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Systematic Review

Effect of Autologous Platelet-Rich Plasma Therapy on the Pregnancy Outcomes of Women with Repeated Implantation Failure: A Systematic Review and Meta-Analysis

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Abstract

Background: A major challenge in reproductive medicine is repeated implantation failure (RIF). Possible benefits of platelet-rich plasma (PRP) for pregnancy outcomes are still uncertain, and more evidence is required to properly evaluate this. The current meta-analysis was therefore carried out to assess the impact of intrauterine PRP infusion on pregnancy outcomes in women with RIF. **Methods**: Various databases (Web of Science, PubMed, Cochrane Library, Embase) were screened for English-language papers that investigated the effect of PRP treatment on pregnancy outcomes in RIF women who underwent *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI). This effect was analyzed in both frozen-thawed and fresh cycles. These studies involved randomized controlled trial (RCT) and quasi-experimental (non-randomized experimental) studies, but excluded case-control, case series, self-control, cross-sectional studies. The Newcastle-Ottawa Scale was employed to determine study quality. Risk ratios (RRs) were calculated for dichotomous outcome variables, and weighted mean difference (WMD) with 95% confidence interval (95% CI) for continuous outcome variables. These were performed under fixed- or random-effect models. **Results**: This meta-analysis evaluated 15 articles from the literature. Improved pregnancy outcomes were observed in RIF women who received PRP, including higher rates of implantation, clinical pregnancy and live birth compared to control patients. **Conclusions**: The results of this study indicate that PRP could be a useful treatment strategy for RIF patients and those with a thin endometrium. Additional large RCTs are required to identify the subpopulation of women who could derive the maximum benefit from PRP.

Keywords: repeated implantation failure; platelet-rich plasma; clinical pregnancy rate; meta-analysis

1. Introduction

Assisted reproductive technology (ART) including *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) have proven to be effective options for infertile couples. Although ART has resulted in major clinical and scientific progress, repeated implantation failure (RIF) remains an emotionally and physically challenging problem for infertile couples and clinicians. The definition of RIF varies, but typically it means failure to achieve clinical pregnancy after transfer of >3 good-quality embryos in >2 fresh or frozen cycles in women aged <40 years [1]. Possible reasons for RIF include impaired endometrial receptivity, immune factors, poor embryo quality, and mismatched coordination between the developing fetus and endometrium. The main factor besides embryo-related causes is impaired endometrial receptivity.

Platelet-rich plasma (PRP) is concentrated PRP protein derived from whole blood and with a 4–5-fold higher concentration of platelets compared to normal [2]. The alpha granules in platelets contain a mixture of proteins that become bioactive in PRP. Intrauterine PRP infusion of PRP is reported to enhance endometrial growth and improve embryo acceptance. Platelet granules are known to contain various factors including interleukin 8 (IL-8), transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) that promote cellular differentiation, proliferation and migration [3,4]. Chang *et al.* [5] in 2015 first reported intrauterine PRP infusion for women with a thin endometrium. More recent work has investigated PRP effects in patients with RIF. Several authors have found that PRP may improve rates of implantation and clinical pregnancy in these women [6–8]. However, there is still no consensus regarding the effect of PRP infusion on pregnancy outcomes in RIF patients.

In this systematic review and meta-analysis, we therefore evaluated whether intrauterine PRP infusion improves clinical pregnancy outcomes in RIF patients.

2. Methods

2.1 Protocol, Information Sources, and Strategy for Literature Search

The present systematic review was carried out as recommended by the Cochrane guidelines and the Pre-

