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Efficacy of platelet-rich plasma in the treatment of thin endometrium: a meta-analysis of randomized controlled trials

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Abstract

Background Thin endometrium (TE) is a common cause of female infertility in clinical practice. Platelet-rich Plasma (PRP) therapy becomes a novel treatment for thin endometrium; however, its clinical application remains controversial. This meta-analysis aims to evaluate the therapeutic effects of intrauterine autologous PRP infusion in women with thin endometrium through relevant randomized controlled trials (RCTs).

Methods We systematically searched studies published in English from inception until June 2024 in databases such as PubMed, The Cochrane Library, Embase, Web of Science, and MEDLINE. Search terms included "Platelet-Rich Plasma," "thin endometrium," "endometrial thickness," "infertility," "pregnancy," "reproduction," and "adverse reactions". RCTs identified through the search were subjected to systematic review and meta-analysis, and data were analyzed using fixed-effects or random-effects models based on heterogeneity.

Results Eight RCTs involving 678 patients with thin endometrium were included. Patients receiving PRP infusion demonstrated significantly superior outcomes compared to the control group in endometrial thickness (MD: 1.23, 95%CI: 0.87 to 1.59, $P=0.000$), clinical pregnancy rate (RR: 2.04, 95%CI: 1.52 to 2.76, $P=0.000$), live birth rate (RR: 2.46; 95%CI: 1.57 to 3.85, $P=0.000$), cycle cancellation rate (RR: 0.46, 95%CI: 0.23 to 0.93, $P=0.000$), and embryo implantation rate (RR: 2.71; 95%CI: 1.91 to 3.84, $P=0.000$). There were no statistically significance in spontaneous abortion rate (RR: 0.85, 95%CI: 0.40 to 1.78, $P=0.659$), chemical pregnancy rate (RR: 1.84, 95%CI: 0.72 to 4.72, $P=0.204$) and endometrial vascular improvement rate (RR: 1.10; 95%CI: 0.89 to 1.38, $P=0.367$) between the two groups. The limitations of this study includes that, we only included single lauguage for literature research, the sample size and heterogeneity which could cause criteria bias.

Conclusion Intrauterine PRP infusion may be an effective and safe treatment for women with thin endometrium. Further high-quality, large-sample, randomized controlled trials are needed to validate the reliability of our results.

Trial registration The review protocol is registered on PROSPERO with registration number CRD42023490421, and no modifications were made to the information provided at registration.

Keywords Meta-analysis, Platelet-rich plasma (PRP), Randomized controlled trials (RCTs), Thin endometrium

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Background

Receptive endometrium and a qualified embryo are indispensable for successful implantation and pregnancy. Various factors influence the endometrial function [1, 2], among them, endometrial thickness is critical for assessing endometrial receptivity [3] and predicting the success rate of live births [4]. It has been proved that [5], when the thickness of endometrium constantly lower than the threshold, the probability of repeated implantation failure will arise intensely [6]. Therefore, insufficient endometrial lining represents a significant contributing factor to female infertility and cycle cancellation [7]. According to a large cohort study released by Rabin Medical Center in 2020, the incidence of thin endometrium is 6.08% [4], which highlights the importance of addressing the treatment of thin endometrium.

It is well-established that the characteristics of thin endometrium involve insufficient cell proliferation and functional imbalance, a point validated by a single-cell sequencing study based on clinical samples [6]. The primary pathological basis of thin endometrium [8] includes delayed growth of uterine glandular epithelium, high resistance in uterine artery blood flow, leading to a reduction in the number of uterine glandular epithelial cells, decreased expression of vascular endothelial growth factor (VEGF), impaired blood vessel development, and restricted growth of the endometrium. Currently, conservative treatment options for thin endometrium include estrogen, gonadotropin-releasing hormone agonists, aspirin, and sildenafil, etc. However, these methods are associated with multiple side effects, poor patient compliance, and inadequate endometrial response [9–11].

Platelet-rich Plasma (PRP), a platelet concentrate extracted from fresh whole blood, has been studied since the 1970s for its role in injury repair and promotion of proliferation [12]. It has been found widespread applications in various medical fields such as dermatology [13–15], orthopaedics [16–18], dentistry [19, 20], and plastic surgery [21]. The mechanism of PRP in medical filed may relate to promote cell proliferation, improve the blood flow, secret anti-inflammatory cytokines and so on, which is essential for tissue regeneration and repair. In recent years, regenerative medical therapies like PRP have become a research focus in the field of reproduction. Numerous clinical studies have demonstrated positive outcomes in the application of PRP for thin endometrium. In 2015, Chinese scholars [22] conducted intrauterine PRP infusion in five refractory thin endometrium patients, resulting in successful endometrial expansion and pregnancies. Based on the previous result, many researches had been conducted [23–25], providing a robust evidence for the effective treatment of thin endometrium with PRP. However, conflicting viewpoints have also emerged. A recent clinical study [26] randomly assigned 390 patients to Granulocyte Colony Stimulating Factor (GCSF), PRP, and saline groups. Although the PRP group significantly improved endometrial vascularization, there were no significant differences in clinical pregnancy rate and live birth rate among the groups. Kim [27], in a prospective study, suggested that there was no statistically significant difference in endometrial thickness after PRP infusion compared to pre-treatment levels. Additionally, several reported studies included small sample sizes [22, 28–30], posed a risk of bias. Consequently, despite the widespread use of PRP in treating patients with thin endometrium undergoing assisted reproductive technologies, its efficacy remains controversial. Further research is needed to determine whether PRP can safely and effectively reverse thin endometrium.

Considering previous systematic reviews and meta-analyses, conclusions have been drawn that intrauterine PRP infusion is a promising treatment for women with thin endometrium in assisted reproductive techniques. Still, problems persist regarding its uncertain efficacy, unclear adverse reactions, and a lack of high-quality studies [31–35]. With recent advancements in clinical research, our goal is to conduct a meta-analysis by collecting randomized controlled trials to explore the effectiveness of PRP in the treatment of thin endometrium. We hypothesize that, compared to a placebo or other treatment methods, PRP treatment influences endometrial growth positively.

Methods

This meta-analysis aim to address the effectiveness and safety of intrauterine PRP injection compared to a control group (placebo or other treatment methods) in improving clinical outcomes post-assisted reproduction in women with thin endometrium.

Literature search and protocol

Computer searches were conducted in databases including Pubmed, The Cochrane Library, Embase, Web of Science, and MEDLINE. Clinical studies involving PRP treatment for thin endometrium in women were screened. The search period extended from the inception of the databases to June 8, 2024. A combination of subject headings and free-text terms was used for the search. Additionally, manual searches of reference lists of relevant reviews and systematic studies were performed to avoid omissions. The search terms included "Platelet-Rich Plasma," "thin endometrium," "endometrial thickness," "infertility," "pregnancy," "reproduction," and "adverse reactions". Appropriate search strategies were employed for each database, and an example of the Embase database search is presented in Table 1. The review protocol is registered on PROSPERO with registration number

Table 1 Embase search strategies

No.	Searches	Results
1	'thrombocyte rich plasma'/exp	21,103
2	'platelet-rich plasma':ab, ti	18,658
3	'platelet rich plasma':ab, ti	18,657
4	'platelet-rich fibrin':ab, ti	2,391
5	'plasma rich in growth factors':ab, ti	416
6	prp: ab, ti	27,549
7	prf: ab, ti	6,903
8	prgf: ab, ti	534
9	endometri*:ab, ti	170,721
10	'thin endometri*':ab, ti	793
11	'endometrial thickness':ab, ti	6,297
12	infertility: ab, ti	98,064
13	pregnancy: ab, ti	642,256
14	reproduction: ab, ti	123,814
15	'adverse reactions':ab, ti	58,104
16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	47,490
17	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	1,009,427
18	#16 AND #17	1,026

Table 2 Different definitions of thin endometrium

Maximum endometrial thickness(on an ultrasound scan)	Stage	Resource
<7 mm	on the day of ovulation or human chorionic gonadotropin (HCG) administration	Chinese expert consensus [36]
<7 mm or <8 mm	on the day of human chorionic gonadotropin (HCG) administration	Canadian clinical practice guideline [37]
≤6 mm	during ovarian stimulation and on the trigger day in IVF cycles	A large study from Rabin Medical Center [4]

CRD42023490421, and no modifications were made to the information provided at registration.

Inclusion criteria

Research subjects

The definition and cut-off for thin endometrium differ between studies(Table 2). According to clinical practice guidelines from the Canadian Fertility and Andrology Society and Chinese expert consensus on diagnosis and management of abnormal endometrium in assisted reproductive technology, women aged over 18 with thin endometrium, defined as endometrial thickness<7 mm on the day of ovulation after the peak of natural cycle luteinizing hormone, the day of gonadotropin-releasing hormone injection in controlled ovarian hyperstimulation cycles, or the day of progesterone initiation in frozen embryo transfer cycles [36, 37].

Interventions

The experimental group received either pure PRP treatment or a combination of PRP treatment with conventional hormone replacement therapy (HRT, which means estradiol valerate or suppository progesterone treatment).

The control group received a placebo or HRT.

Outcome measures

Primary efficacy indicator: Endometrial thickness post-PRP or progesterone initiation in the frozen embryo transfer cycle.

Secondary efficacy indicators: ① Chemical pregnancy rate. ② Clinical pregnancy rate. ③ Sustained pregnancy rate or live birth rate. ④Spontaneous abortion rate. ⑤ Cycle cancellation rate. ⑥ Implantation rate.⑦ Endometrial vascular improvement rate.

Research type

Randomized Controlled Trials.

