Effects of Intrauterine Infusion of Autologous Platelet-Rich Plasma in Women Undergoing Treatment with Assisted Reproductive Technology: a Meta-Analysis of Randomized Controlled Trials

Auswirkungen einer intrauterinen Infusion von autologem plättchenreichem Plasma bei mit assistierter Reproduktionstechnologie behandelten Frauen: eine Metaanalyse randomisierter kontrollierter Studien

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platelet-rich plasma (PRP), assisted reproductive technology, randomized controlled trials (RCTs)

Schlüsselwörter
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ABSTRACT

Purpose This meta-analysis was conducted to systematically retrieve relevant randomized controlled trials (RCTs) and evaluate the effects of intrauterine infusion of autologous platelet-rich plasma (PRP) in women with thin endometrium, implantation or pregnancy failure undergoing treatment with assisted reproductive technology (ART).

Methods We conducted a systematic review and meta-analysis of the retrieved RCTs. Studies on the intrauterine infusion of PRP in women undergoing treatment with ART that were published in PubMed, the Cochrane library, Web of Science, and Embase from inception until June 2022 were included. The data were extracted and analyzed independently using the fixed-effects or random-effects model according to heterogeneity.

Results Seven RCTs involving 861 patients (435 in the intervention group and 426 in the control group) were included. The rates of clinical pregnancy (risk ratio [RR]: 2.51; 95% confidence interval [CI]: 2.0–3.13; $P < 0.00001$), chemical pregnancy (RR: 1.96; 95% CI: 1.58–2.45; $P < 0.00001$), live births (RR: 7.03; 95% CI: 3.91–12.6; $P < 0.00001$), and implantation (RR: 3.27; 95% CI: 1.42–7.52; $P = 0.005$) were significantly higher in the women who received PRP infusion than in the control group. No significant differences were noted in the miscarriage rate (RR: 0.98; 95% CI: 0.39–2.42; $P = 0.96$) between the two groups.

Conclusion In summary, intrauterine infusion of PRP may be an effective therapy for women with thin endometrium and recurrent implantation failure (RIF) undergoing treatment with ART. More population-based RCTs are warranted to verify the efficacy of our evidence.

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ZUSAMMENFASSUNG

Zielsetzung Bei dieser Metaanalyse wurden die Daten von randomisierten kontrollierten Studien (RCTs) systematisch gesammelt, um die Auswirkungen einer intrauterinen Infusion von autologem plättchenreichem Plasma (PRP) auszuwerten bei Frauen mit dünner Gebärmutterschleimhaut, Implantationsversagen oder Schwangerschaftsmisserfolg, die sich einer Behandlung mit assistierter Reproduktionstechnologie (ART) unterziehen.

Methoden Wir haben eine systematische Auswertung und Metaanalyse der gefundenen relevanten RCTs durchgeführt. Die in PubMed, der Cochrane-Datenbank, Web of Science und Embase von Anbeginn bis Juni 2022 veröffentlichten Studien zur intrauterinen Infusion von PRP bei mit ART behandelten Frauen wurden in unsere Analyse aufgenommen. Die Daten wurden entnommen und, je nach Heterogeneität, einer unabhängigen Analyse mithilfe des Fixed-Effects- oder Random-Effects-Modell zugeführt.

Ergebnisse Sieben RCTs mit 861 Patientinnen (435 in der Interventionsgruppe und 426 in der Kontrollgruppe) wurden in unsere Metaanalyse aufgenommen. Die klinische Schwangerschaftsrate (Risikoquote [RR]: 2,51; 95 %-Konfidenzintervall [KI]: 2,0–3,13; $p < 0,00001$), Anzahl chemischer Schwangerschaften (RR: 1,96; 95 %-KI: 1,58–2,45; $p < 0,00001$), Zahl der Lebengeburten (RR: 7,03; 95 %-KI: 3,91–12,6; $p < 0,00001$) sowie Implantationsraten (RR: 3,27; 95 %-KI: 1,42–7,52; $p = 0,005$) waren signifikant höher in der Gruppe der Frauen, die eine PRP-Infusion erhielten, verglichen mit der Kontrollgruppe. Es gab keine signifikante Unterschiede in den Fehlgeburtenraten (RR: 0,98; 95 %-KI: 0,39–2,42; $p = 0,96$) zwischen den beiden Gruppen.

Schlußfolgerung Die intrauterine Infusion von PRP könnte sich als effektive Therapie herausstellen bei Frauen mit dünnem Gebärmutterschleimhaut und rezidivierendem Implantationsversagen (RIF), die sich einer ART-Behandlung unterziehen. Mehr populationsbezogene RCTs werden benötigt, um die Aussagekraft unserer Daten zu bestätigen.