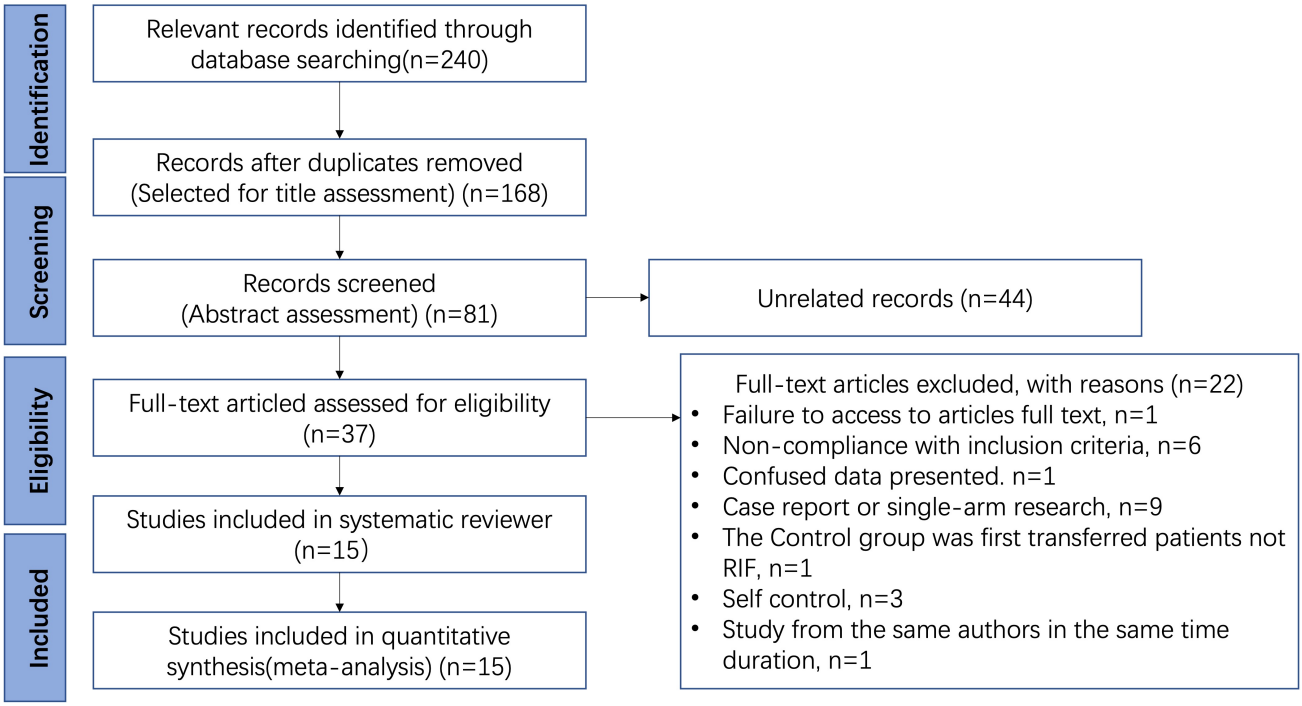

Fig. 1. Study selection. RIF, repeated implantation failure.

ferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [9]. Databases used in this search were: Cochrane Library, MEDLINE, PubMed, Web of Science, Google Scholar, and Embase. Articles published in English from the beginning of the database to January 2023 were identified with the following search terms as words in the title or abstract: "*In Vitro* Fertilization" or "IVF" or "Intracytoplasmic sperm injection" or "ICSI" or "Embryo transfer" and "Platelet-rich plasma" or "Platelet rich plasma" or "PRP" and "Repeated Implantation Failure" or "Recurrent implantation failure" or "RIF". In addition, references from candidate articles and reviews were manually searched for further relevant reports.

2.2 Outcome Measures, Study Selection, and Data Extraction

Selected articles reported one or more of these outcomes: rate of clinical pregnancy, rate of live birth, rate of miscarriage, rate of chemical pregnancy, and endometrial thickness. Randomized controlled trials (RCTs) as well as quasi-experimental studies were assessed. After searching the database by keywords, two authors (TTM and YP) separately checked the abstract of studies. Extraction of data was carried out independently by two authors (TTM and YP) using full-text copies of relevant papers.

2.3 Inclusion and Exclusion Criteria for This Review

Studies were included in our review if they fulfilled the following criteria: (1) the study was a RCT, quasi-experimental and cohort study in which medically confirmed pregnancy outcomes were the endpoints; (2) the intervention was IU infusion of PRP around the time of embryo transfer; (3) the population were diagnosed as having had an RIF; (4) the control group was any other active intervention, no intervention or placebo. Studies were excluded if those were case-control, case series, self-control, cross-sectional. Also, we excluded studies if we were unable to obtain adequate details of the study methodology or results.

2.4 Risk of Bias and Data Synthesis

RevMan 5.3 (Cochrane Collaboration, Oxford, UK) was used to assess bias. These were deemed low, unclear risk, or high bias according to the following: allocation concealment, random sequence generation, blinding, selective reporting, incomplete outcome data, and other types of bias. The quality of cohort studies was evaluated with the Newcastle–Ottawa scaling system. A specific judgment was also made with regard to the following: study group selection, group comparability, and measurement of exposures and outcomes. Table 1 (Ref. [6,8,10–22]) lists the studies evaluated in this review.