Exclusion criteria

The exclusion criteria for literature were as follows:

1. Duplicate publications.
2. Studies combining other diseases with the research subjects.
3. Literature where other treatments interfered with the interpretation of causality for the final treatment.
4. Literature with incomplete data.
5. Inaccessible full-text literature.
6. Review conference abstracts, non-clinical studies involving animal experiments, cell experiments, etc.

Data extraction

After removing duplicates using EndNote X9 software, two evidence-trained researchers (XY Liu, CY Qian) independently read titles, abstracts, and full texts, extracted and summarized relevant information, excluded ineligible literature, collected qualified literature, and downloaded full texts. The researchers cross-checked the data to prevent important information from being missing or disordered. In cases of disagreement, a third researcher (XY Jiang) was consulted for discussion, and verification was performed.

The data extraction table was saved as a Microsoft Excel file and included: (1) Basic information about the included articles, such as title, first author, and publication year; (2) Relevant information about the research subjects in the literature, such as sample size, age, intervention measures, and course of treatment; (3) Outcome indicators and related elements involved in the assessment of publication bias risk.

Inclusion evaluation

The Cochrane Evaluation Manual 5.1.0 recommended bias risk assessment tools for the quality evaluation of RCTs. The assessment included seven items: generation of random sequences, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, completeness of outcome data, selective reporting of results, and other biases. Two researchers (XY Liu, CY Qian) independently made judgments for each item as "low risk of bias," "high risk of bias," or "unclear." After completion, cross-checking was performed, and in case of disagreement, a third researcher (XY Jiang) was consulted. If all the above criteria were fully met, the quality rating was classified as (A) If partially met, it was rated as (B) If not met at all, it was rated as (C) Studies of low quality were excluded from this research.

Statistical analysis

Review manager 5.4 software was used for bias risk assessment and result visualization. Endometrial thickness was treated as a continuous variable, with mean difference (MD) and its 95% CI representing the effect size. Other outcome indicators were binary variables, and relative risk (RR) was used as the effect size. If there were three-arm trials, they were split into two-arm trials for analysis.

Stata/SE 15.0 was used for heterogeneity testing. If $I^2 \leq 50\%$ and $P \geq 0.05$, it indicated no significant statistical heterogeneity and a fixed-effects model was used for meta-analysis. If $I^2 > 50\%$ and $P < 0.05$, it suggested substantial heterogeneity among the studies, and a random-effects model was employed for meta-analysis. A significance level of $P < 0.05$ was considered statistically significant.

Results

Summary of the literature search

A total of 2154 articles were initially identified through the search, and an additional 25 articles were obtained through reference tracing, making a total of 2179 articles. After removing duplicates using EndNote X9 software, 1,308 articles remained. Following title, abstract, and full-text reviews, 1,113 irrelevant articles were excluded, leaving 195 articles. After further full-text readings, 8 English-language articles were finally included in the analysis. The literature screening process is illustrated in Fig. 1.

Basic characteristics of the included articles and evaluation

Eight RCTs involving 678 patients with thin endometrium were included. The experimental group received PRP or combined HRT (333 participants), while the control group received HRT or placebo (345 participants). The basic characteristics of the included studies are shown in Table 3. Random number table methods were mainly used for random grouping, and details regarding

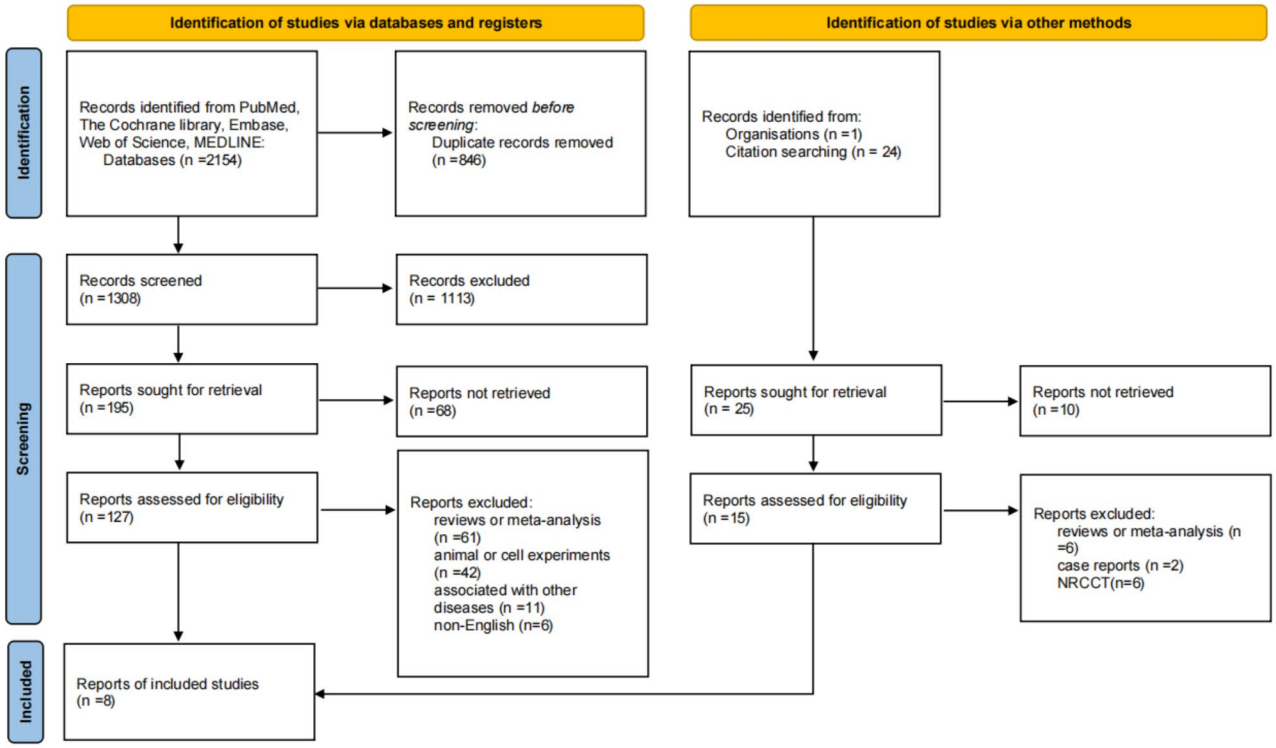

Fig. 1 Flow chart of the study search

Table 3 General characteristic of the included studies($n=8$)

Author	No. of patients (PRP vs. Control)	Age (years, PRP vs. Control)	Treatment		Outcome
			Platelet-rich plasma (PRP) treatment	Conventional therapy	
Eftekhar 2018 [39]	33/33	18 ~ 42/18 ~ 42	PRP (0.5-1 ml, 1-2times) + C	Estradiol valerate (2 mg tid, D2-13; 10 mg qd, D14-15) + Vaginal suppository progesterone (400 mg bid, 3 days)	①②③④⑤⑥⑦
Chang 2019 [38]	34/30	34.77 ± 0.75/32.64 ± 1.70	PRP (0.5-1 ml, 1-2times) + C	Estradiol valerate (6–10 mg qd, D2-?) + Suppository progesterone (vaginal,200 mg qd + intramuscular injection, 40 mg qd)	①③⑤⑥⑦
Nazari 2019 [25]	30/30	33.93 ± 2.76/32.33 ± 4.79	Estradiol valerate (6 mg qd, D2-8; 8 mg qd, D9-10) + PRP(0.5 ml, 2times, D11-12) + Vaginal suppository progesterone (400 mg bid)	Estradiol valerate (6 mg qd, D2-8; 8 mg qd, D9-10) + Sham_catheter(D11-12) + Vaginal suppository progesterone (400 mg bid)	①②③⑥⑦
Coksuer, H 2019 [44]	34/36	29.41 ± 4.54/28.89 ± 3.91	PRP (1 ml) + C	Ovulation induction + Estradiol valerate (6-12 mg qd, D1-?) + Vaginal suppository progesterone(400 mg bid)	①②④⑤
Abduljabbar, H. S 2022 [42]	35/35	35.91 ± 4.49/34.63 ± 4.26	Receive PRP(0.5 ml, 1time) after OPU	Not receive PRP	①②
Efendieva, Z 2023 [41]	42/30	35.1 ± 4.2/33.9 ± 3.7	PRP (0.5-1 ml)	HRT	①③④⑤⑥⑧
	38/30	35.4 ± 4.1/33.9 ± 3.7	PRP (0.5-1 ml) + HRT	HRT	①③④⑤⑥⑧
	5/30	Not mentioned/33.9 ± 3.7	autologous endometrial cells suspended in PRP	HRT	①
Pandey, D 2023 [40]	59/58	29.2 ± 1.89/29.11 ± 1.89	PRP (0.5-1 ml) + C	Ovulation induction + Estradiol valerate (6 mg qd, D8) + Vaginal suppository progesterone	①②③⑧
Yu, N 2024 [43]	55/23	37.9 ± 6.9/39.0 ± 6.6	PRP(Intrauterine Infusion-2 ml twice) + C	The COH protocol + oral estradiol valerate (qd, D3-) + suppository progesterone (oral and vaginal for 5 daysc)	①②③⑦
	38/23	40.0 ± 5.9/39.0 ± 6.6	PRP(Hysteroscopic Injection-2 ml in four directions) + C	The COH protocol + oral estradiol valerate (qd, D3-) + suppository progesterone (oral and vaginal for 5 daysc)	①②③⑦

Ps: ①Endometrial thickness post-PRP or progesterone initiation in the frozen embryo transfer cycle. ② Chemical pregnancy rate. ③ Clinical pregnancy rate. ④Sustained pregnancy rate or live birth rate. ⑤Spontaneous abortion rate. ⑥ Cycle cancellation rate. ⑦ Implantation rate. ⑧ Endometrial vascular improvement rate.

other biases were not explicitly described in most studies. One study [25] implemented double-blinding, one study [38] implemented blinding for outcome assessors, and the rest did not specify whether blinding was implemented. All eight studies ensured the completeness of outcome data and had no selective reporting of results. The quality assessment of the two-arm trials is detailed in Figs. 2 and 3.

