CELLULAR THERAPY AND REGENERATIVE MEDICINE

Review

Platelet rich plasma for assisted reproduction: an overview of systematic reviews

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Background - In recent years, platelet-rich plasma (PRP) has been used to improve endometrial receptivity in infertile women undergoing assisted reproduction. This article aims to review the literature and critically appraise the available evidence regarding the efficacy of PRP for assisted reproduction.
Materials and methods - An overview of systematic reviews (SRs) (umbrella review) of PRP use for assisted reproduction. The methodological quality of the SRs was assessed using the AMSTAR-2 checklist; quality of the evidence from the trials included in each SR was appraised following the GRADE approach.
Results - Twenty-five SRs published between 2020 and 2024 were included in this overview. The SRs reported data from 306 overlapping reports based on 112 individual primary studies. The overlap among primary studies was slight across all reports included (CCA index 1.9%). With the AMSTAR 2 tool, the SRs showed only some non-critical weakness, but no critical flaws. Thus, confidence in the results of the SRs can be considered high or moderate. Clinical pregnancy rate was reported in 17 SRs, chemical pregnancy in 8, implantation rate in 8, and live birth rate in 16 SRs. Almost uniformly the SRs showed increased rates of positive outcomes in PRP recipients compared to controls (from very low to high certainty of evidence). Miscarriage rate, ectopic pregnancy and multiple pregnancy, reported in some of the SRs, resulted uncertainty about the effect of PRP infusion compared with no intervention on these outcomes (no statistically significant differences between groups).
Discussion - The evidence from SRs shows beneficial effects of PRP compared to controls in terms of clinical and chemical pregnancy rates, implantation rates and live birth rates. The level of evidence varied from very low to high (more commonly low or moderate) in relation to methodological flaws and clinical heterogeneity of primary studies included in the SRs.

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Keywords: *platelet-rich plasma, umbrella review, systematic review, assisted reproduction technology, endometrial thickness.*

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INTRODUCTION

Platelet-rich plasma (PRP) was first used in hematology in the 1970s to treat patients with thrombocytopenia and subsequently has been employed in a variety of clinical conditions,

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basing on its capacity of promoting cell recruitment, proliferation and angiogenesis, which may be implicated in tissue regeneration and healing[1-4].

PRP is a mixture of highly concentrated platelets and associated growth factors. It is obtained from whole blood through a two-phase centrifugation process: currently there are more than 40 commercial systems developed to concentrate autologous whole blood into a platelet-rich substance[5]. Besides platelets, PRP contains some inflammatory cells (i.e., monocytes and polymorphonuclear neutrophils) and large amounts of proteins, including platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), epithelial growth factor (EGF) and adhesion molecules (i.e., fibrin, fibronectin and vitronectin)[5-6]. Such growth factors and cells have been shown to promote cell recruitment, proliferation and angiogenesis, which may be implicated in tissue regeneration and healing[7-9]. Due to these biological regenerative properties, a number of investigators have studied the potential clinical benefit of PRP, also from human umbilical cord blood, in a wide array of conditions ranging from dermatologic disorders to oro-maxillofacial surgery and orthopedics[10-12].

More recently, PRP has begun to be used in fertility treatments in conjunction with assisted reproductive technologies such as IVF (*in vitro* fertilization) and IUI (intrauterine insemination) to enhance fertility outcomes and to improve embryo implantation rates. In women with low ovarian reserve, PRP was used to stimulate ovarian function and improve egg quality, and in men with conditions such as low sperm count or poor sperm motility, it can potentially improve sperm quality and function[13]. In women with a history of recurrent implantation failure (RIF), PRP seems to stimulate the growth of the endometrial lining, addressing the issue of inadequate thickness, which is crucial for embryo implantation, and when the cause of infertility remains unclear, PRP may be considered as a complementary treatment to improve overall reproductive health[13].