Data was analyzed using RevMan 5.3 (Cochrane Collaboration, Oxford, UK). PRP treatment effects on the outcomes were evaluated using pooled risk ratios (RRs) with 95% confidence interval (95% CI). In the absence of heterogeneity, RRs were estimated with the Mantel–Haenszel fixed effects model. Otherwise, a random effects model was used. The heterogeneity between studies was assessed statistically with Cochran's Q-test, with $I^2 > 50\%$ indicating significant heterogeneity. Subgroup analysis was performed to determine the effect of PRP on pregnancy outcome in relation to the study design (i.e., RCT *vs.* cohort) as a cause of any heterogeneity. The robustness of pooled

Table 1. Major details of the included studies.

No.	Author, Year	Study type	Country	Study period	Age (years)	Blinded	No. of patients	Embryo stage	Blood volume (mL)	Comparison	Outcomes
1	Allahveisi *et al*., 2020 [11]	RCT	Iran	2018–2019	<40	not given	50	blastocyst	35	PRP/Control	CPR, IR, ET
2	Dawood *et al*., 2022 [12]	RCT	Egypt	2018.12–2021.10	20–35	open label	104	blastocyst	15	PRP/Control	CPR, IR, BCPR, ET
3	Ershadi *et al*., 2022 [13]	RCT	Iran	since 2019	<40	not given	85	cleavage embryo	8	PRP/Control	CPR, BCPR, IR, SAR, ET
4	Nazari *et al*., 2020 [14]	RCT	Iran	2016–2017	not given	not given	138	blastocyst	8.5	PRP/Control	CPR, BCPR
5	Nazari *et al*., 2022 [6]	RCT	Iran	2018–2020	18–38	not given	418	blastocyst	8.5	PRP/Control	BCPR, CPR, LBR, SAR, ET
6	Obidniak *et al*., 2017 [8]	RCT	Russia	not given	28–39	open label	90	not given	not given	PRP/Control	CPR, IR
7	Safdarian *et al*., 2022 [15]	RCT	Iran	2017.10–2020.4	20–40	not given	120	blastocyst	8.5	PRP/Control	CPR, BCPR, IR, LBR, OGR
8	Zamaniyan *et al*., 2021 [16]	RCT	Iran	2016.2–2019.1	20–40	blind	120	blastocyst	17.5	PRP/Control	CPR, OGR, SAR
9	Zargar *et al*., 2021 [17]	RCT	Iran	not given	<41	single blind	80	cleavage embryo	8.5	PRP/Control	CPR, BCPR, LBR, SAR
10	Coksuer *et al*., 2019 [18]	retrospective cohort	Turkey	2014.1–2017.1	21–39	not given	273	blastocyst	8	PRP/Control	CPR, BCPR, SAR
11	Mehrafza *et al*., 2019 [19]	retrospective cohort	Iran	2016–2017	not given	not given	123	both	8.5	PRP/GCSF	CPR, IR, BCPR,
12	Tehraninejad *et al*., 2021 [20]	Non-RCT	Iran	2016–2018	<35	not given	85	blastocyst	10	PRP/Control	CPR, BCPR, OGR
13	Noushin *et al*., 2021 [10]	prospective cohort	UK	2019.5–2020.5	<40	not given	318	cleavage embryo	10	PRP/Control	CPR, BCPR, LBR, SAR
14	Xu *et al*., 2022 [21]	retrospective cohort	China	2019.1–2021.1	23–40	not given	410	both	20	PRP/Control	CPR, IR, BCPR, LBR, SAR, ET
15	Yuan *et al*., 2022 [22]	retrospective cohort	China	2019–2021	25–40	not given	64	cleavage embryo	8.5	PRP/Control	CPR, IR

RCT, randomized controlled trial; PRP, platelet-rich plasma; CPR, clinical pregnancy rate; IR, implantation rate; ET, endometrial thickness; BCPR, biochemical pregnancy rate; SAR, sponteneous abortion rate; LBR, live birth rate; OGR, ongoing pregnancy rate; GCSF, granulocyte colony stimulating factor.

estimates was examined by sensitivity analysis. Egger's test and the visual analysis of funnel plots were used to estimate possible publication bias when >10 trials were evaluated.

3. Results

3.1 Study Selection

In all, 240 potentially relevant articles were found in the databases using the search strategy. Following removal of duplicates, the 168 remaining studies underwent title evaluation, leaving 81 possibly relevant studies for further assessment of the abstract. One study was presented in abstract form only (conference paper) and was excluded from the analysis because it contained insufficient data. Six papers were non-compliant for the inclusion criteria. Nine papers were case series, case reports, and single-arm research. One study was excluded because the control patients were patients from the first time of embryo transfer, rather than RIF. Three studies were excluded because the control group were self-control. One study was excluded because the researcher had published another study which included patients from the same institute at the same time duration. Finally, 15 articles meeting the inclusion criteria were further evaluated. A flowchart of the study selection and inclusion processes is shown below (Fig. 1).

