 6 studies reported transvaginal ultrasound PI in infertile women undergoing IVF-ET. There was no significant heterogeneity (I^2=0.0%, P=0.508). The pooled results of the random-effects model showed that the difference between PI in the pregnancy group and the non-pregnancy group after receiving IVF-ET was not statistically significant (WMD=-0.04, 95% CI: -0.13-0.05; P=0.364) (Fig. 5).

S/D. A total of 2 studies reported transvaginal ultrasound S/D in infertile women undergoing IVF-ET. There was no significant heterogeneity (I^2=0.0%, P=0.355). The pooled results of the random-effects model showed that the S/D of

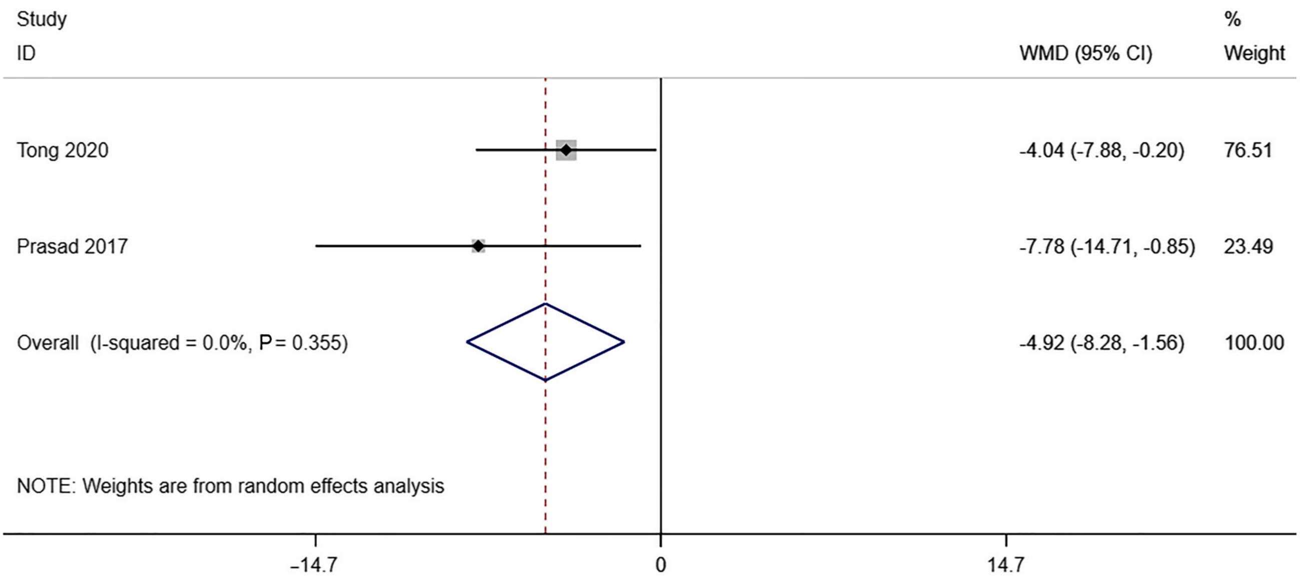

Figure 6. S/D of the uterine artery in infertile women undergoing IVF-ET. IVF-ET, *in vitro* fertilization-embryo transfer; WMD, weighted mean difference; CI, confidence interval.