Introduction

Infertility is defined as failure to achieve a successful pregnancy after at least 1 year of regular and unprotected intercourse, and its prevalence ranges between 9 % and 18 % among the general population [1]. Despite recent advancements in the field of assisted reproduction technology (ART), it is challenging to promote embryo implantation and prevent abortion. A thin endometrium, poor endometrial receptivity, embryo defects, and abnormal cross-talk between the endometrium and embryo are the main reasons for recurrent implantation failure (RIF) and recurrent pregnancy loss (RPL) [2, 3]. Endometrial quality is of paramount importance for successful embryo implantation [4].

A large number of individuals suffer from infertility; thus, methods such as the use of vaginal sildenafil, endometrial scratching, the intrauterine administration of granulocyte colony-stimulating factor or stem cells, blastocyst-assisted hatching and pre-implantation genetic diagnosis for aneuploidy, high-dose estrogen therapy, and treatment of thin endometrium have been proposed to improve the pregnancy outcomes in couples with implantation defects and pregnancy failure [5, 6, 7, 8]. However, these treatments do not help to improve the endometrial thickness and/or quality in the affected women. Therefore, a safer and more effective treatment method that can improve the pregnancy outcomes of couples with implantation defects and pregnancy failure is warranted.

Increasing evidence shows that intrauterine infusion of autologous platelet-rich plasma (PRP) is a novel potential method for treating thin endometrium via ART [9, 10]. PRP, also known as autologous conditioned plasma, is prepared by centrifuging patients' peripheral blood samples and comprises high numbers of platelets [11]. A growing body of evidence suggests that platelets contain numerous proteins; several growth factors (GFs); and cytokines such as platelet-derived GF (PDGF), vascular endothelial GF (VEGF), transforming GF-β1 (TGF-β1), and anti-inflammatory cytokines [12]. These molecules are released upon activation and contribute to cell proliferation, migration, differentiation, chemotaxis, angiogenesis, and anti-inflammatory properties, resulting in improved endometrial growth and receptivity [7, 10]. PRP may thus be a novel treatment for women with a thin endometrium [9]. Moreover, Russell et al. [4] reported the effectiveness of PRP in inducing endometrial growth.

To date, several randomized controlled trials (RCT) have evaluated the efficiency of intrauterine infusion of autologous PRP in women undergoing treatment with ART; however, the results of those RCTs are not consistent. Therefore, the present meta-analysis aimed to screen RCTs that compared the effects of intrauterine infusion of PRP in women undergoing treatment with ART and summarize their results. The results of this meta-analysis will increase awareness among physicians in reproductive medicine, helping to formulate better treatment strategies to improve the pregnancy outcomes of couples with implantation defects and pregnancy failure.

Materials and Methods

Literature search

Two independent reviewers (HSF and JZS) conducted a systematic electronic literature search of PubMed, the Cochrane library, Embase, and Web of Science and identified all relevant studies published in English from inception until June 2022. The search strategy used the following keywords: ("Platelet-rich plasma" OR "Autologous platelet-rich plasma" OR "Platelet-rich plasma gel" OR "PRP") and ("In vitro fertilization" OR "IVF" OR "Intracytoplasmic sperm injection" OR "ICSI" OR "Embryo transfer" OR "Assisted reproduction technologies" OR "ART") and ("Randomised controlled trial" OR "RCT"). The end-list references of all relevant papers were also screened to further obtain potentially eligible studies.

Inclusion and exclusion criteria

The studies were included if they
1. were RCTs;
2. included patients undergoing treatment with ARTs, including in vitro fertilization (IVF) or intracytoplasmic sperm injection;
3. were already published;
4. compared intrauterine infusion of autologous PRP with no injection/placebo; and
5. included at least one of the following reported outcomes: chemical pregnancy rate, clinical pregnancy rate, and miscarriage rate.

The studies were excluded if they
1. were review articles, commentaries, letters, or observational studies;
2. were non-clinical trials;
3. were not RCTs; and
4. reported inability to extract data from the literature.

Data extraction and quality assessment

Using a standardized extraction form, two review authors (HSF and JZS) independently extracted the following data from the included studies: first author, year of publication, country, sample size, population characteristics, interventions, and main results. The quality of all of the included studies was appraised by two reviewers (JZS and TQQ) in accordance with the Cochrane Collaboration's tool [13]. A risk-of-bias table including the following elements was created: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias. Discrepancies, if any, were resolved through consultation with a third reviewer (TQQ).