3.2 Details of Included Studies and Quality Assessment

Table 1 lists the major details for the 15 studies evaluated in this review. These were published between 2017 and 2022. Nine of the papers reported RCTs and 6 were cohort studies. Overall, the 15 studies included 2478 women aged between 20–41 years. All women in the PRP and control patients were RIF. Sample size for each study ranged from 50 to 418 women. The volume of peripheral blood for the preparation of PRP ranged from 8 mL to 35 mL. Embryo transfer was "cleavage stage" in 4 studies, "blastocyst stage" in 8 studies, both cleavage and blastocyst stages in two studies, and in one study the stage was not given. One study compared PRP administered to the sub-endometrial (SE-PRP) or endometrial surface (intrauterine, IU-PRP) with the control group. This found there was no advantage of SE-PRP compared to the less invasive IU-PRP. SE-PRP cannot be administered during the index cycle of FET preparation because it is invasive and risks damaging the growing endometrium [10]. Twelve studies transferred the embryo only in frozen-thawed cycles, two in fresh condition [8,22], and one in both fresh and frozen condition [17]. One study compared PRP administration with that of granulocyte colony stimulating factor (GCSF) [19], whereas all others used untreated controls. The risk of bias for nine RCTs is shown in Fig. 2. The quality of the six cohort studies was assessed using the Newcastle-Ottawa Scale (NOS). Four cohort studies scored 7, and two cohort studies scored 8. The quality of the literature was high.

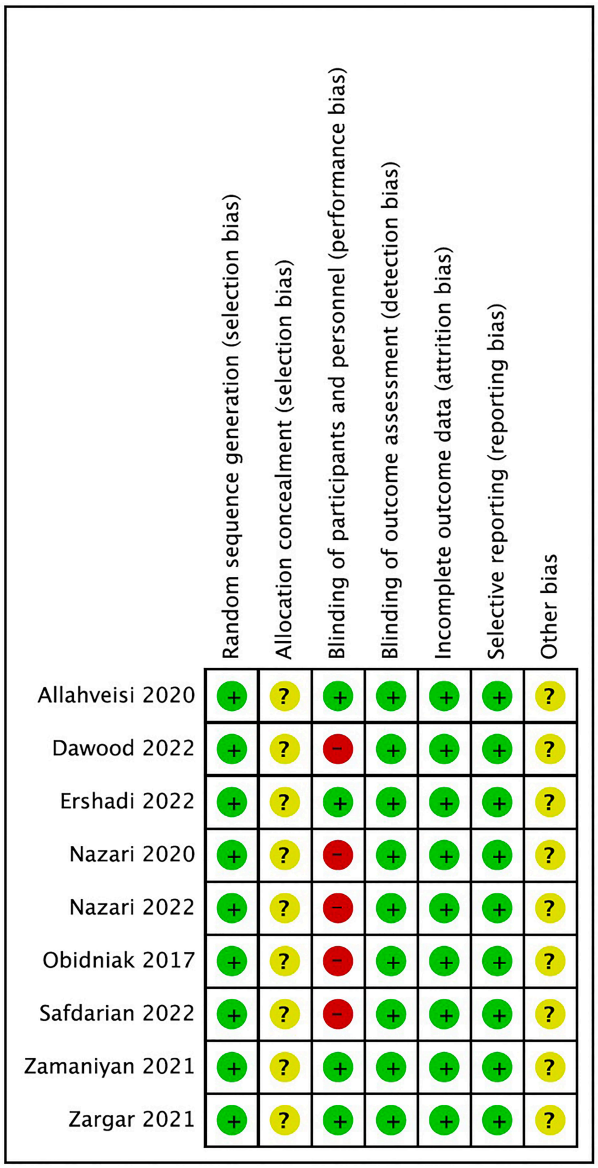

Fig. 2. Summary of risk of bias for randomized controlled trials.