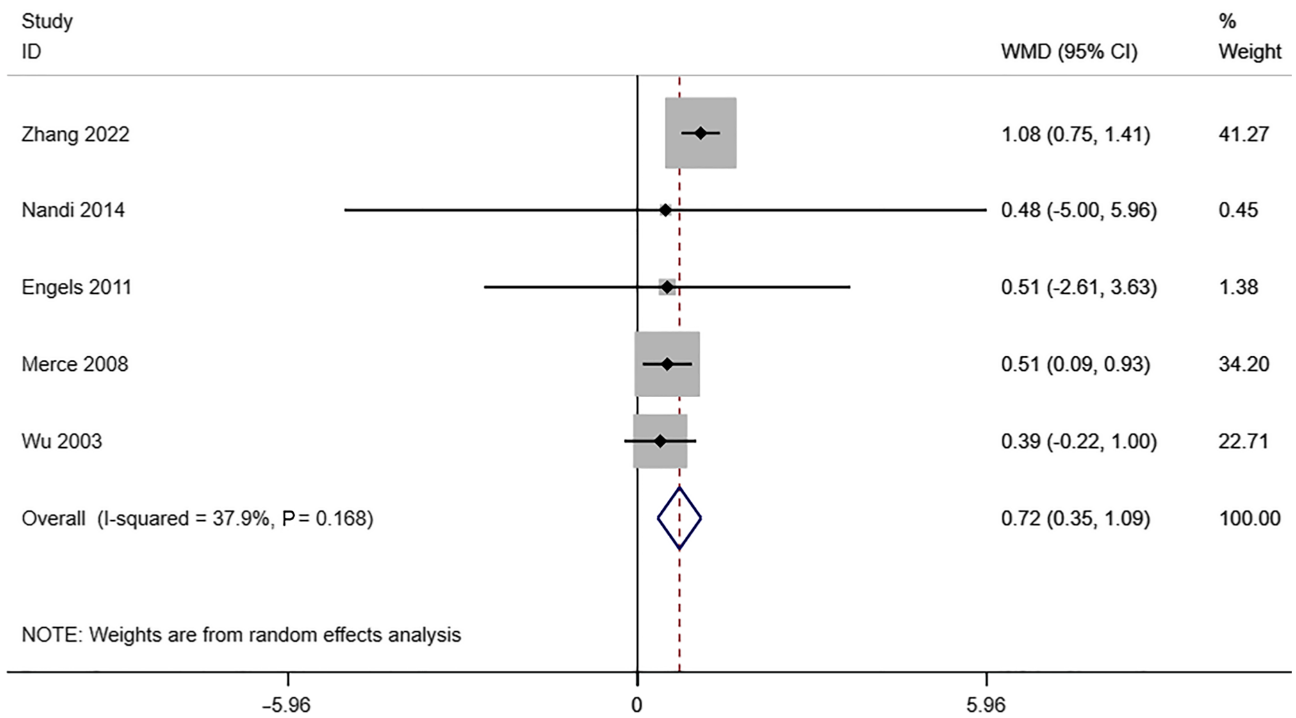

Figure 7. VI of the uterine arteries in infertile women undergoing IVF-ET. IVF-ET, *in vitro* fertilization-embryo transfer; WMD, weighted mean difference; CI, confidence interval.

the pregnancy group after receiving IVF-ET was significantly lower than that of the non-pregnancy (WMD=-4.92, 95% CI: -8.28- -1.56; P=0.004) (Fig. 6).

VI. A total of 5 studies reported transvaginal ultrasound VI in infertile women undergoing IVF-ET. There was no significant heterogeneity (I^2=37.9%, P=0.168). The pooled results of the random-effects model showed that the VI of the pregnancy group after receiving IVF-ET was significantly higher than that of the non-pregnancy (WMD=0.79, 95% CI: 0.35-1.09; P<0.0001) (Fig. 7).

FI. A total of 5 studies reported transvaginal ultrasound FI in infertile women undergoing IVF-ET. There was significant heterogeneity (I^2=55.2%, P=0.063) and a meta-analysis was performed using a random effects model. The pooled results showed that the FI of the Pregnancy group after receiving IVF-ET was significantly higher than that of the non-pregnancy (WMD=1.82, 95% CI: 0.83-2.81; P=0.000) (Fig. 8).

VFI. A total of 4 studies reported transvaginal ultrasound VFI in infertile women undergoing IVF-ET. There was no significant heterogeneity (I^2=34.9%, P=0.203). The pooled