Outcomes

Endometrial thickness

Seven studies [25, 38–43] involving 608 patients reported endometrial thickness after intrauterine PRP injection. Due to significant heterogeneity ($I^2=84.0\%$, $P=0.000$) (Fig. 4), a random-effects model was used for analysis, revealing a statistically significant difference in endometrial thickness between the PRP group and the control group (MD: 1.23, 95%CI: 0.87 to 1.59, $P=0.000$) (Fig. 5; Table 2). One study [44] that only reported changes in endometrial thickness within the PRP group without intergroup comparison was not included.

Chemical pregnancy rate

Five studies [25, 39, 40, 42, 44] involving 383 patients reported the chemical pregnancy rate after intrauterine PRP injection. Due to significant heterogeneity ($I^2=77.6\%$, $P=0.000$) (Fig. 6), a random-effects model was applied for analysis, showing no statistically significant difference in the chemical pregnancy rate between the PRP group and the control group (RR: 1.84, 95%CI: 0.72 to 4.72, $P=0.204$) (Fig. 7; Table 2).

Clinical pregnancy rate

Seven studies [25, 38–41, 43, 44] involving 603 patients reported the clinical pregnancy rate after intrauterine PRP injection. Meta-analysis showed a significant difference in clinical pregnancy rates between the two groups (RR: 2.04, 95%CI: 1.52 to 2.76, $P=0.000$), and there was

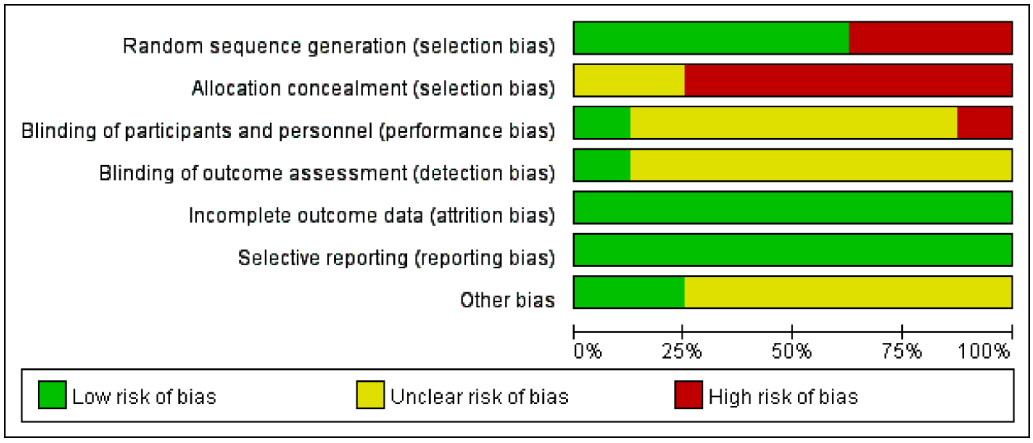

Fig. 2 Risk of bias graph ($n=8$)

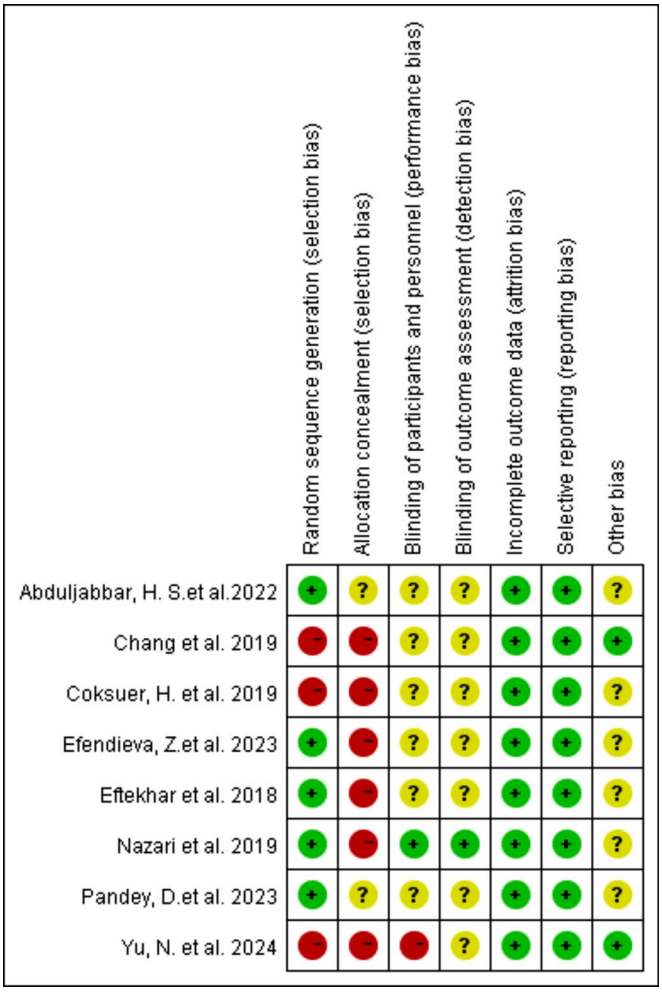

Fig. 3 Risk of bias summary ($n=8$)

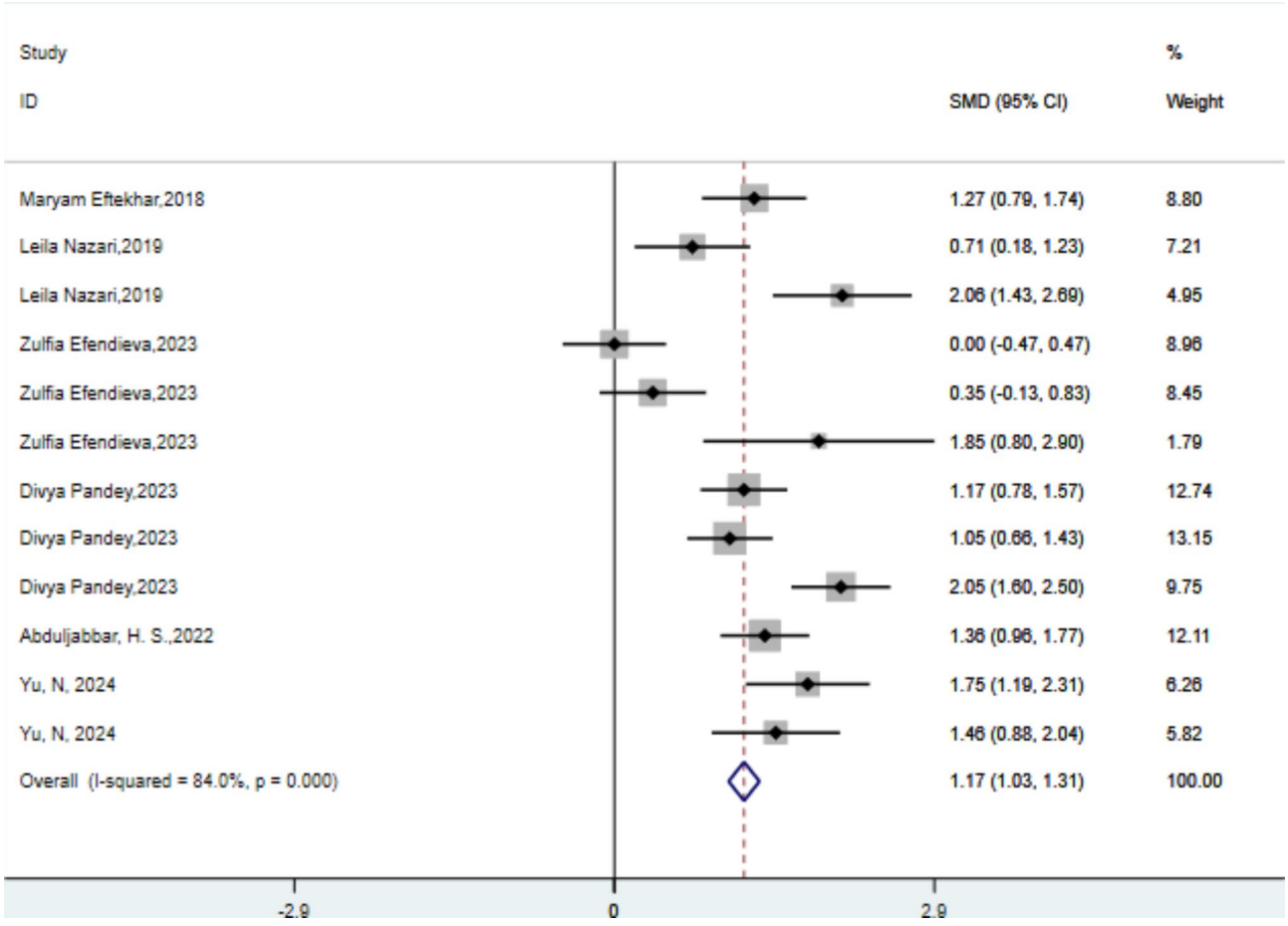

Fig. 4 Forest plot displaying the EMT in the study group versus the control group

no significant heterogeneity among the studies (I^2=0.0%, P=0.800) (Fig. 8; Table 2).