3.3 Clinical Results

3.3.1 Rate of Clinical Pregnancy

Meta-analysis of results from 14 studies was carried out to estimate the impact of PRP on the rate of clinical pregnancy [6,8,10,11,13–22]. When considering only the 8 RCTs [6,8,11,13–17], a significant improvement in pregnancy was seen for PRP patients compared to control patients (risk ratios (RR) = 2.02, 95% CI: 1.56–2.61, $p < 0.00001$) (Fig. 3). Analysis of the study heterogeneity revealed an I^2 value of 31%, indicating the absence of significant heterogeneity. When the 8 RCTs were considered together with the 6 non-RCT studies [10,18–22], a similar improvement in pregnancy was observed in PRP patients (RR = 1.78, 95% CI: 1.51–2.1, $p < 0.00001$) (Fig. 4). No significant heterogeneity was observed between studies ($p = 0.18$; $I^2 = 26\%$) (Fig. 3).

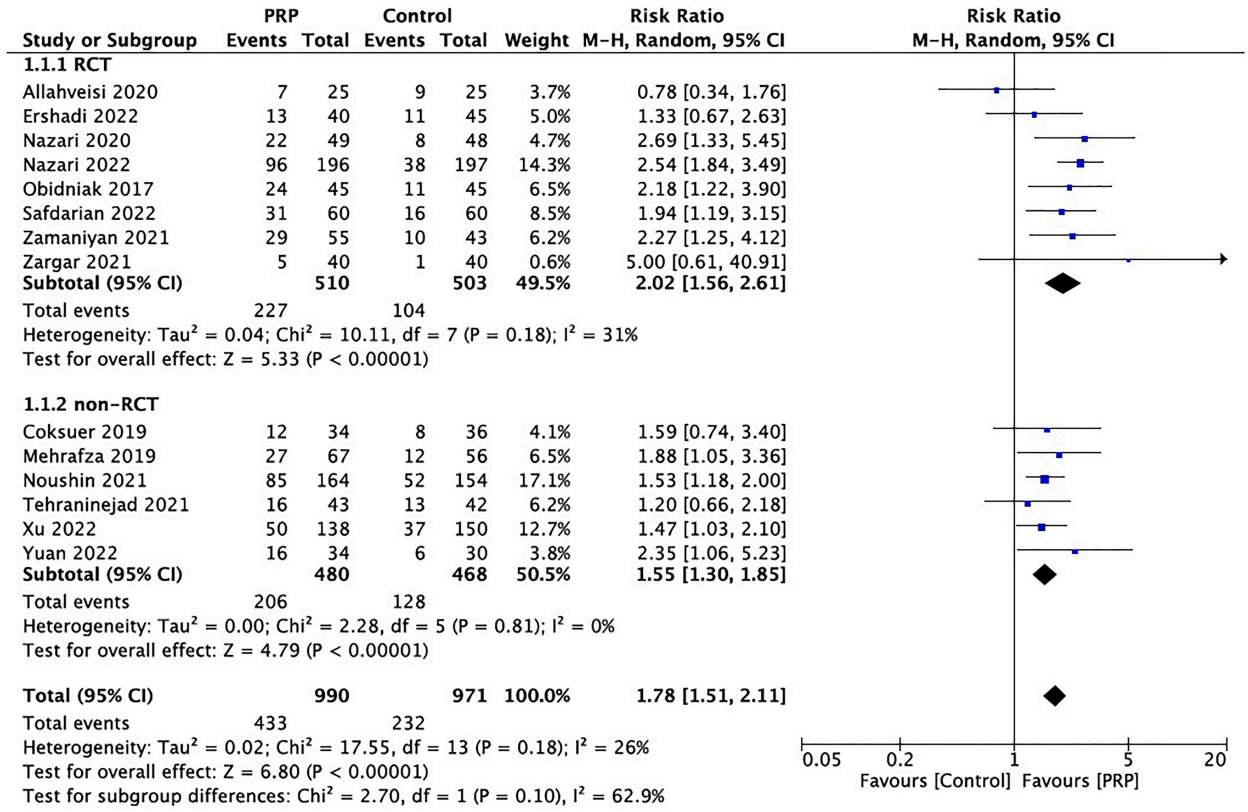

Fig. 3. Forest plot showing risk ratios (RRs) and 95% confidence interval (95% CI) for clinical pregnancy in RCT and non-RCT studies. M-H, Mantel-Haenszel.