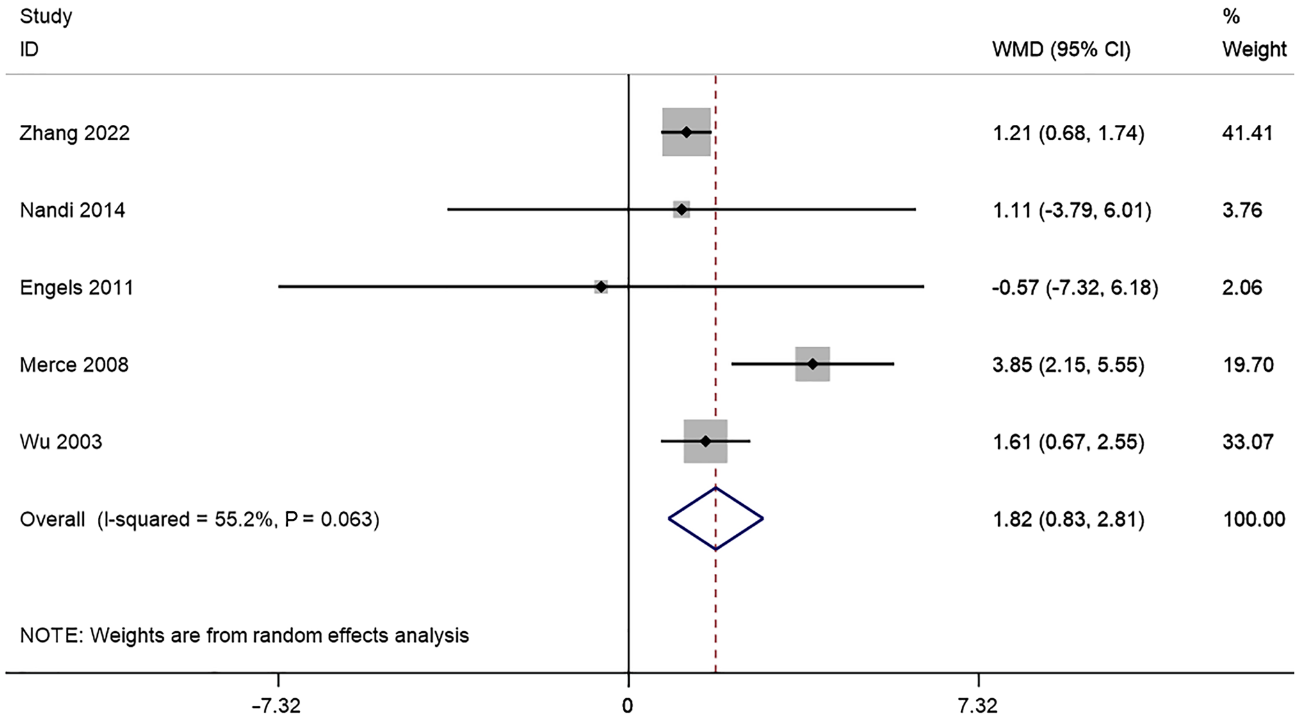

Figure 8. FI of the uterine artery in infertile women undergoing IVF-ET. IVF-ET, *in vitro* fertilization-embryo transfer; WMD, weighted mean difference; CI, confidence interval.

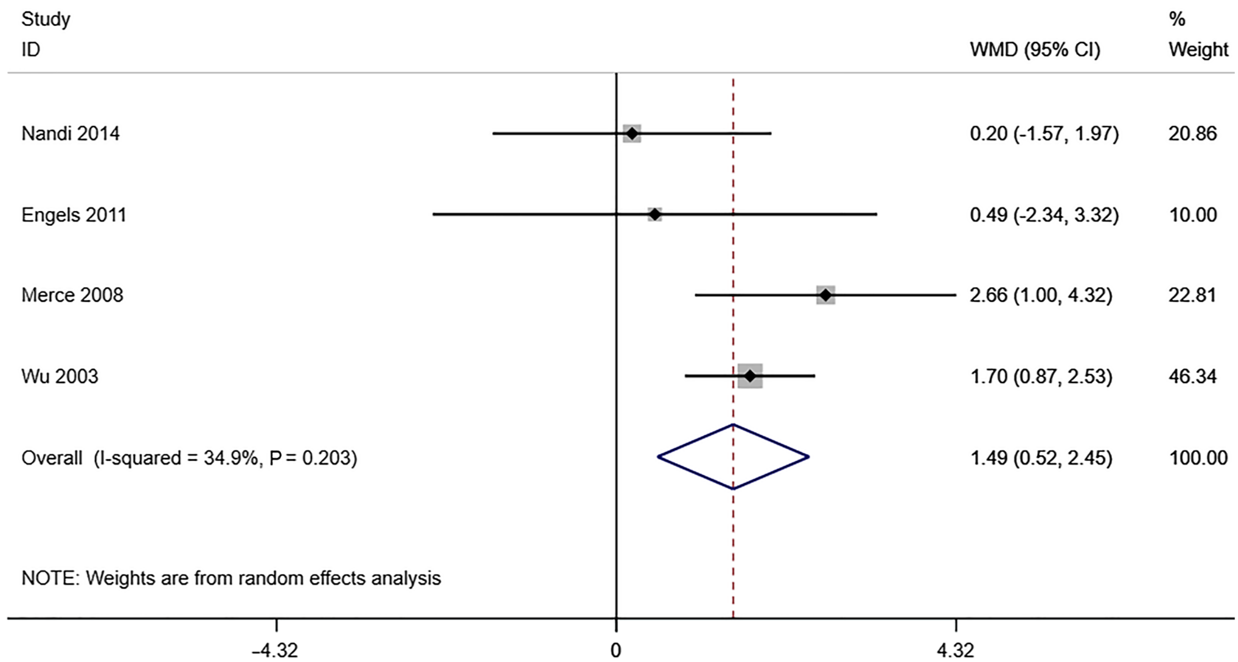

Figure 9. VFI of the uterine artery in infertile women undergoing IVF-ET. IVF-ET, *in vitro* fertilization-embryo transfer; WMD, weighted mean difference; CI, confidence interval.

results of the random-effects model showed that the VFI of the pregnancy group after receiving IVF-ET was significantly higher than that of the non-pregnancy (WMD=1.49, 95% CI: 0.52-2.45; P=0.003) (Fig. 9).