Live birth rate

Four studies [39, 41, 43, 44] involving 362 patients reported the live birth rate. The live birth rate in the PRP group was significantly higher than that in the control group (RR: 2.46, 95%CI: 1.57 to 3.85, P=0.000), and there was no significant heterogeneity among the studies (I^2=0.0%, P=0.650) (Fig. 9; Table 2).

Spontaneous abortion rate

Four studies [38, 39, 41, 44] involving 310 patients reported the rate of spontaneous abortion after pregnancy. Meta-analysis showed no significant difference in the spontaneous abortion rate between the PRP group and the control group (RR: 0.85, 95%CI: 0.40 to 1.78, P=0.659), and there was no significant heterogeneity among the studies (I^2=0.0%, P=0.763) (Fig. 10; Table 2).

Cycle cancellation rate

Four studies [25, 38, 39, 41] involving 300 patients reported the cycle cancellation rate. Due to significant heterogeneity (I^2=59.9%, P=0.041) (Fig. 11), a random-effects model was used for analysis, revealing a significantly lower cycle cancellation rate in the PRP group compared to the control group (RR: 0.46, 95%CI: 0.23 to 0.93, P=0.000) (Fig. 12; Table 2).

Implantation rate

Four studies [25, 38, 39, 43] involving 306 patients reported the implantation rate. The implantation rate in the PRP group was significantly higher than that in the control group (RR: 2.71, 95%CI: 1.91 to 3.84, P=0.000), and there was no significant heterogeneity among the studies (I^2=16.6%, P=0.309) (Fig. 13; Table 2).

Endometrial vascular improvement rate

Two studies [40, 41] involving 227 patients reported the improvement of endometrial vascularization. Meta-analysis showed no significant difference in endometrial vascular improvement rate between the PRP group and the control group (RR: 1.10, 95%CI: 0.89 to 1.38, P=0.367), and there was no significant heterogeneity among the studies (I^2=39.0%, P=0.194) (Fig. 14; Table 2).

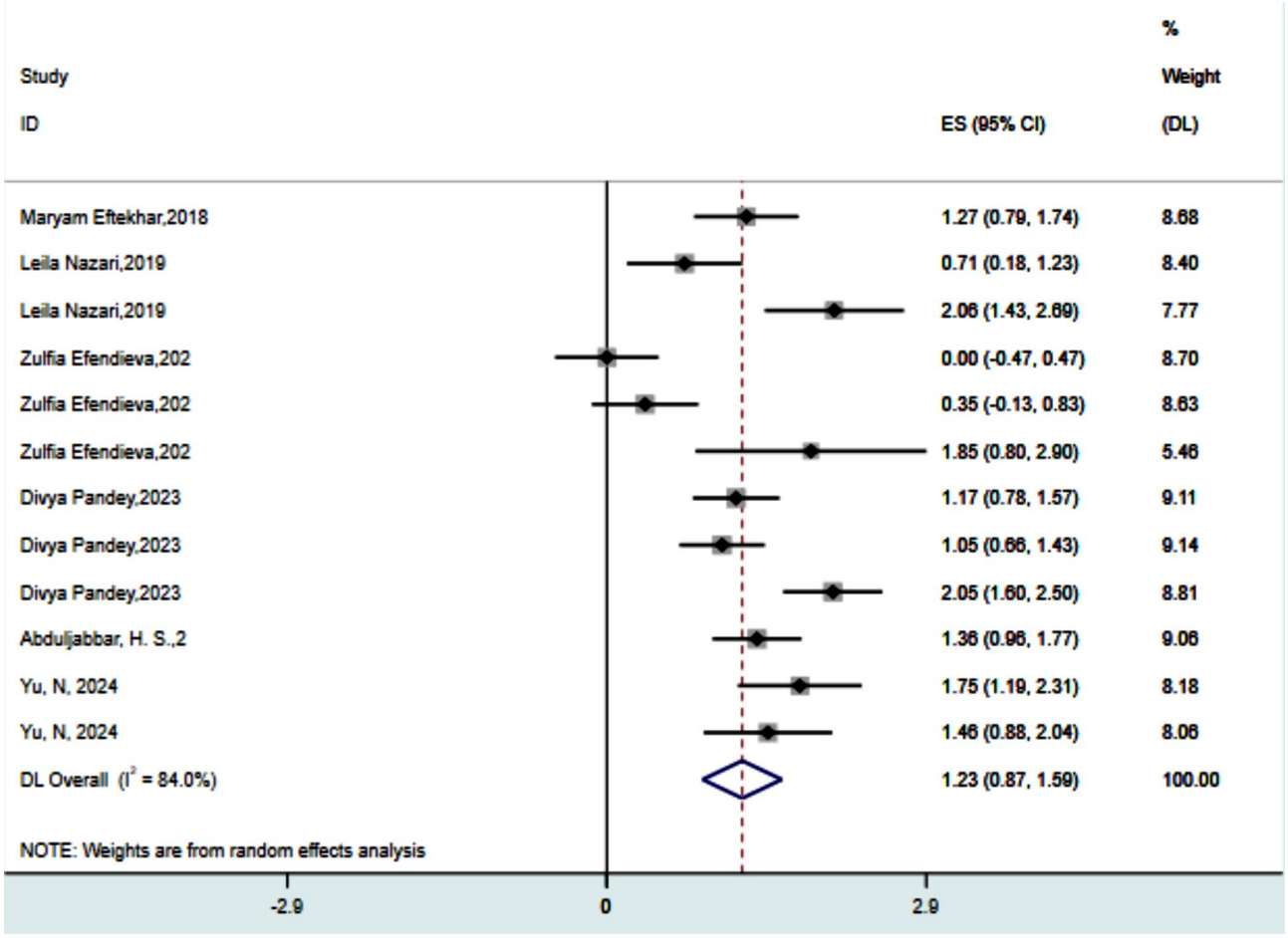

Fig. 5 Forest plot displaying the EMT in the study group versus the control group(use random-effects models)

Risk of bias assessment

Due to the limited number of studies, a publication bias analysis for the above results was not performed.

Discussion

This meta-analysis, including eight RCTs, aimed to assess the effects of intrauterine platelet-rich plasma (PRP) treatment on endometrial thickness, endometrial vascular improvement, and subsequent pregnancy outcomes in patients with thin endometrium, compared to traditional hormone therapy or placebo groups. The data synthesis consistently demonstrated that intrauterine PRP injection significantly increased endometrial thickness, improved endometrial receptivity, and enhanced chemical pregnancy rate, clinical pregnancy rate, live birth rate, and implantation rate compared to the control group. Nearly half of the studies had follow-up data until successful childbirth, and no adverse events were reported in subjects treated with PRP compared to the control group.

In assisted reproductive cycles, endometrial thickness persistently<7 mm may result in the cancellation of frozen embryo transfer (FET) cycles and embryo implantation. Even if embryos are obtained, the risk of natural miscarriage is higher, reducing the likelihood of a sustained pregnancy. Properly increasing endometrial thickness before initiating progesterone in frozen embryo transfer cycles can help avoid these situations, making endometrial thickness a crucial criterion for evaluating treatment effectiveness.

In the included studies, both groups had endometrial thickness below 7 mm before treatment, with the PRP group fluctuating between 4.66 ~ 6.32 mm and the control group fluctuating between 4.99 ~ 6.39 mm. Interestingly, the control group showed a slight increase in endometrial thickness compared to the PRP group. However, the meta-analysis demonstrated an overwhelming advantage of endometrial thickness in the PRP group over the control group ($P<0.05$), confirming the effectiveness of PRP in endometrial regeneration. Although Coksuer's study [44] did not show the individual endometrial thickness of both groups, it reported a significant increase in endometrial thickness (10 mm) after PRP injection compared to before treatment (6.25 mm). The significant statistical heterogeneity in studies assessing endometrial thickness,