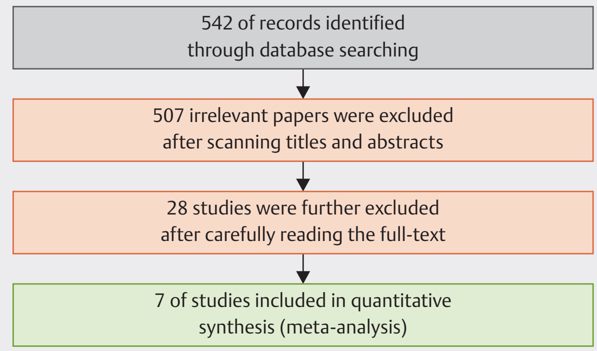
Statistical analysis

All data were assessed using Review Manager 5.3 (Cochrane Collaboration, 2014). Dichotomous data are expressed as risk ratios (RRs) with 95 % confidence intervals (CI). The heterogeneity across studies was evaluated based on the P and I^2 values and using standard chi-square tests. $I^2 < 50\%$ indicated moderate heterogeneity, and a fixed-effects model was used for the meta-analysis; by contrast, a random-effects model was used when severe heterogeneity was identified ($I^2 \geq 50\%$). Subgroup analyses were conducted to assess different populations, and sensitivity analysis was conducted by excluding each study one by one. Publication bias was evaluated by applying funnel plots.

Results

Study characteristics and quality assessment

▶ **Fig. 1** presents a flow chart of the study inclusion process. In total, 542 published articles were selected upon initial screening of the electronic databases. Based on the exclusion criteria, 507 obviously irrelevant papers were excluded after scanning the titles and abstracts. An additional 28 studies were excluded after carefully reading the full texts. Finally, seven eligible studies [14, 15, 16, 17, 18, 19, 20] were included for analysis. These seven studies involved a total of 861 patients (426 in the control group and 435 in the treatment group). The basic characteristics of each study are presented in ▶ **Table 1**. ▶ **Table 2** presents the authors' judgments regarding the risk of bias across all RCTs.



▶ **Fig. 1** Flow diagram of search strategy for the randomized controlled trials (RCT).

Clinical pregnancy rate

All seven studies [14, 15, 16, 17, 18, 19, 20] reported on the clinical pregnancy rates of the 861 patients. There was no heterogeneity across the studies (I^2 = 0%; P = 0.39). The pooled analysis with the fixed-effects model showed a statistically significant increase in the clinical pregnancy rate in the PRP group as compared with the control group (RR: 2.51; 95% CI: 2.0–3.13; P < 0.00001; ▶ **Fig. 2**).

A subgroup analysis was conducted to examine whether a thin endometrium, RPL, and RIF affected the patient outcomes. Compared with the control group, in the treatment group, patients with a thin endometrium, RPL, and RIF had RRs of 3.46 (95 % CI: 1.58–7.59; two studies), 1.75 (95 % CI: 0.61–5.05; one study), and 2.46 (95 % CI: 1.93–3.12; four studies), respectively. Similarly, a subgroup analysis was performed to explore whether the PRP dose affected the patient outcomes. The results of the meta-analysis showed that the RRs of the subgroups that were administered PRP at doses of ≤0.5ml, ≥1ml, and 0.5–1ml were 2.58 (95% CI: 2.01–3.32; P=0.65; I^2 =0%; five studies), 2.18 (95% CI: 1.22–3.90; P=0.009; one study), and 2.33 (95% CI: 0.98–5.54; P=0.06; one study), respectively, relative to the controls. Finally, the stability of our meta-analysis results was examined using sensitivity analyses by sequentially excluding each study one by one; the results indicated that our results were stable.

▸**Table 1** Characteristics of the studies included in the review.