Sensitivity analysis. Sensitivity analysis was performed by eliminating each included study one by one and performing a summary analysis of the remaining studies. The results found that none of the studies had an excessive impact on the results of the meta-analysis, which suggests that the results of this meta-analysis are stable and reliable.

Publication bias. The funnel plot of this study is shown in Fig. 10. The funnel plot was largely symmetrical, and Egger's test demonstrated P=0.055, which indicated that there was no obvious publication bias in this study.

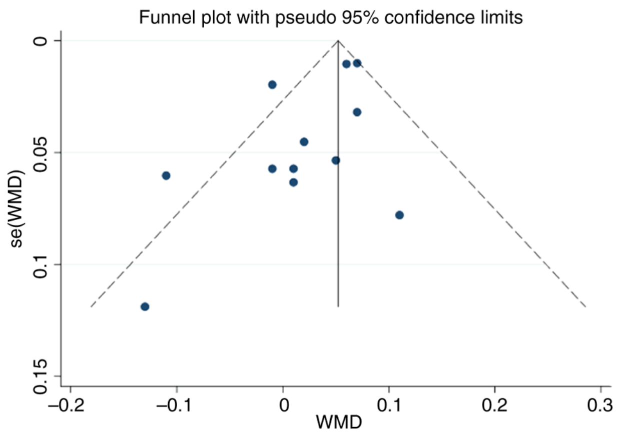

Figure 10. Funnel plot for evaluating the publication bias of this meta-analysis; WMD, weighted mean difference; se, standard error.

Discussion

In recent years, IVF-EF has attracted increasing attention as an important means of treating infertility, and endometrial receptivity is one of the important factors affecting embryo implantation. As a common means of assessing endometrial receptivity, ultrasound has been widely used to evaluate endometrial receptivity to predict IVF-ET clinical pregnancy outcomes given its advantages of being non-invasive, providing real-time information, the ease of reproducibility, convenience, and the fact that it is relatively inexpensive. The validity and accuracy of different endometrial receptivity measures in predicting clinical pregnancy outcomes are contested due to inconsistent results in existing clinical studies. The present meta-analysis included 14 articles for a total of 4,842 infertile women, to pool the measures of endometrial receptivity on transvaginal ultrasound, which may be used to predict pregnancy outcomes following IVF-ET.

The pooled results showed that the endometrial thickness and endometrial volume of the pregnancy group after receiving IVF-ET were all significantly higher than that of non-pregnancy. These results suggest that changes in endometrial thickness and endometrial volume can be observed by ultrasound to predict pregnancy outcomes of IVF-ET. In addition, measurements of the endometrial volume provide a reliable method for assessing the size of the endometrial cavity; however, its effective use requires extensive clinical experience and may require multiple attempts before the test is successfully completed, which may challenge the accuracy of predicting pregnancy outcomes (30).

Compared with a single uterine spiral artery, the uterine artery reflects the blood flow perfusion of the entire uterus, and the uterine artery S/D is not a commonly used measurement index to assess endometrial receptivity during IVF-ET and typically requires the assessment of uterine artery PI, RI, and other indicators for a comprehensive judgment, and measuring uterine artery PI and RI on IVF-ET days is more useful in determining whether the endometrium is in a state suitable for embryo adhesion and completion of implantation (31). The pooled results showed that the S/D of the pregnancy group after receiving IVF-ET were significantly lower than that of the non-pregnancy, while the difference between RI and PI in the pregnancy group and the non-pregnancy group after receiving IVF-ET was not statistically significant. In the analysis of S/D, although the pooled results were consistent with the results of the two included individual studies, the objectivity of the included studies deserves further exploration as there were only two included studies. In addition, pooled results also showed that the VI, FI, and VFI of the pregnancy group after receiving IVF-ET was significantly higher than that of the non-pregnancy. This indicates that as a pregnancy progresses, the number of blood vessels in the endometrium increases, blood flow increases and blood perfusion increases. Observation of vascular and blood flow changes can predict pregnancy outcomes in infertile women undergoing IVF-ET.

The present meta-analysis has some limitations. The measurement of endometrial receptivity-related indicators by transvaginal ultrasound will be affected by objective factors such as the patient being examined, the equipment used, and the treatment measures. Additionally, the lack of studies for certain outcomes may result in less reliable results.

In conclusion, vaginal ultrasound may be used to predict the pregnancy outcomes of infertile women undergoing IVF-ET by measuring the thickness and volume of the endometrium, combined with the S/D, VI, FI, and VFI of the uterine artery.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JW wrote the manuscript and analyzed the data. JS, XW and QW collected data (literature search and data extraction) and participated in data analysis. QW provided general supervision of the research group. JW and QW confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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