Implantation failure is considered a situation in which a woman undergoing assisted reproductive techniques (ART) fails to become pregnant, despite the transfer of high-quality embryos; since the pathophysiology of implantation failure is multifactorial, endometrial receptivity plays a pivotal role in this process[14]. A thin endometrium that does not respond to standard treatments is still a challenge in ART since successful embryo implantation requires a receptive endometrium and the minimum endometrial thickness required for embryo transfer is seven millimeters after the follicular phase[15]. For this reason, several strategies have been developed to treat thin endometrium, including the prolonged use of exogenous estrogen, the use of low-dose aspirin, vitamin E and vaginal sildenafil citrate, electro acupuncture, and the application of granulocyte colony-stimulating factor (G-CSF)[16].

Over the past decade, an increasing number of studies have reported an increase in endometrial thickness due to endometrial PRP infusion, consequently favoring embryo implantation and pregnancy outcomes[17-19]. Likewise, a number of controlled clinical trials have been conducted in order to evaluate the efficacy and safety of PRP in women with RIF or thin endometrium, and these primary studies have been the object of a variety of systematic reviews (SRs) and meta-analyses. Their conclusions are, however, quite inconsistent and reflect the wide heterogeneity between different studies in terms of design, conduct, and reporting. The current study is an overview of SRs, also called umbrella review[20-21], and is aimed to reappraise the validity of the conclusions of the SRs and meta-analyses of PRP in women undergoing assisted reproduction.

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MATERIALS AND METHODS

The protocol of this overview of reviews has been registered on the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42024564833. The results are reported according to the PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions[22].

Review question/objective

The aim of this umbrella review is to evaluate the efficacy and safety of PRP infusion in ART.

Inclusion and exclusion criteria

For inclusion in this overview, we considered SRs that comprised randomized controlled trials (RCTs) and

non-RCTs (i.e., prospective and retrospective comparative cohort studies, and non-comparative studies such as case-control studies and case-series) assessing the safety and efficacy of PRP in ART. Traditional reviews with no clear methodological approach were excluded from this umbrella review.

Clinical setting and participants

For this umbrella review, we considered SRs evaluating PRP therapy administered in women with diminished ovarian reserve (DOR), premature ovarian failure (POF), or premature ovarian insufficiency (POI), women with intrauterine adhesion and women with experience of RIF. RIF was defined as a failure to have a clinical pregnancy after at least 3 attempts of embryo transfer (ET) with high-quality embryos or 10 or more embryos in multiple transfers.

Intervention and outcomes

Participants were assessed before and after intra-ovarian injection of PRP or the application of PRP in the uterine cavity. Women 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). Treatment with PRP was compared to the control consisting of no intervention or placebo.

The SRs analyzed, reported one or more of the following outcomes: chemical and clinical pregnancy, multiple pregnancy, the rate of live birth, miscarriage, implantation rate and the endometrial thickness before and after infusion of PRP. Also, hormonal levels (Anti-Müllerian hormone [AMH], Follicle stimulating hormone [FSH], Luteinizing hormone [LH], Estradiol [E2]) and IVF parameters like antral follicle count, number of oocytes, and embryo count were reported. For this umbrella review, we considered the following outcomes: chemical pregnancy, clinical pregnancy, implantation rate, live birth, the number of embryo count and the adverse events.

Search strategy

The search was conducted from inception to April 2024 in the following databases: MEDLINE (through PubMed), medRxiv and bioRxiv, Embase, Epistemonikos, and Cochrane library. The searches were carried out without languages restriction using Medical Subjects Heading: ("Platelet rich plasma/PRP") AND ("systematic review" OR "meta-analysis") AND ("treatment" OR "therapy") AND ("assisted reproduction" OR "endometrial thickness" OR "recurrent implantation failure" OR "ovarian insufficiency"). Furthermore, we checked the reference lists of the most relevant manuscripts (original studies and reviews) to identify potentially eligible studies not captured by the electronic literature search.

Study selection and data extraction

Two assessors (MC and FM) screened all titles. Eligibility assessment was based on the title or abstract and on the full text if required. Both reviewers compared the articles identified. The two assessors also independently extracted quantitative and qualitative data from each selected study, with disagreements resolved through discussion and on the basis of the opinion of a third reviewer (IP). Findings are presented in tabular format with supporting text. Tabulation of results include: first author name and year of publication, clinical setting (e.g., implantation failures or ovarian insufficiency), number of RCTs and non-RCTs included in the SR, intervention and control group, outcomes and the main conclusion of the review as reported by Authors.