First author (Year)	Country	Population	Age of the participants	Time of PRP infusion	Method of PRP infusion	Transfer type	Interventions	Sample size (n)		Outcomes included in the meta-analysis
								Case	Control	
Eftekhar (2018) [14]	Iran	Women with thin endometrium (endometrium thickness < 7 mm)	Between 18 and 42 years	The 13 th day of HRT cycle	Intrauterine insemination catheter	Frozen embryo transfer	0.5–1 ml platelet-rich plasma	40	43	Chemical pregnancy, clinical pregnancy, Miscarriage
Nazari (2022) [18]	Iran	Recurrent pregnancy loss	Below 40 years	48 h before embryo transfer	Using a catheter	Fresh blastocyst embryos	0.5 ml of platelet-rich plasma	20	20	Chemical pregnancy, clinical pregnancy, Miscarriage
Nazari (2020) [16]	Iran	Recurrent implantation failure	Below 40 years	48 h before embryo transfer	Embryo transfer catheter under ultrasound guidance	Frozen embryo transfer	0.5 ml of platelet-rich plasma	49	48	Chemical pregnancy, clinical pregnancy
Nazari (2022) [17]	Iran	Recurrent implantation failure	Between 18 and 38 years	48 h before embryo transfer	Intrauterine insemination catheter	Frozen embryo transfer	0.5 ml of platelet-rich plasma	196	197	Chemical pregnancy, clinical pregnancy, Live birth
Nazari (2019) [15]	Iran	Women with thin endometrium (endometrium thickness < 7 mm)	Age ≤ 38 years	The 11–12 th day of HRT cycle	Intrauterine insemination catheter under ultrasound guidance	Frozen embryo transfer	0.5 ml of platelet-rich plasma	30	30	Chemical pregnancy, clinical pregnancy
Zamaniyan (2020) [19]	Iran	Recurrent implantation failure	Between 20–40 years	48 h before embryo transfer	Intrauterine insemination catheter	Frozen embryo transfer	0.5 ml of platelet-rich plasma	55	43	Chemical pregnancy, clinical pregnancy, miscarriage, implantation rates
Obidniak (2017) [20]	Russia	Recurrent implantation failure	Aged 28–39 years	Not Mentioned	Not Mentioned	Frozen embryo transfer	2.0 ml of autologous PRP	45	45	Implantation Rate, clinical pregnancy

Chemical pregnancy rate

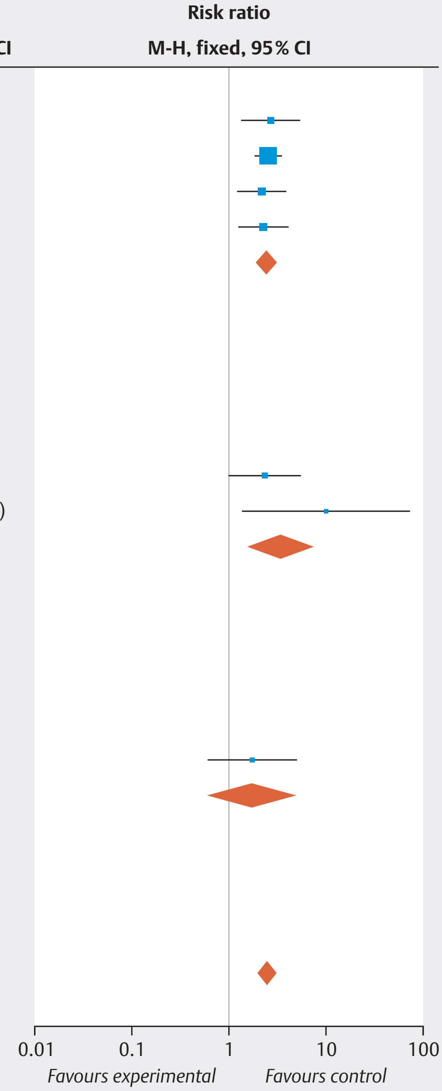
Of the seven studies, four [14, 16, 17, 19] studies involving 671 patients reported on the patients' chemical pregnancy rates. The heterogeneity among these studies was low (I^2 = 0%; P = 0.89); therefore, the fixed-effects model was used. The results of our meta-analysis indicated a statistically significant increase in the chemical pregnancy rate in the PRP group as compared with the control group (RR: 1.96; 95% CI: 1.58–2.45; P < 0.00001; ▸ **Fig. 3**).

Furthermore, a subgroup analysis was conducted to examine whether a thin endometrium or RIF would affect the patients' outcomes. The results of our meta-analysis revealed that patients with a thin endometrium or RIF who were administered PRP had an RR of 1.97 (95 % CI: 1.57–2.48; P = 0.73; I^2 = 0 %; three studies) and 1.88 (95 % CI: 0.88–4.00; P = 0.73; one study), respectively, as compared with the controls.

Miscarriage rate

Three of the reported studies [14, 18, 19] included data on the miscarriage rate for a total of 221 patients (115 in the treatment group and 106 in the control group). As shown in ▸ **Fig. 4**, our meta-analysis results indicated an I^2 of 0% and P value of 0.64, suggesting that the heterogeneity across the studies was low. Therefore, the fixed-effects model was applied. There was no obvious difference in the miscarriage rate between the two groups (RR: 0.98; 95% CI: 0.39–2.42; P = 0.96; ▸ **Fig. 4**).