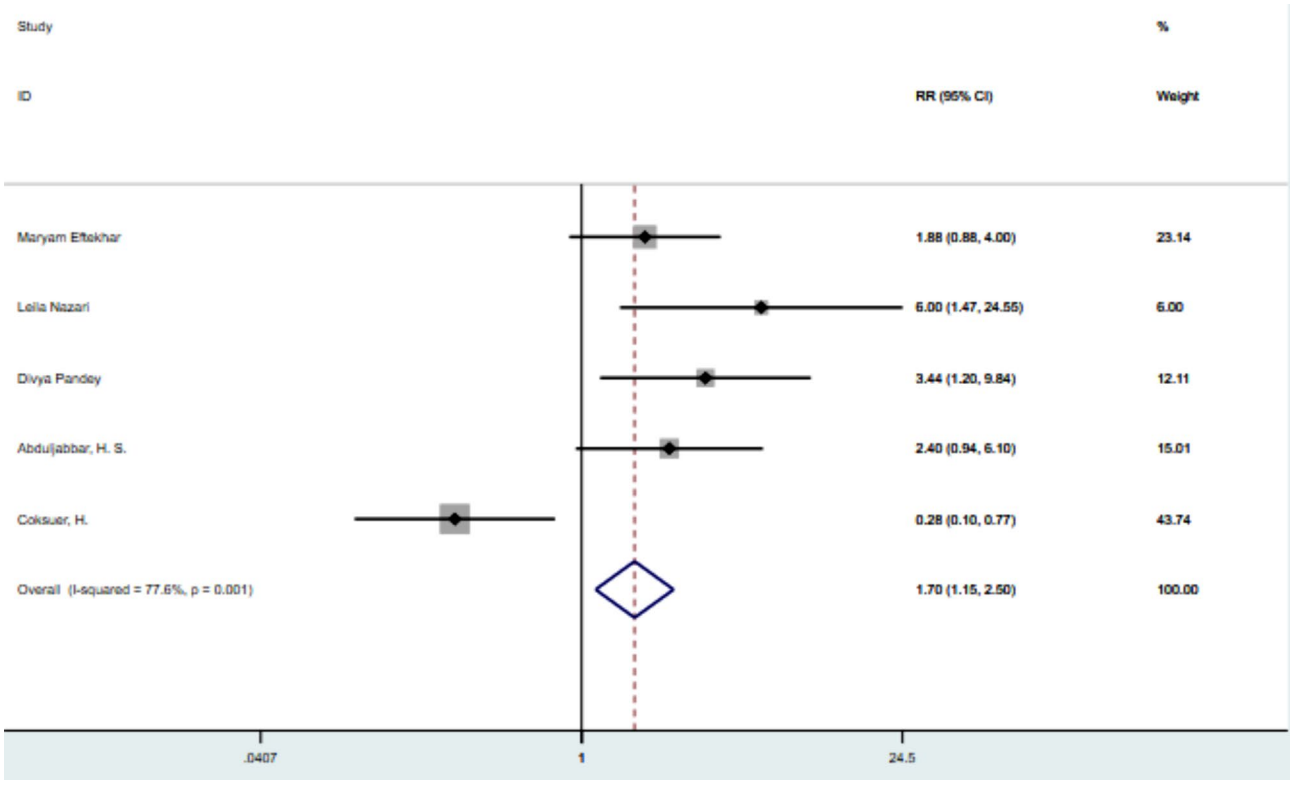

Fig. 6 Forest plot displaying the chemical pregnancy in the study group versus the control group

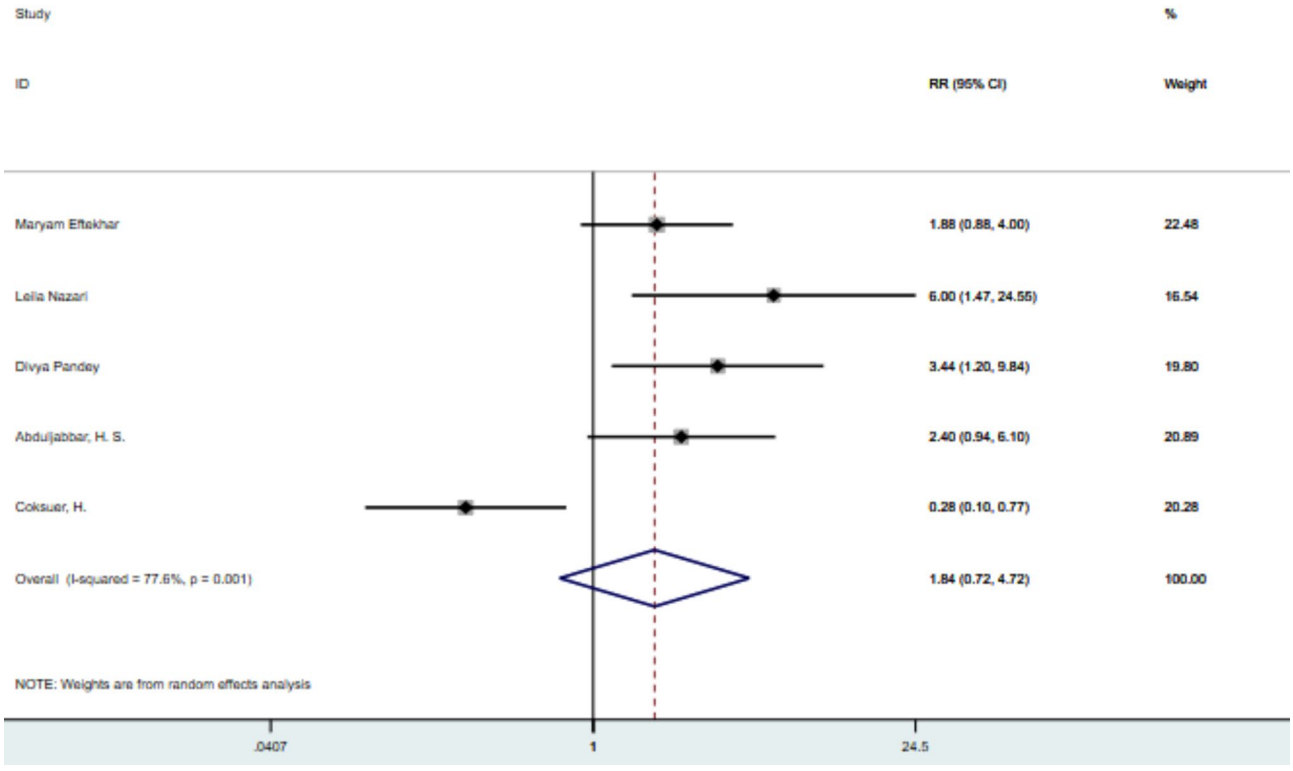

Fig. 7 Forest plot displaying the chemical pregnancy in the study group versus the control group(use random-effects models)

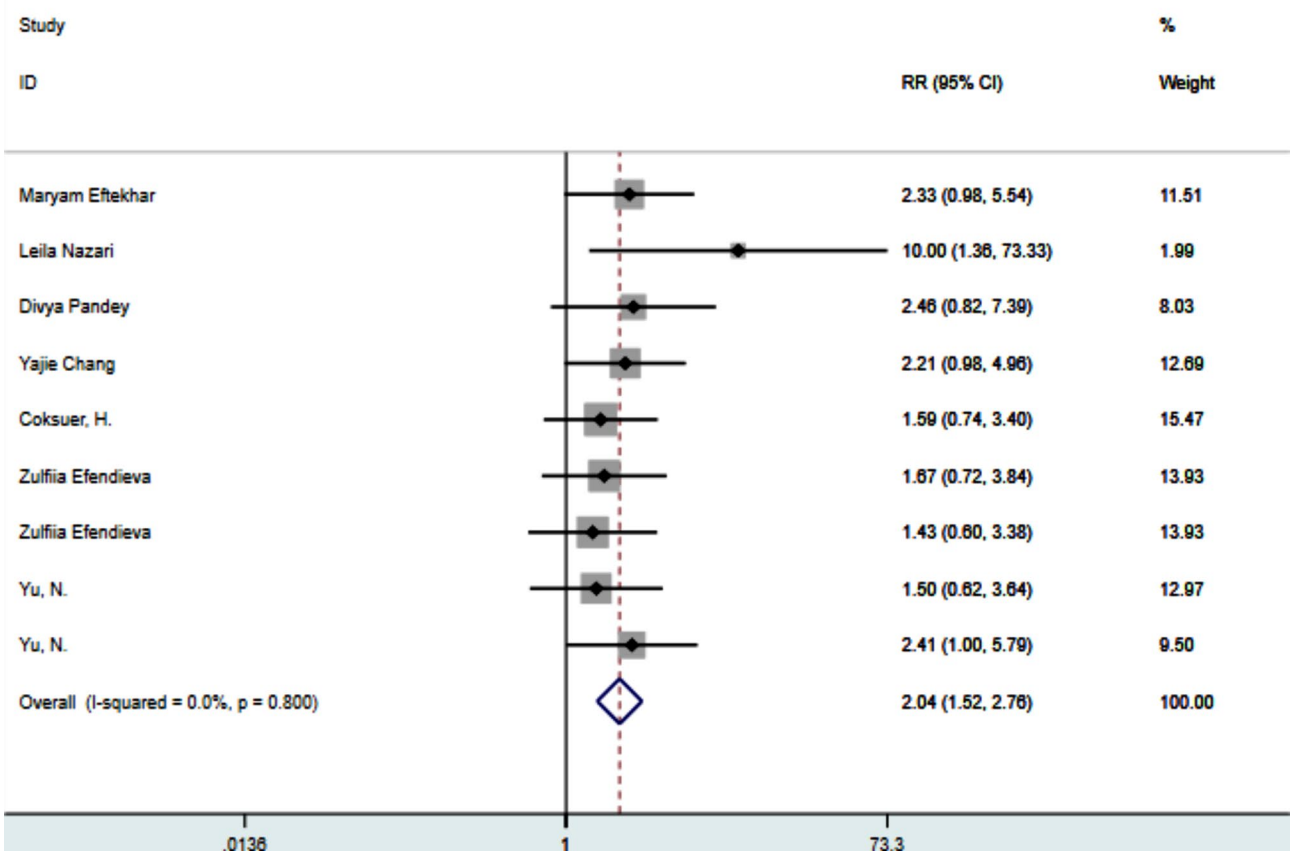

Fig. 8 Forest plot displaying the clinical pregnancy in the study group versus the control group

treated as the primary efficacy indicator in this analysis, prompted the use of a random-effects model for analysis. This heterogeneity might be attributed to differences in PRP preparation methods, doses, frequencies, and study populations. While all studies reported PRP preparation through a two-step centrifugation process, the choice of anticoagulants varied. Eftekhar [39] and Chang [38] used acidic citrate A anticoagulant solution (ACDA), a commonly used anticoagulant in clinical PRP preparation, effectively maintaining platelet activity but expensive. On the other hand, Pandey [40] opted for citrate-phosphate-dextrose-adenosine (CPDA) as an anticoagulant, which is easily accessible and cost-effective but slightly less effective in maintaining platelet activity [45]. Regarding PRP dosage and frequency, only Nazari [25], Abduljabbar [42], Yu [43] and Coksuer [44] explicitly reported PRP doses. Other studies had PRP doses fluctuating between 0.5 and 1 ml, with the majority considering further injections based on changes in endometrial thickness after PRP administration (usually not exceeding two additional injections). Some studies [40, 41, 44] did not specify the number of PRP injections in the text. Regarding the study population, in Chang's study [38], patients with inadequate endometrial growth after treatment could decide to cancel the current cycle or proceed with embryo transfer, potentially introducing bias compared to other studies. Pandey [40], Yu [43] and Coksuer [44] included patients who underwent ovulation induction treatment before PRP injection and existing meta-analyses [46] have shown that ovulation-inducing drugs like clomiphene can thin the endometrium, potentially offsetting the regenerative effects of PRP. Additionally, only two studies [25, 38] employed a blinded method for measuring endometrial thickness under ultrasound, enhancing the credibility and reliability of their results, while the remaining studies did not mention blinding. Considering these factors, there may be some inherent risks associated with the results.