Assessment of methodological quality and overlap in systematic reviews

We used the AMSTAR-2 critical appraisal checklist for SRs, a tool that evaluates both quantitative and qualitative reviews[23]. The tool is suitable for reviews including randomised and non-randomised studies. It includes 16 domains (7 considered critical) relating to the research question, review design, search strategy, study selection, data extraction, justification for excluded studies, description of included studies, risk of bias, sources of funding, meta-analysis, heterogeneity, publication bias, and conflicts of interest. Two review authors (MC, FM) independently assessed the quality of evidence in the included reviews and the methodological quality of the SRs. We resolved discrepancies through discussion or, if needed, a third review author (IP). We did not exclude reviews based on AMSTAR 2 ratings, but considered the ratings in interpretation of our results. We rated overall

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confidence in the results of the review according to Shea *et al.*[24], as follows:

- high, no or one non-critical weakness;
- moderate, more than one non-critical weakness but no critical flaws;
- low, one critical flaw with or without non-critical weaknesses;
- critically low, more than one critical flaw with or without non-critical weaknesses.

Methods to describe and quantify the overlap in overviews of reviews have been described, and for the current overview, we have narratively discussed it and applied the corrected covered area (CCA) index, calculated as follows[25]:

$$CCA = k - r / r(c - r)$$

where k is the number of reports in reviews (sum of ticked boxes), r is the number of rows (index publications), and c is the number of columns (SRs included). Criteria for interpreting the overlap index are: slight (0-5%), moderate (6-10%), high (11-15%) or very high (>15%) overlap. The CCA was calculated across all reports included.

Summary of the evidence and appraisal of the quality of evidence

For the quantitative synthesis, we report the effect size [odds ratio (OR), risk ratio (RR), risk difference (RD), or standardized mean difference (SMD) with the 95% confidence intervals (CIs)] as reported in individual reviews, and their main conclusions.

The quality of evidence was appraised following the GRADE approach (Grades of Recommendation, Assessment, Development, and Evaluation)[26]. Whenever available, the grading of the quality of evidence reported in each SR was considered to define the quality of evidence. When the authors of the study did not report grading of evidence, the GRADE approach was applied based on the information available from the individual review. Studies can be downgraded for concerns over risk of bias, indirectness (applicability of the results to the question), inconsistency (heterogeneity between study results), imprecision (low number of studies and/or participants), and publication bias. The GRADE approach has four levels of certainty; very low (the true effect is probably markedly different from the estimated effect), low (the true effect might be markedly different from the estimated effect), moderate (the true effect is probably close to the estimated effect), and high (the true effect is similar to the estimated effect).

RESULTS

The electronic and manual search retrieved 99 references. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is reported in **Figure 1**.

At the first stage of screening titles and abstracts, 66 references were selected for eligibility, and the full text examined. After the full texts were examined concerning inclusion and exclusion criteria, 41 records were excluded (traditional reviews, SRs on other gynecology conditions). Finally, 25 SRs were included in the umbrella review[27-51]. We also excluded some SRs from the analysis after downloading them because of lacking quantitative data[52] or because they were not relevant to assisted reproduction[53-54].

Description of the studies

The 25 SRs included 306 overlapping reports based on 112 individual primary studies. The main characteristics of the SRs included are summarized in **Table I**.

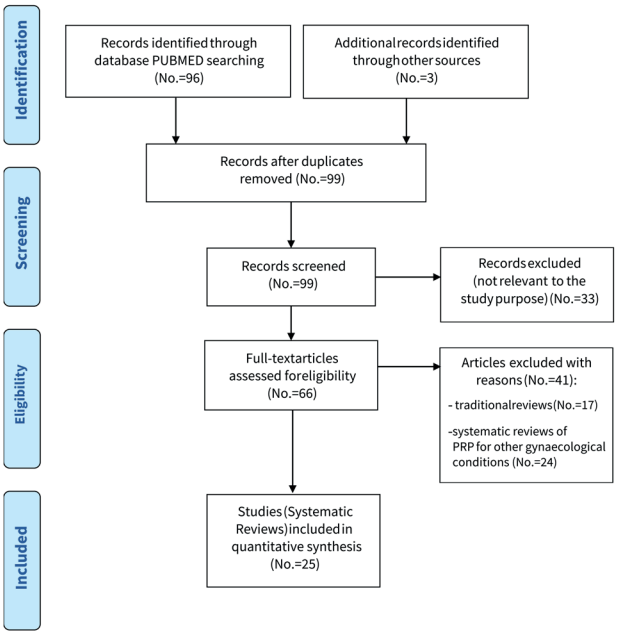


Figure 1 - PRISMA flow chart of study selection process

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Table I - *Main characteristics of SRs included in the overview update*