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, fixed, 95% CI
1.1.1 RIF						
Nazari 2019a	22	49	8	48	10.2%	2.69 (1.33, 5.45)
Nazari 2021	96	196	38	197	48.0%	2.54 (1.84, 3.49)
Obidniak 2017	24	45	11	45	13.9%	2.18 (1.22, 3.90)
Zamaniyan 2020	29	55	10	43	14.2%	2.27 (1.25, 4.12)
Subtotal (95% CI)		**345**		**333**	**86.3%**	**2.46 (1.93, 3.12)**
Total events	171		67			
Heterogeneity: $\chi^2 = 0.34$, df = 3 (p = 0.95); $I^2 = 0\%$						
Test for overall effect: Z = 7.37 (p < 0.00001)						
1.1.2 Thin endometrium						
Eftekhar 2018	13	40	6	43	7.3%	2.33 (0.98, 5.54)
Nazari 2019b	10	30	1	30	1.3%	10.00 (1.36, 73.33)
Subtotal (95% CI)		**70**		**73**	**8.6%**	**3.46 (1,58, 7.59)**
Total events	23		7			
Heterogeneity: $\chi^2 = 1.89$, df = 1 (p = 0.17); $I^2 = 47\%$						
Test for overall effect: Z = 3.10 (p = 0.002)						
1.1.3 RPL						
Nazari 2022	7	20	4	20	5.1%	1.75 (0.61, 5.05)
Subtotal (95% CI)		**20**		**20**	**5.1%**	**1.75 (0.61, 5.05)**
Total events	7		4			
Heterogeneity: not applicable						
Test for overall effect: Z = 1.03 (p = 0.30)						
Total (95% CI)		**435**		**426**	**100.0%**	**2.51 (2.00, 3.13)**
Total events	201		78			
Heterogeneity: $\chi^2 = 2.69$, df = 6 (p = 0.85); $I^2 = 0\%$						
Test for overall effect: Z = 8.06 (p < 0.00001)						
Test for subgroup differences: $\chi^2 = 1.11$, df = 2 (p = 0.57); $I^2 = 0\%$						

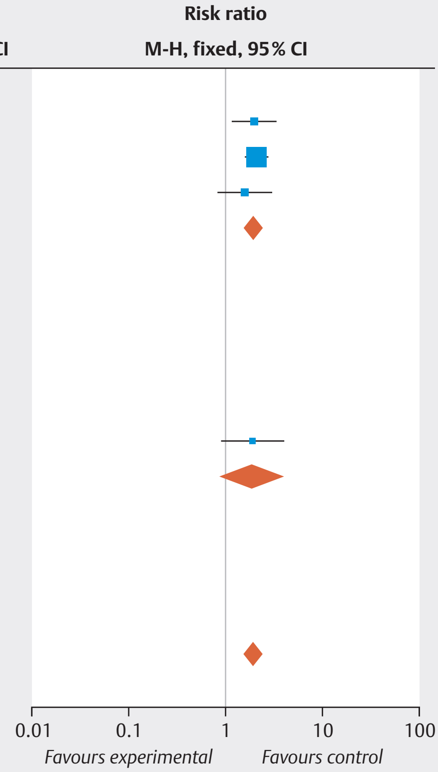


▶ **Fig. 2** Forest plot diagram showing the clinical pregnancy rate in women who received intrauterine platelet-rich plasma versus controls regarding population type (recurrent implantation failure (RIF), recurrent pregnancy loss (RPL) and thin endometrium). CI = confidence intervals.

▶**Table 2** Quality assessment of the included studies.

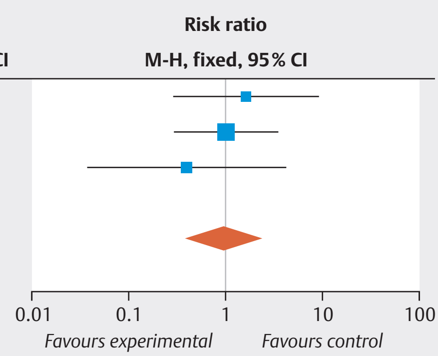
Author (year)	Random Sequence Generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Eftekhar (2018) [14]	Yes	Yes	Yes	No	Yes	Yes	Yes
Nazari (2022) [18]	Yes	No	No	No	Yes	Yes	Yes
Nazari (2020) [16]	Yes	Yes	Yes	No	Yes	Yes	Yes
Nazari (2022) [17]	Yes	No	No	No	Yes	Yes	Yes
Nazari (2019) [15]	Yes	No	No	No	Yes	Yes	Yes
Zamaniyan (2020) [19]	Yes	No	Yes	No	Yes	Yes	Yes
Obidniak (2017) [20]	Yes	No	No	No	Yes	Yes	Yes