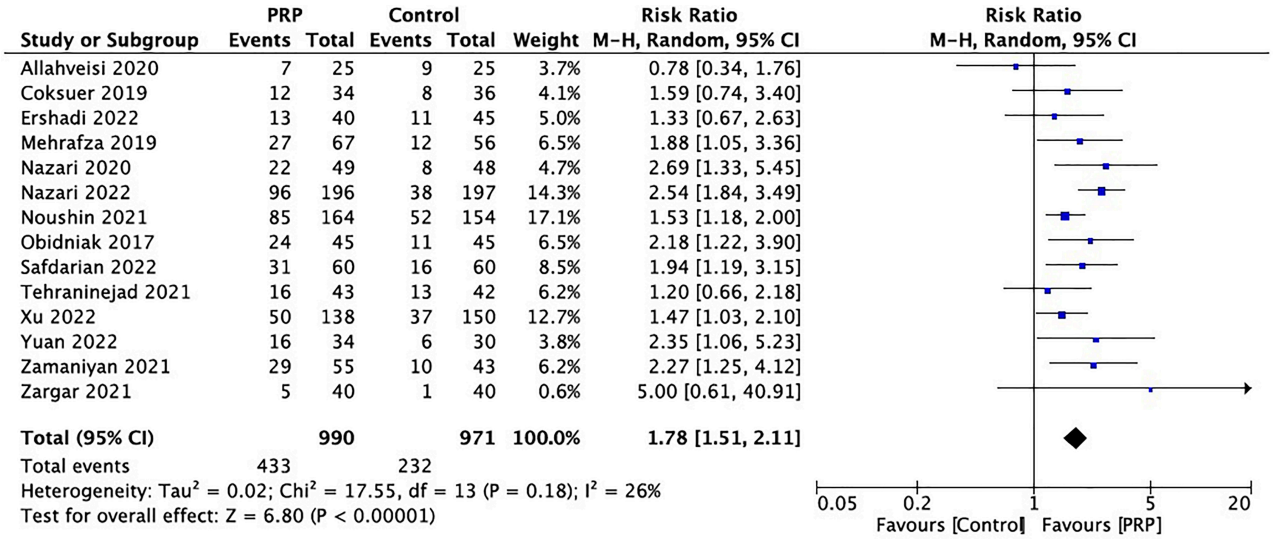

Fig. 4. Forest plot showing RRs and 95% confidence interval (95% CI) for clinical pregnancy. M-H, Mantel-Haenszel.

3.3.2 Rate of Live Birth

Four papers reported the rate of live birth [6,11,17,21]. These included 811 RIF women, of whom 399 were PRP patients and 412 were control patients. A random-effects model (Fig. 5) revealed no significant difference in the live birth rate between the two patient groups (RR = 2.62, 95% CI: 0.87–7.92, $p = 0.09$). Moreover, an I^2 of 87% was found for this analysis. This indicates considerable study heterogeneity, probably because of the relatively small sizes.

3.3.3 Rate of Implantation

Four papers reported the rate of implantation [15,19,21,22]. As shown in Fig. 6, a highly significant difference was found between PRP and control patients (RR = 1.79, 95% CI: 1.39–2.29, $p < 0.00001$), with no heterogeneity between studies ($p = 0.48$; $I^2 = 0\%$).

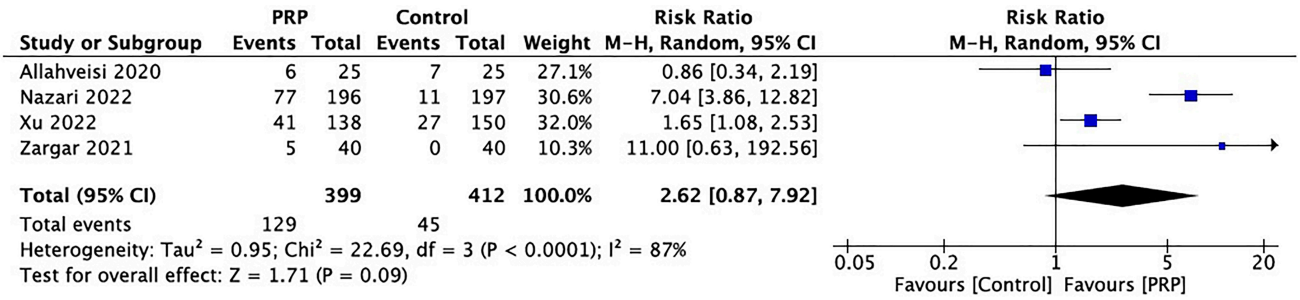

Fig. 5. Forest plot showing individual and combined effect size estimates and 95% CI in studies reporting rate of live birth in RIF patients.