First Author, year[ref]	Clinical setting	Studies included in quantitative analysis for assisted reproduction			Interventions		Main outcomes	Main results as reported in the SR
		Overall (patients)	RCT/ pRCT	Other	Experimental	Control		
Panda, 2020[27]	Ovarian insufficiency	4 (606)	-	4	PRP	No PRP	AMH, FSH, AFC, number of oocytes, embryo Count	PRP infusion increases ovarian reserve parameters resulting in increased mature oocytes
Maleki-Hajiagha, 2020[28]	IVF/ICSI	7 (625)	3	4	PRP	No PRP	Chemical pregnancy, clinical pregnancy, implantation rate, miscarriage, endometrial thickness	PRP infusion increases the clinical pregnancy rate in assisted reproduction
Wang, 2021[29] ***(A network meta-analysis)***	Implantation failures	3 (195)	3	-	PRP	No PRP or placebo	Implantation rate, miscarriage, endometrial thickness, live birth	PRP administration could potentially positively affect the effectiveness of the IVF treatment
Jin, 2022[30] ***(A network meta-analysis)***	Implantation failures	4 (708)	4	-	PRP	No PRP	Clinical pregnancy, live birth, multiple pregnancy, miscarriage	PRP is the most effective intrauterine intervention in improving pregnancy outcome
Li, 2022[31]	Implantation failures	10 (1629)	6	4	PRP	No PRP	Clinical pregnancy, miscarriage, implantation rate, live birth	PRP appears to improve the results of IVF/ICSI treatments
Liu, 2022[32]	Implantation failures	8 (1219)	5	3	PRP (intrauterine perfusion, sub-endometrial injection in one study)	No PRP or placebo	Clinical pregnancy, miscarriage, multiple pregnancy, live birth	PRP treatment is recommended for women with more than three implantation failures
Anitua, 2023[33]	Implantation failures	11 (1176)	11	-	PRP	No PRP or placebo	Chemical pregnancy, clinical pregnancy, miscarriage, implantation rate, live birth	PRP therapies might be an effective treatment in cases of poor responsiveness
Deng, 2023[34]	Implantation failures	10 (1555)	6	4	PRP	No PRP	Chemical pregnancy, clinical pregnancy, miscarriage, implantation rate, live birth	PRP infusion improves pregnancy outcome compared to control without PRP
Hu, 2023[35]	IVF/ICSI	7 (861)	7	-	PRP	No PRP	Chemical pregnancy, clinical pregnancy, miscarriage, implantation rate, live birth	PRP increases the pregnancy rate and implantation rate among women with thin endometrium
Huang, 2023[36]	Implantation failures	14 (1081)	5	9	PRP	No PRP or placebo	Chemical pregnancy, clinical pregnancy, miscarriage, implantation rate, endometrial thickness	PRP may be an alternate therapeutic approach for individuals with thin endometrium
Kong, 2023[37] ***(A network meta-analysis)***	Implantation failures	7 trials (921)	7	-	PRP and other interventions	Blank or placebo	Clinical pregnancy, miscarriage, live birth	PRP intrauterine infusion therapy was the most effective in increasing the clinical pregnancy and live birth rates
Li, 2023[38]	Poor ovarian responder	10 (793)	-	10	PRP	No PRP	AMH, number of oocytes, embryo count fertilization rate	PRP injection can promote ovarian regeneration

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Table I - *Main characteristics of SRs included in the overview update (continued from previous page)*