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, fixed, 95% CI
1.2.1 RIF						
Nazari 2019a	26	49	13	48	16.2%	1.96 (1.15, 3.34)
Nazari 2021	101	196	49	197	60.4%	2.07 (1.57, 2.74)
Zamaniyan 2020	20	55	10	43	13.9%	1.56 (0.82, 2.98)
Subtotal (95% CI)		**300**		**288**	**90.5%**	**1.97 (1.57, 2.48)**
Total events	147		72			
Heterogeneity: $\chi^2 = 0.62$, df = 2 (p = 0.73); $I^2 = 0\%$						
Test for overall effect: Z = 5.79 (p < 0.00001)						
1.2.2 Thin endometrium						
Eftekhar 2018	14	40	8	43	9.5%	1.88 (0.88, 4.00)
Subtotal (95% CI)		**40**		**43**	**9.5%**	**1.88 (0.88, 4.00)**
Total events	14		8			
Heterogeneity: not applicable						
Test for overall effect: Z = 1.64 (p = 0.10)						
Total (95% CI)		**340**		**331**	**100.0%**	**1.96 (1.58, 2.45)**
Total events	161		80			
Heterogeneity: $\chi^2 = 0.63$, df = 3 (p = 0.89); $I^2 = 0\%$						
Test for overall effect: Z = 6.01 (p < 0.00001)						
Test for subgroup differences: $\chi^2 = 0.01$, df = 1 (p = 0.91); $I^2 = 0\%$						



▶ **Fig. 3** Forest plot diagram showing the chemical pregnancy rate in women who received intrauterine platelet-rich plasma versus controls regarding population type (recurrent implantation failure (RIF), and thin endometrium). CI = confidence intervals.

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, fixed, 95% CI
Eftekhar 2018	3	40	2	43	23.6%	1.61 (0.28, 9.16)
Nazari 2022	4	20	4	20	48.9%	1.00 (0.29, 3.45)
Zamaniyan 2020	1	55	2	43	27.5%	0.39 (0.04, 4.17)
Total (95% CI)		**115**		**106**	**100.0%**	**0.98 (0.39, 2.42)**
Total events	8		8			
Heterogeneity: $\chi^2 = 0.90$, df = 2 (p = 0.64); $I^2 = 0\%$						
Test for overall effect: Z = 0.05 (p = 0.96)						



▶ **Fig. 4** Forest plot diagram showing the miscarriage rate in women who received intrauterine platelet-rich plasma versus controls. CI = confidence intervals.

Implantation rate

Only one of the included studies [19] reported data on the implantation rate. A statistically significant increase in the implantation rate was noted in the PRP group as compared with the control group (RR: 3.27; 95% CI: 1.42–7.52; P = 0.005; ▶ **Fig. 5**).

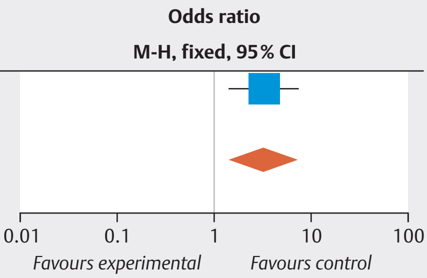
Live birth rate

Two studies [17, 18] including 433 patients reported data on the live birth rate. Heterogeneity was not examined ($I^2 = 0\%$ and P = 1.00). A pooled analysis with the fixed-effects model demonstrated a statistically significant increase in the live birth rate in the

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M-H, fixed, 95% CI
Zamaniyan 2020	35	55	15	43	100.0%	3.27 (1.42, 7.52)
Total (95% CI)		**55**		**43**	**100.0%**	**3.27 (1,42, 7.52)**
Total events	35		15			

Heterogeneity: not applicable

Test for overall effect: Z = 2.78 (p = 0.005)

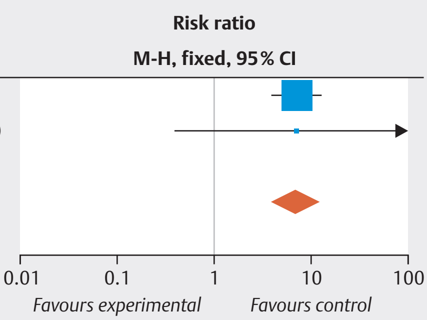


▶ **Fig. 5** Forest plot diagram showing the implantation rate in women who received intrauterine platelet-rich plasma versus controls. CI = confidence intervals.