In the context of secondary efficacy indicators, the Platelet-Rich Plasma (PRP) group, when compared to the control group, demonstrates statistically significant differences in clinical pregnancy rate, live birth rate, cycle cancellation rate, and embryo implantation rate. However, there are no significant differences in chemical pregnancy rate, natural miscarriage rate, and endometrial vascular improvement rate. This discrepancy may be attributed to the fact that most studies in the control group adopted estrogen hormone therapy as a conventional treatment method for patients with thin endometrium. These patients also received luteal phase support

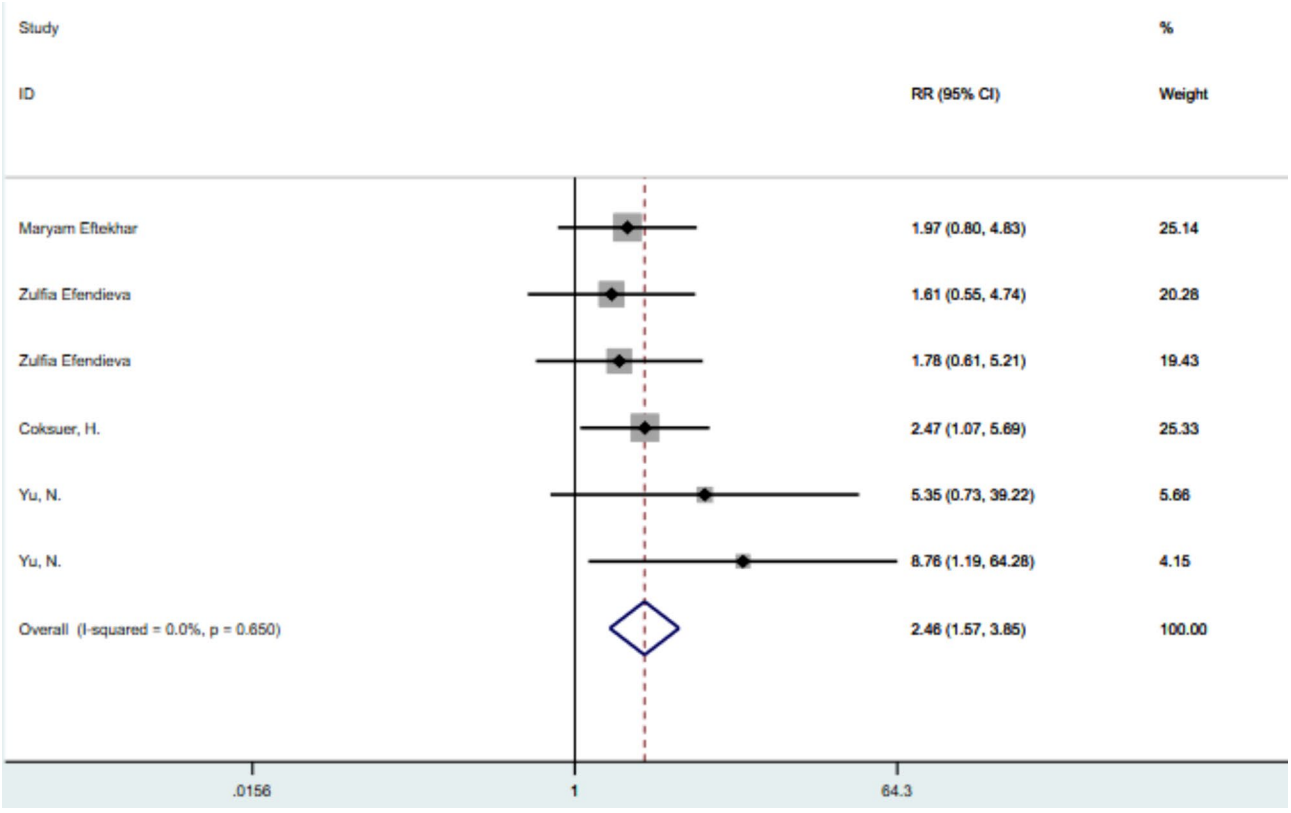

Fig. 9 Forest plot displaying the live birth rate in the study group versus the control group

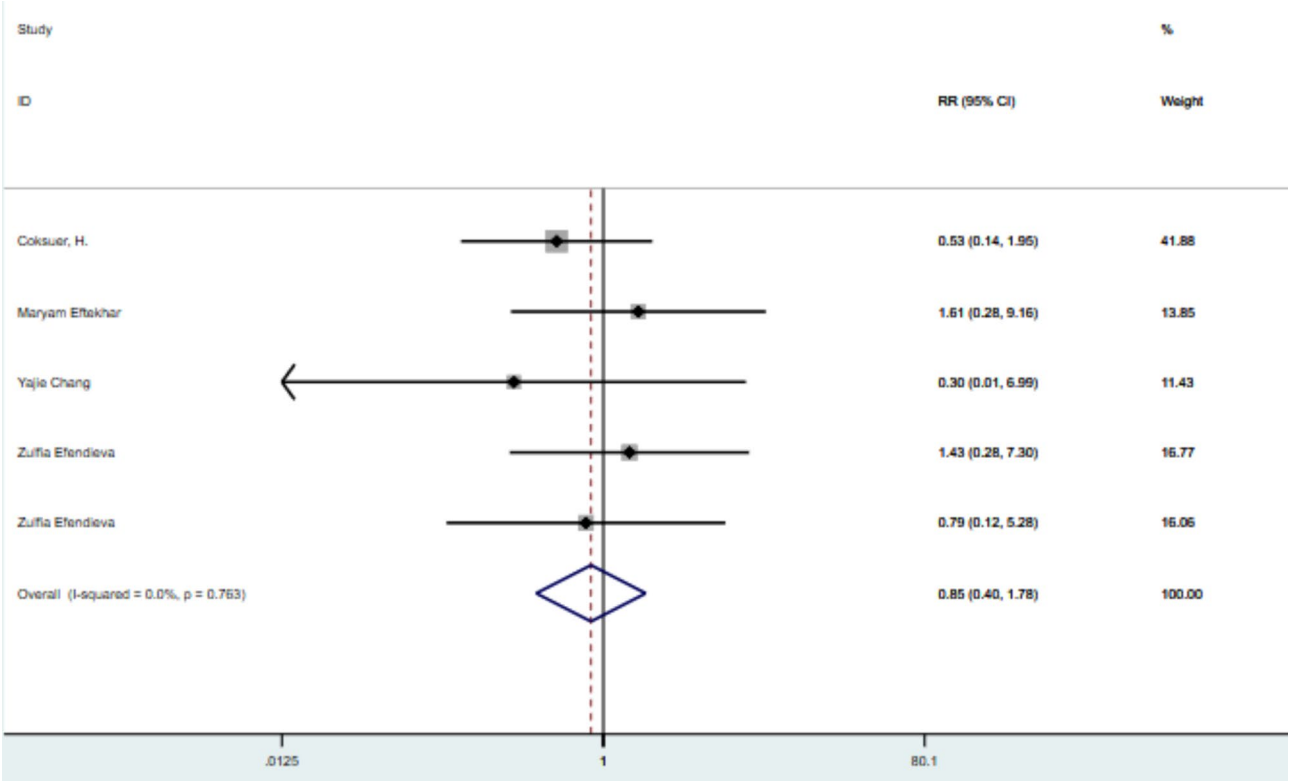

Fig. 10 Forest plot displaying the spontaneous abortion rate in the study group versus the control group