First Author, year[ref]	Clinical setting	Studies included in quantitative analysis for assisted reproduction			Interventions		Main outcomes	Main results as reported in the SR
		Overall (patients)	RCT/ pRCT	Other	Experimental	Control		
Maged, 2023[39]	Implantation failures	27 (3,308)	13	14	PRP	No PRP or placebo	Clinical pregnancy, miscarriage, implantation rate, endometrial thickness	PRP infusion improves implantation, clinical pregnancy, chemical pregnancy, ongoing pregnancy, live birth rates, and endometrial thickness
Shalma, 2023[40]	IVF/ICSI	23 (2,391)	14	9	PRP	No PRP or placebo	Clinical pregnancy, miscarriage, live birth, endometrial thickness, ectopic pregnancy	PRP infusion improves clinical pregnancy, live birth and miscarriage in women undergoing IVF/ICSI
Soliman, 2023[41]	Implantation failures	8 (1,038)	8	-	PRP	No PRP	Chemical pregnancy, clinical pregnancy, miscarriage, live birth, endometrial thickness	PRP infusion can increase implantation and pregnancy outcomes
Tang, 2023[42]	Intrauterine adhesion	10 (730)	6	4	PRP	No PRP or placebo	Menstruation flow and duration, recurrence of adhesions, clinical pregnancy, endometrial thickness, live birth, adverse events	PRP treatment shows promise in the management of uterine adhesions, and it appears to be safe
Vaidakis, 2024[43]	IVF/ICSI	12 (1,069)	12	-	PRP	No PRP or placebo	Clinical pregnancy, miscarriage, live birth, multiple pregnancy, ectopic pregnancy, adverse events	Authors are uncertain about PRP injections into ovaries of poor ovarian responders affecting ongoing pregnancy and clinical pregnancy compared with no intervention
Rodrıguez-Eguren, 2024[44]	Endometrial disorders	23 (1,380)	7	16	PRP	No PRP	Menstruation flow and duration, endometrial thickness	Heterogeneity of the methodologies and outcome measures of the included studies led to challenges in pooling data and prevented the feasibility of meta-analysis
Dastjerdi, 2024[45]	Poor ovarian responder	12 (1,289)	-	12	PRP	No PRP	AMH, estradiol, AFC, FSH, number of oocytes, embryo count	PRP improves ovarian reserve markers increasing AFC
Elias, 2024[46]	Poor ovarian responder	38 (2,256)	-	38	PRP	No PRP	AMH, estradiol, AFC, FSH, number of oocytes, embryo count	PRP treatment appears to be a suitable and effective procedure for improving several key fertility parameters in women with low ovarian reserve
Kaur, 2024[47]	Implantation failures	9 (1,168)	9	-	PRP	No PRP	Chemical pregnancy, clinical pregnancy, miscarriage, live birth, multiple pregnancy, adverse events	There may be some beneficial effects of PRP in women with RIF

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Table I - *Main characteristics of SRs included in the overview update (continued from previous page)*

First Author, year[ref]	Clinical setting	Studies included in quantitative analysis for assisted reproduction			Interventions		Main outcomes	Main results as reported in the SR
		Overall (patients)	RCT/ pRCT	Other	Experimental	Control		
Li, 2024[48]	Poor ovarian responder	10 (836)	-	10	PRP	No PRP	AMH, estradiol, AFC, FSH, number of oocytes, embryo count, clinical pregnancy, live birth, adverse events	Application of PRP is beneficial the ovarian response of patients with poor ovarian responder, obtaining more antral follicles
Maged, 2024[49]	Poor ovarian responder	14 (1,632)	-	14	PRP or PRP plus BMSC	No PRP	AMH, estradiol, AFC, FSH, number of oocytes, embryo count, fertilization rate, chemical pregnancy, live birth	There is a non-significant improvement in ovarian hormones and AFC. Well-designed RCT should be conducted to provide the needed evidence
Wu, 2024[50]	Poor ovarian responder	10 (876)	-	10	PRP	No PRP	AMH, FSH, number of oocytes, embryo count, AFC	PRP seems to provide a positive impact on ovarian hormone, but RCT should be conducted to provide the needed evidence
Xie, 2024[51]	Implantation failures	14 (1,718)	9	5	PRP	No PRP	Clinical pregnancy, live birth, embryo count, miscarriage	PRP may be the most effective intrauterine intervention in improving pregnancy outcome

AFC: antral follicle count; AMH: anti-Müllerian hormone; BMSC: bone marrow stem cells; ET: embryo transfer; FSH: follicle-stimulating hormone; HRT: hormone replacement therapy; ICSI: intracytoplasmic injection; IVF: in-vitro fertilization; LIF: leukemia Inhibitory factor; PBMC: peripheral blood mononuclear cells; PRP: platelet-rich plasma, RIF: recurrent implantation failure; RCT: randomized controlled trial; SR: systematic review.