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, fixed, 95% CI
Nazari 2021	77	196	11	197	95.6%	7.04 (3.86, 12.82)
Zamaniyan 2020	3	20	0	20	4.4%	7.00 (0.38, 127.32)
Total (95% CI)		**216**		**217**	**100.0%**	**7.03 (3.91, 12.66)**
Total events	80		11			

Heterogeneity: $\chi^2 = 0.00$, df = 1 (p = 1.00); $I^2 = 0\%$

Test for overall effect: Z = 6.51 (p < 0.00001)



▶ **Fig. 6** Forest plot diagram showing the live birth rate in women who received intrauterine platelet-rich plasma versus controls. CI = confidence intervals.

PRP group as compared with the control group (RR: 7.03; 95% CI: 3.91–12.6; P < 0.00001; ▶ **Fig. 6**).

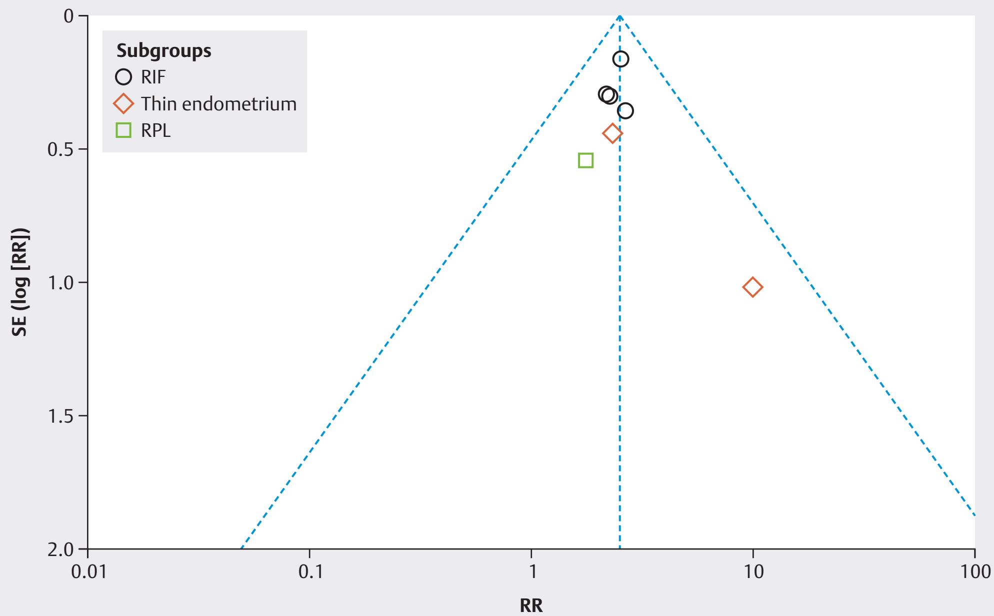
Publication Bias

A funnel plot was applied to qualitatively evaluate the publication bias. The funnel plot presented in ▶ **Fig. 7** is symmetrical, indicating that there was no publication bias among the included studies.

Discussion

Previous studies have reported that RIF or RPL may be caused by many factors, including poor endometrial receptivity, anatomic abnormalities, immune factors, endometrial thinning, embryonic quality, and infectious and genetic diseases [3, 21]. Moreover, previous meta-analyses have assessed the effects of PRP infusion in women undergoing treatment with ART [6]. However, the clinical reliability of those meta-analyses is uncertain because of the different article types (three RCTs and four cohort studies), which has increased the risk of bias. RCTs are generally considered the best approach for evaluating the effects of a treatment. In the present meta-analysis, we screened seven RCTs to evaluate the effectiveness of intrauterine infusion of PRP in women undergoing frozen–thawed embryo transfer. The results of our meta-analysis are partially consistent with those of a previous study [6]. We found that the treatment group had an improved clinical pregnancy rate, chemical pregnancy rate, live birth rate, and endometrial thickness as compared with the control group. Furthermore, our subgroup analyses specifically evaluated the effects of different PRP doses on the various outcomes of the patients undergoing treatment with ART. Our data showed that when PRP was administered at a dose of ≤ 0.5 ml or ≥ 1 ml, the clinical pregnancy rate was significantly higher in the treatment group than in the control group. However, the results related to the clinical efficacy of the possible PRP dose response are ambiguous, which may be attributable to differences in the PRP preparation methods.