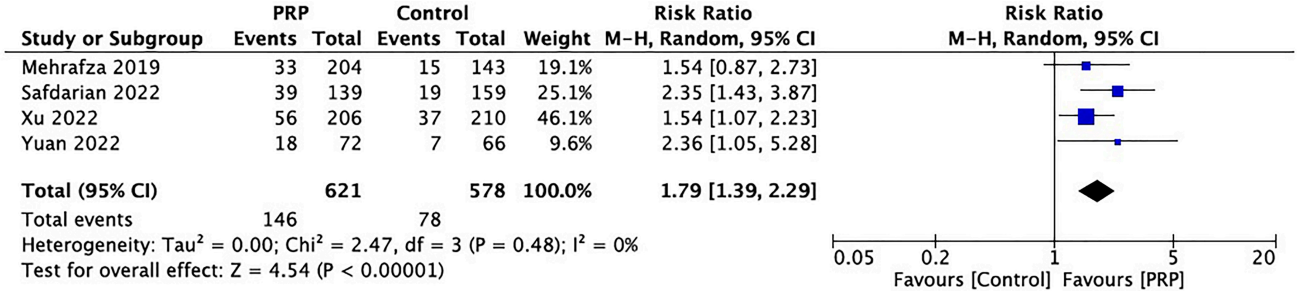

Fig. 6. Forest plot showing individual and combined effect size estimates and 95% CI in studies assessing rate of implantation in RIF patients.

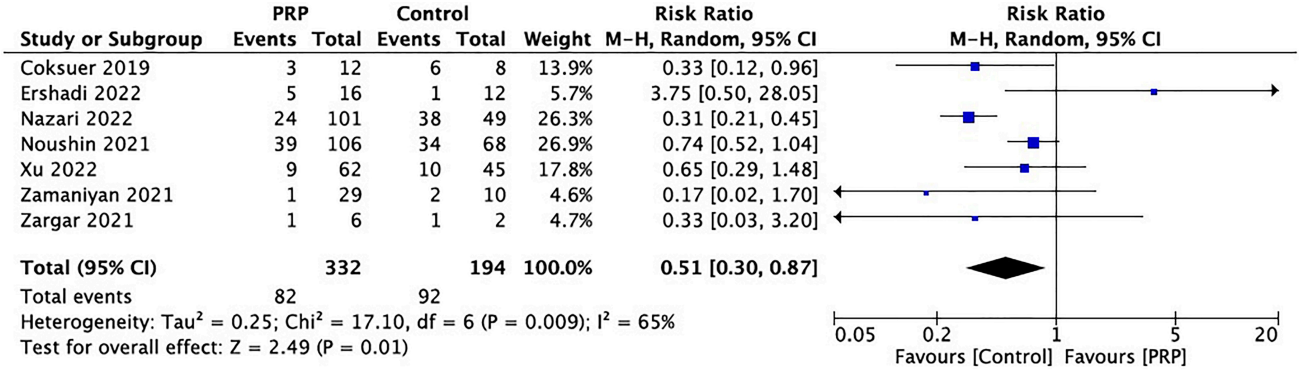

Fig. 7. Forest plot showing individual and combined effect size estimates and 95% CI in studies assessing spontaneous abortion in RIF women.

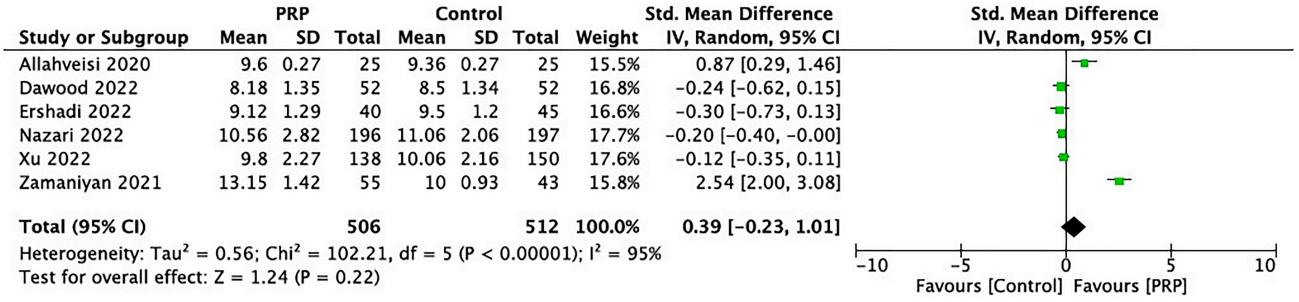

Fig. 8. Forest plot showing individual and combined effect size estimates and 95% CI in studies reporting standardized mean differences for endometrial thickness in RIF patients. SD, standard deviation; IV, Inverse-Variance Weighted.