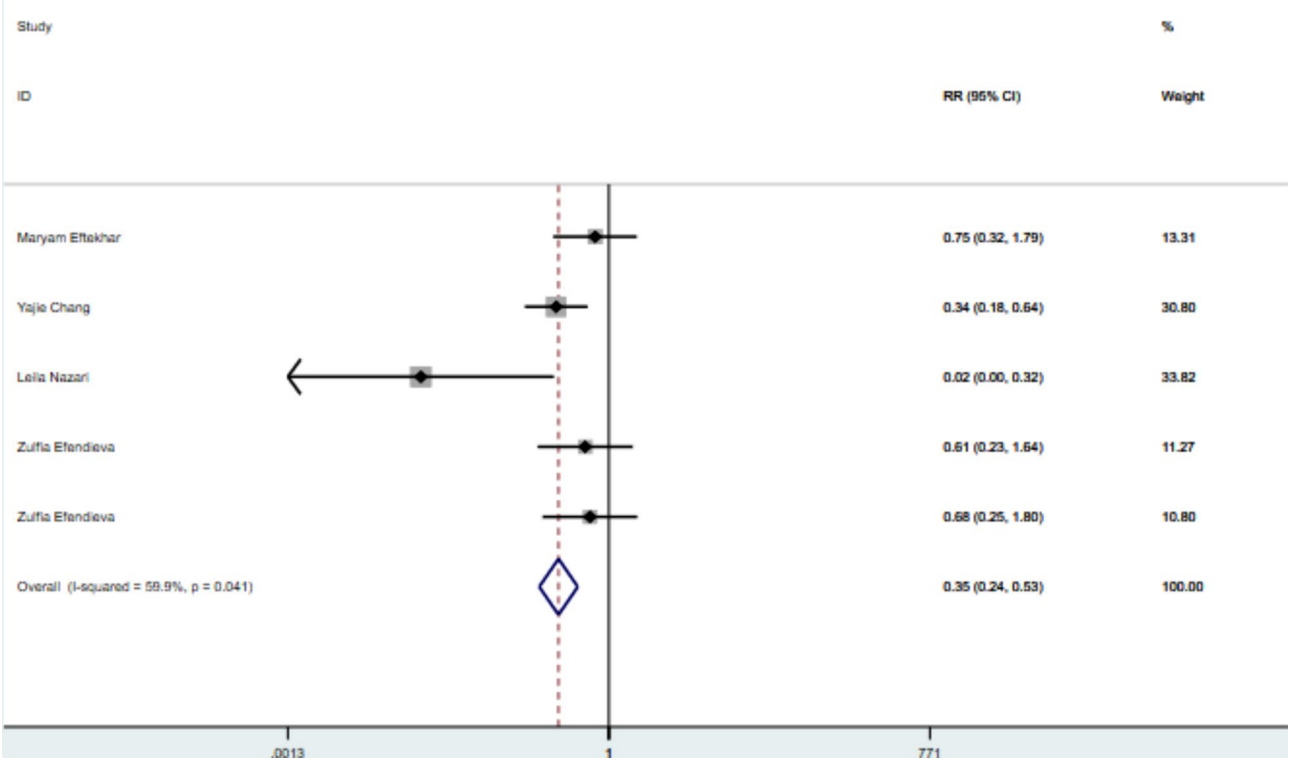

Fig. 11 Forest plot displaying the cycle cancellation rate in the study group versus the control group

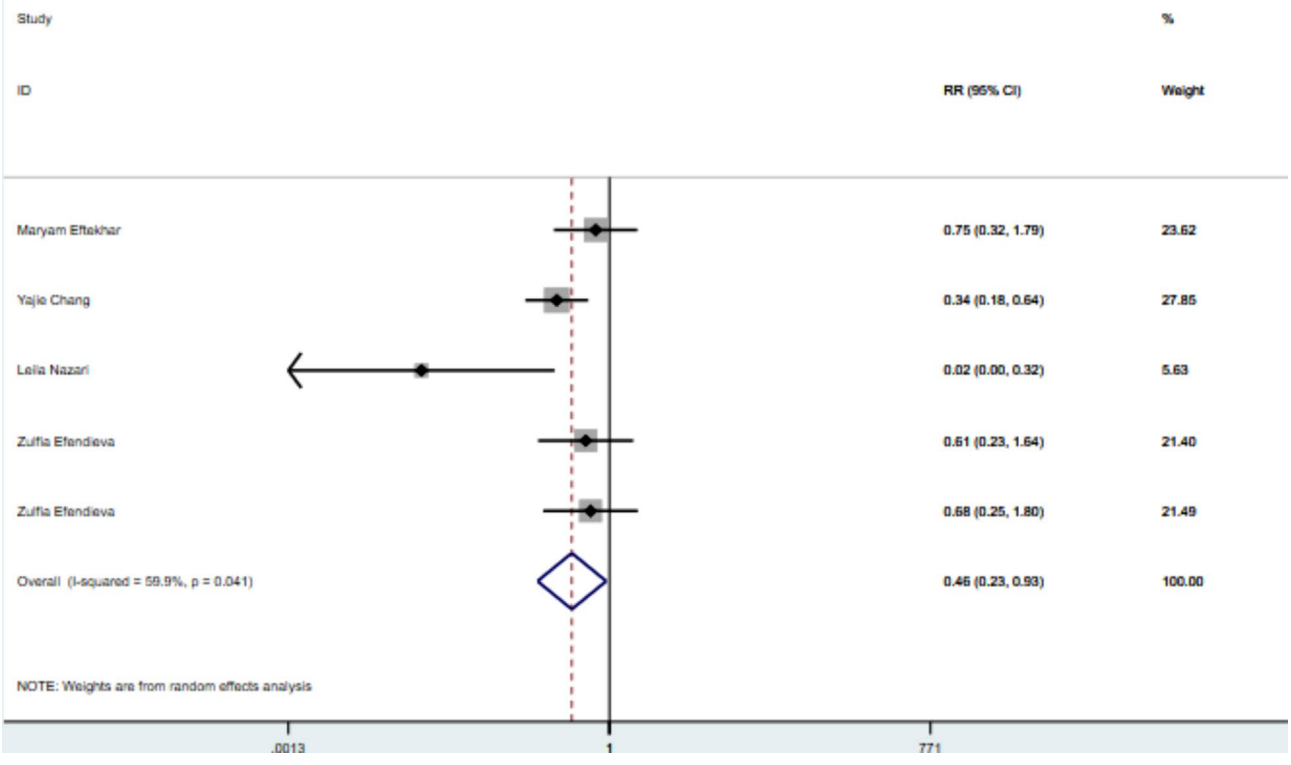

Fig. 12 Forest plot displaying the cycle cancellation rate in the study group versus the control group(use random-effects models)

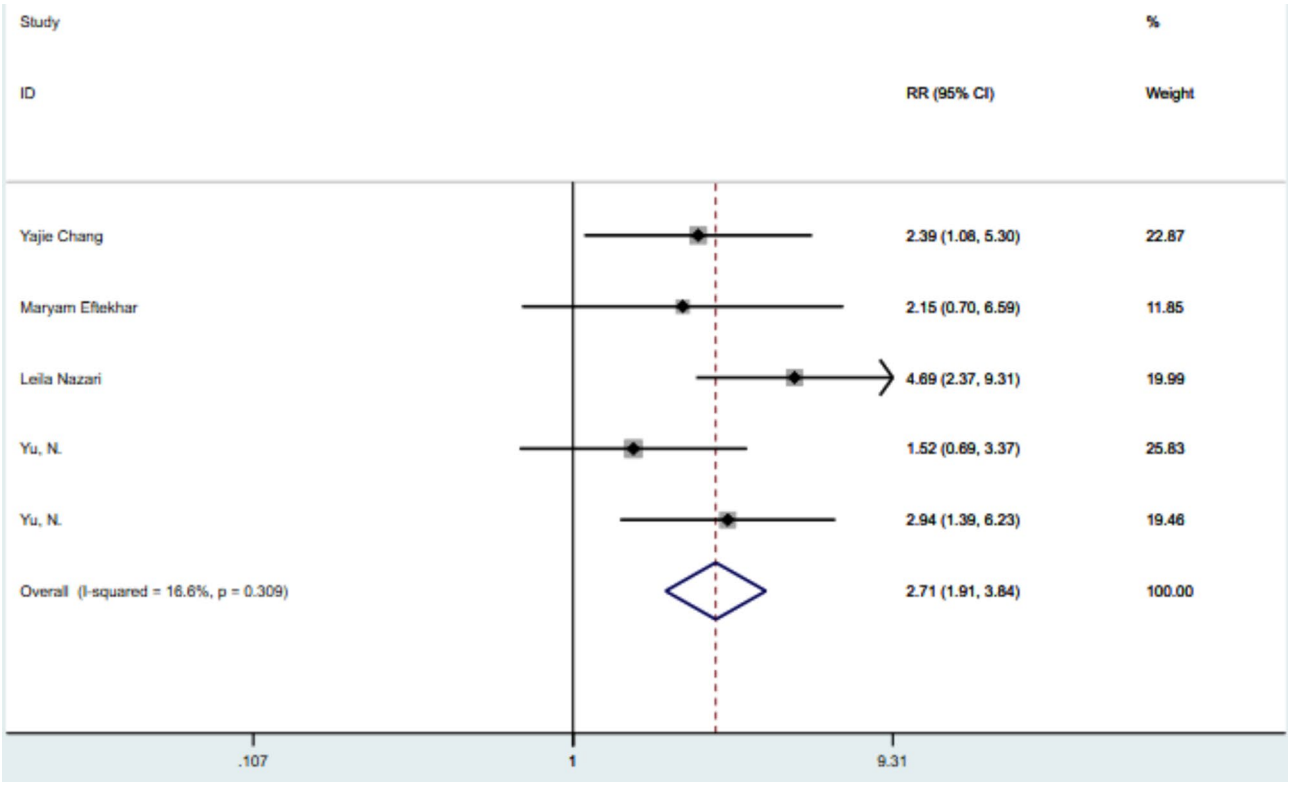

Fig. 13 Forest plot displaying the implantation rate in the study group versus the control group