An optimal endometrial status is important for correct implantation, subsequent embryonic development, and successful pregnancy. An endometrium is considered thin when its thickness is < 7 mm. A thin endometrium is associated with a reduced possibility of pregnancy through IVF [10, 22]. Intrauterine infusion of PRP is a novel approach that was first used in 2015 in the field of infertility for promoting endometrial growth [9]. Chang et al. reported that the intrauterine infusion of autologous PRP can increase the endometrial thickness and improve the pregnancy outcomes of women with inadequate endometrial growth [9]. Similarly, our



▶ **Fig. 7** Funnel plot of publication bias analysis.

study indicated that PRP therapy may be successful in improving the pregnancy outcomes of patients with a thin endometrium. Furthermore, Eftekhar et al. reported that the endometrial thickness increased significantly from 6.09 mm to 8.67 mm in the PRP group and from 6.15 mm to 8.04 mm in the control group [14]. Kusumi et al. recently reported that some patients became pregnant although their endometrium was not receptive to PRP treatment [23]. This indicates that PRP not only improves the endometrial thickness but also enhances the endometrial quality. However, the exact molecular mechanism through which PRP therapy improves patients' pregnancy outcomes remains unclear. The improvement of endometrial thickness and receptivity is the most accepted theory explaining the positive effects of PRP.

The endometrium starts becoming receptive during the middle-secretory phase of the 19th–23rd days of each IVF cycle; this is defined as the implantation window. Furthermore, GFs, interleukins, cytokines, prostaglandins, and adhesion molecules are expressed throughout the implantation window, and impairment of these agents can decrease the chances of implantation and pregnancy [24]. Indeed, PRP is a plasma fraction of autologous blood with a platelet concentration that is 4–5× greater than that normally contained in whole blood. PRP contains significant concentrations of GFs and cytokines such as vascular endothelial GF, PDGF, TGF, interleukin (IL)-6, and IL-8 [9, 25]. Various cytokine receptors for PDGF, TGF, and PDGF in the human endometrium are considered to promote endometrial tissue healing, play a role in paracrine and autocrine signaling, and be related to endometrial receptivity and embryo implantation and development [26, 27]. Furthermore, the stimulating, proliferation-inducing, and tissue regenerative effects of PRP have been explored in various areas of medicine, including osteoarthritis, ocular epithelial defects, dental disorders, and wound healing [28, 29]. Accordingly, we speculate that the intrauterine infusion of PRP stimulates cell proliferation and regeneration, enhances endometrial receptivity, and promotes implantation.

Although intrauterine infusion of autologous PRP is a novel technique, it is cost-effective and easily accessible for women with a refractory endometrium. However, data on the safety of intrauterine infusion of PRP and research on the possible adverse effects of this therapy on pregnancy-related outcomes are limited. Thus, this issue should be addressed in future studies.

Our study has some strengths. First, our meta-analysis focused on quantitatively evaluating the efficacy of intrauterine infusion of autologous PRP in women undergoing treatment with ART. Second, our meta-analysis involved a rigorous search strategy and included only those studies with a prospective RCT design. Third, all of the included studies were of high quality. Finally, the funnel plot showed no significant asymmetry, indicating the lack of publication bias across the included studies.

However, our study has some limitations as well. First, most of our research was performed in Iran, and our findings may thus not be generalizable to other populations. Furthermore, four of the seven studies were performed by the same first author and their colleagues; this may considerably affect the judgment of the meta-analysis results because there is not only geographical bias but also a great risk of personal systematic bias (for example, all four studies conducted by Nazari et al. used 0.5 ml of PRP). Second, our meta-analysis included only seven RCTs with small numbers of patients. Third, subgroup analyses were not performed for some outcomes because of the limited number of the studies included; therefore, we could not determine the source of heterogeneity. Fourth, only those RCTs published in English were included;

thus, relevant studies in other languages may have been missed, which may have introduced a language bias. Fifth, to produce consistent and accurate results, a standardized PRP preparation scheme is needed. Finally, although all of the included studies were RCTs, some did not adequately describe the randomization methods, allocation concealment, blinding procedures, or missing data, thus conferring high risks of publication, selection, and reporting biases. Therefore, large, well-designed, and multi-center RCTs are warranted to obtain further evidence.

In conclusion, despite the aforementioned limitations of this meta-analysis, our results suggest that the intrauterine infusion of PRP increases the clinical pregnancy rate, chemical pregnancy rate, live birth rate, and implantation rate among women with thin endometrium and recurrent implantation failure (RIF) undergoing treatment with ART. However, these findings need to be verified through larger, more elegantly designed RCTs.

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Contributors' Statement

HSF and JZS conceived and designed the study. HSF and TQQ conducted the data searches. SFH and JZS performed the analysis, wrote and revised the manuscript. TQQ gave the final approval of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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