3.3.4 Spontaneous Abortion Rate

Seven studies reported the spontaneous abortion rate [6,10,13,16,18,21]. As shown in Fig. 7, a significant difference in spontaneous abortion was found between PRP and control patients (RR = 0.51, 95% CI: 0.30–0.81; I^2 = 65%).

3.3.5 Endometrial Thickness

Six studies reported changes to endometrial thickness after PRP treatment [11,13,16,17,21,23]. These included a total of 506 cases and 512 controls. As shown in Fig. 8, endometrial thickness in RIF patients treated with PRP was greater than in the controls (standardized mean difference (SMD): 0.39, 95% CI: –0.23 to 1.1; $p = 0.22$, $I^2 = 95\%$).

4. Discussion

This systematic review assessed studies of PRP intervention aimed at improving pregnancy outcomes in RIF women. Our evaluation revealed significantly higher rates of implantation, clinical pregnancy, implantation, and endometrial thickness in women who received intrauterine PRP administration versus controls. Endometrial thickness was also improved by PRP treatment. Positive effects of PRP therapy were reported in almost all studies included in this meta-analysis, including higher rates of clinical pregnancy and live birth, and lower rates of implantation failure and miscarriage. This study also updates earlier systematic reviews with larger sizes [24–27]. The increased rates of live births and biochemical, clinical and ongoing pregnancies found in the present analysis of PRP-treated RIF women concurs with the findings of the previous reviews. RCTs are usually considered to be more convincing than cohort ones owing to the former's objectivity. Involving studies that included nine RCTs and six cohort studies also made this meta-analysis more objective and convincing after subgroup analysis. Two studies involved some participants undergoing a fresh embryo transfer [8,22], and one study involved both fresh and frozen-thawed transfer [17]. Therefore, we did not extract them from the statistics to conduct a subgroup analysis.

The statistical measure of homogeneity, was low across all pregnancy endpoints, which suggests consistent effects throughout the studies. The first meta-analysis reported by Maleki-Hajiagha *et al*. [27] in 2020 found that IU-PRP increased the rate of clinical pregnancy in the FET cycle, thereby supporting current observations. The meta-analysis by Maleki-Hajiagha *et al*. [27] included 3 RCTs and 4 cohort studies, with significant heterogeneity observed between the studies. As another previous meta-analysis [24,25] also proved that the IU-PRP has a positive effect on the pregnancy results for RIF patients, additional large RCTs on the regular use of PRP in RIF women are warranted in order to provide more conclusive results. More carefully designed studies are also required to confirm the impact of IU-PRP in RIF patients.

Platelet-rich plasma is a platelet concentrate obtained by centrifugation. PRP is an inexpensive way to deliver high concentrations of VEGF, TGF-β, and PDGF through the release of platelet alpha granules [28]. Platelet bioactivity is one of several factors involved in determining endometrial receptivity, together with the embryo itself and various cytokine, growth factor, hormone, proteomic, metabolomic, genomic, and transcriptomic factors [29].

Several limitations should be considered in the present meta-analysis. Firstly, most of the studies were from only a few countries and ethnic groups, thus making it difficult to generalize the findings. Strengths of the meta-analysis include the homogeneity of pooled indices across studies, as well as the robustness to sensitivity and subgroup analysis, as included studies from different embryo transfer cycles and embryo types. First, only a limited number of relevant studies with high-quality evidence, which included studies (n = 14) and the fact that only 8 RCT compared PRP with placebo, were available for analysis. Although we conducted comprehensive and time-consuming literature searches to identify all relevant studies, we cannot exclude the possibility that publication bias might have affected our results.

5. Conclusions

Our systematic review and meta-analysis suggest that intrauterine administration of autologous PRP treatment can improve implantation, clinical pregnancy, and live birth in RIF patients. But, comprehensive data regarding complications, and adverse pregnancy outcomes was not available, so, we are not able to provide conclusive results. Further large, multicenter RCTs with a double-blind design are required to accurately ascertain the effectiveness of PRP in these patients.

Availability of Data and Materials

All data points generated or analyzed during this study are included in this article and there are no further underlying data necessary to reproduce the results.

Author Contributions

TTM and YP Performed the literature search and performed the extraction of data. TTM performed the risk of bias assessment. YP performed the statistical analysis. Both authors contributed to the writing of the manuscript. Both authors have read and agreed to the published version of the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.ceog5102048.

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