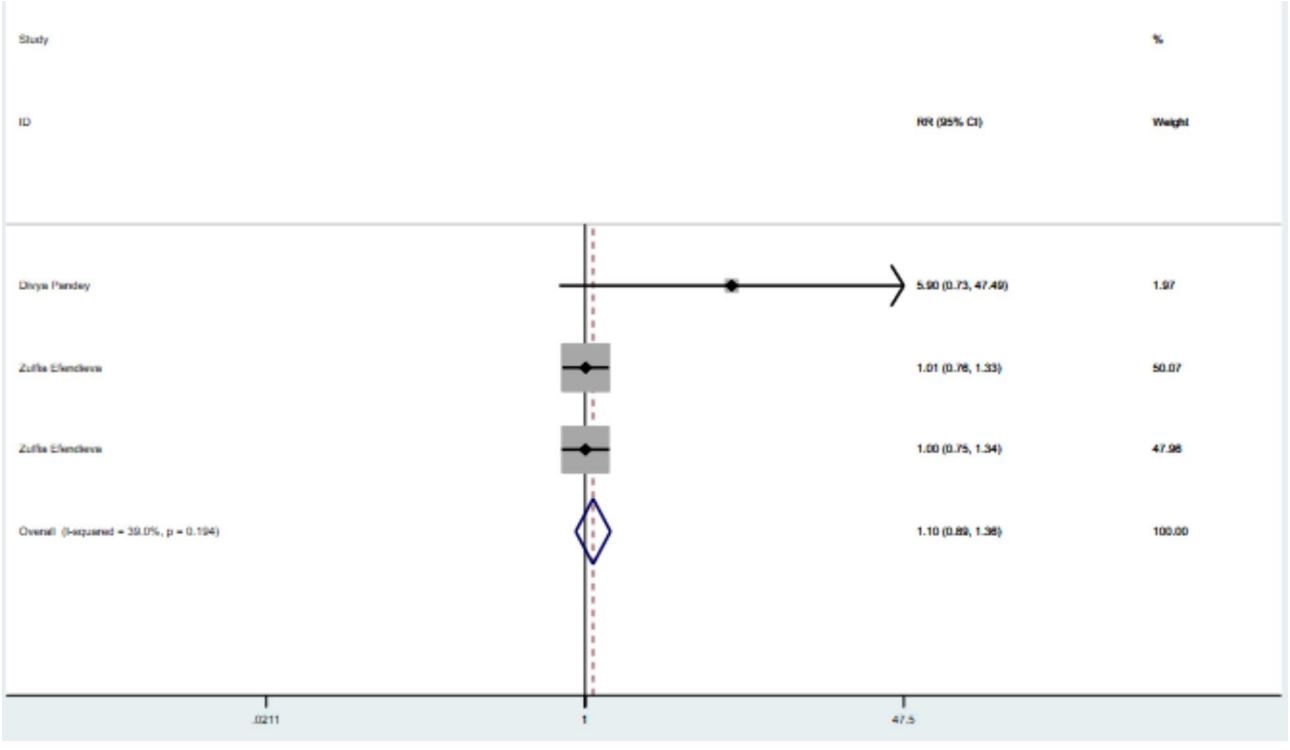

Fig. 14 Forest plot displaying the Endometrial vascular improvement rate in the study group versus the control group

post-embryo transfer, which to some extent increased the occurrence of positive events for Human Chorionic Gonadotropin (HCG) two weeks after embryo transfer and mitigated the risk of miscarriage. It is crucial to note that a positive chemical pregnancy rate does not necessarily indicate successful embryo development; clinical pregnancy is confirmed only after ultrasound detection of fetal heartbeats, making it a more critical and reliable indicator than the chemical pregnancy rate. Additionally, only two studies addressed monitoring and statistical analysis of endometrial vascular blood flow status, highlighting the need for further relevant clinical research to visually assess the improvement of endometrial blood flow in patients with thin endometrium following PRP infusion, providing a basis for understanding the mechanism of action of PRP.

While previous studies have preliminarily confirmed the efficacy of PRP for thin endometrium, they suffer from a broad scope of study populations [47, 48] (including patients with repeated implantation failures), a lack of recent clinical research reports [31], and unclear side effects. Considering that randomized controlled trials are widely acknowledged as the best strategy for evaluating clinical treatment outcomes, we attempted to include all currently available randomized controlled trials, focusing specifically on premenopausal women with thin endometrium. Notably, none of the studies reported complications or adverse events associated with PRP injection. Our meta-analysis results align with previous research findings, indicating that intrauterine PRP injection for thin endometrium is not only clinically effective but also safe and reliable.

Our study indicates that PRP treatment for thin endometrium is effective, and its mechanism of action is outlined as follows. Firstly, PRP can increase endometrial thickness by promoting cell proliferation. Existing research has demonstrated that PRP contains a substantial amount of growth factors and cytokines, such as epidermal growth factor (EGF), fibroblast growth factor (FGF), transforming growth factor (TGF), interferon-γ (IFN-γ), Cytokeratin (CK)18, CK19, Zona Occludin-1 (ZO-1), Ki-67, and Vimentin (Vim) [49, 50]. CK and Vim serve as markers for uterine epithelial and stromal cells, respectively, while Ki-67 is a marker for cell proliferation. Following intrauterine PRP injection, these factors are transported to the endometrium to enhance tissue regenerative capacity and accelerate endometrial cell growth. Secondly, PRP improves the blood flow status of the endometrium, promoting neovascularization. VEGF plays a crucial role in uterine vascular formation and decidualization [51], serving as a core factor in regulating vascular permeability. After PRP treatment, the expression of VEGF significantly increases, suggesting its favourable role in vascular formation and blood circulation, laying the foundation for endometrial growth. Thirdly, PRP optimizes the function of the endometrium, increasing the likelihood of embryo implantation. Important factors involved in regulating endometrial function and development, such as homeobox A10 (HOXA10), leukaemia inhibitory factor (LIF), and integrin β3, show increased expression with the use of PRP [52]. This improves endometrial receptivity, avoiding the occurrence of natural miscarriage. Additionally, most patients with thin endometrium undergo repeated uterine interventions, leading to a higher risk of inflammation and fibrosis in the uterine cavity. Activated PRP produces chemokines such as Chemokine C–C motif ligand 2 (CCL2), C-X-c motif ligand (CXCL) 8, CXCL10, Claudin-1 (Cla-1), which act as chemoattractants [50]. They play a role in reducing inflammatory reactions and downregulating fibrosis, stimulating the expression of uterine endometrial stem cell marker c-Kit (CD117), and expediting the natural healing process. This provides relevant evidence for reshaping and restoring the normal morphology and function of the endometrium. Recent basic scientific research [53] suggests that PRP may also inhibit the death of uterine epithelial cells by regulating processes such as iron death, autophagy, and pyroptosis, providing new insights into further exploring the mechanism of action of PRP.

Limitations of this study include the following: Firstly, we only had studies that were accessible in full and reported in English, which may lead to retrieval omissions, exclusion of literature written in other languages, and limitations in methods for accessing full text, warranting further exploration. Secondly, our meta-analysis only included eight studies without subgroup analysis, and the sample size may impose restrictions and influence the statistical and credible nature of the results. Thirdly, we acknowledged that heterogeneity exists among different studies, possibly due to various factors such as the preparation method, concentration, dosage, timing of PRP, the skill and proficiency of clinical doctors, clarity of ultrasound equipment, and the number and quality of embryos transplanted per cycle. Fourthly, the longest follow-up in the included studies extended to the successful delivery of offspring, with no mention of the subsequent growth and development of the offspring. Consequently, it is challenging to assess the long-term safety of PRP for women of childbearing age and their offspring. Lastly, some of the included literature studies inadequately elaborated on allocation concealment, blinding implementation, and research bias, leading to uncertainties or high-risk factors during the evaluation. Therefore, further large-scale, high-quality, multicenter, and rigorously designed randomized controlled trials are required for validation.

To the best of our knowledge, this is the first study that focuses on patients with thin endometrium, incorporating all available randomized controlled trials to explore the effectiveness and safety of PRP treatment for thin endometrium in a meta-analysis. Despite some limitations, we believe that the conclusions of this study can play a significant role in the clinical application of PRP.

Conclusion

In summary, our meta-analysis suggests that intrauterine injection of Platelet-Rich Plasma (PRP) may be a novel therapeutic approach for thin endometrium. It not only effectively increases endometrial thickness in patients with thin endometrium but also improves pregnancy outcomes, with reported safety and the absence of adverse events. However, further validation is warranted through additional large-scale, high-quality, multicenter, and rigorously designed studies.

Abbreviations

PRP	Platelet-Rich Plasma
EMT	Endometrial Thickness
TE	Thin Endometrium
IVF	In vitro fertilization
EnMSCs	Endometrial mesenchymal stem cells
MD	Mean difference
RR	Risk ratio
mm	Millimeter
ml	Milliliter
RCT	Randomized controlled trial
ACDA	Anticoagulant solution
CPDA	Citrate-phosphate-dextrose-adenosine
VEGF	Vascular endothelial growth factor
EGF	Epidermal growth factor
FGF	Fibroblast growth factor
TGF	Transforming growth factor
IFN-γ	Interferon-γ
CK	Cytokeratin
ZO-1	Zona Occludin-1
Vim	Vimentin
HOXA10	Homeobox A10
LIF	Leukemia inhibitory factor
CCL2	Chemokine C–C motif ligand 2
CXCL	C-X-c motif ligand
Cla-1	Claudin-1

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Author contributions

X.L. completed the conception and design of the work. X.L., C.Q. and X.J. wrote the main manuscript text. X.L. , C.Q., X.J., and Y.Z completed the acquisition, analysis, and interpretation of data. X.F. and Y.D prepared Figs. 1, 2, 3, 4, 5, 6 and 7. J.J. and M.H. prepared Figs. 8, 9, 10, 11, 12, 13 and 14. W.Z. and B.L prepared Tables 1, 2 and 3. H.Z completed project administration and funded acquisition. All authors reviewed the manuscript.

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Data availability

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

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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