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Methodological quality of SRs

Of the 25 included SRs, two met all the AMSTAR-2 methodological requirements[29,43] and twelve had only one or two methodological requirements partially met or not specified (**Table II**)[28,31-33,40-42,46-49,51]. Eleven SRs had three or more methodological requirements partly met, but none had unmet methodological requirements. Only 2 reviews reported the source of funding for the studies included in the review, and 10 did not report a list of excluded studies and reasons for exclusion, or only partially did so. Two SRs did not perform a quantitative synthesis[27,44]. Concerning the overlap among primary studies, the CCA index was slight across all reports included (1.9%). Overall, confidence in the results of the SRs can be considered high or moderate.

Summary of the effect of PRP on the main outcomes

The most commonly reported outcomes were clinical and chemical pregnancy, implantation rate and live birth rates. Other less commonly reported outcomes were change in endometrial thickness, antral follicle or embryo count, multiple pregnancy, adverse events, and rate of miscarriage. The results of the analyses for the most commonly reported outcomes are summarized in **Table III** (Summary of findings table).

Clinical pregnancy (defined as the presence of a fetal heartbeat on an ultrasound scan at seven weeks of gestation) was reported in 17 of the 25 SRs, and all reported an increase of clinical pregnancy rate in PRP recipients compared to controls. However, subgroup analysis of a subset of patients with 1 or 2 IVF and thin endometrium shows no differences in rates of clinical pregnancy between PRP and controls[32,39]. The certainty of the evidence with the GRADE assessment was judged moderate in 11 comparisons, low in 8, high in 2 and very low in 2 (**Table III**).

Chemical pregnancy is referred to a positive result on a blood or urine test for the presence of human chorionic gonadotropin (hCG) to detect a pregnancy; this outcome was reported in 8 of the 25 SRs, all reporting increased rates in PRP recipients compared to controls, with the

Table II - *Assessment of methodological quality with AMSTAR 2 tool for each comparison of the efficacy and safety outcomes*

First author, year[ref]	AMSTAR-2 DOMAIN															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Panda, 2020[27]											Np*	Np*				
Maleki-Hajiagha, 2020[28]																
Wang, 2021[29]																
Jin, 2022[30]																
Li, 2022[31]																
Liu, 2022[32]																
Anitua, 2023[33]	P															
Deng, 2023[34]	P															
Hu, 2023[35]																
Huang, 2023[36]																
Kong, 2023[37]	P															
Li, 2023[38]	P															
Maged, 2023[39]	P															
Shalma, 2023[40]																
Soliman, 2023[41]	P															
Tang, 2023[42]	P															
Vaidakis, 2024[43]	P															
Rodrıguez-Eguren, 2024[44]	P										Np*	Np*				
Dastjerdi, 2024[45]																
Elias, 2024[46]	P															
Kaur, 2024[47]	P															
Li, 2024[48]	P															
Maged, 2024[49]	P															
Wu, 2024[50]	P															
Xie, 2024[51]	P															

Methodological requirement met	Methodological requirement partly met, or not specified	Methodological requirement unmet

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AMSTAR-2 domains. Although AMSTAR 2 consists of 16 items, critical domains include items 2, 4, 7, 9, 11, 13, and 15.

1. Did the research questions and inclusion criteria for the review include the components of PICO?
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
3. Did the review Authors explain their selection of the study designs for inclusion in the review?
4. Did the review Authors use a comprehensive literature search strategy?
5. Did the review Authors perform study selection in duplicate?
6. Did the review Authors perform data extraction in duplicate?
7. Did the review Authors provide a list of excluded studies and justify the exclusions?
8. Did the review Authors describe the included studies in adequate detail?
9. Did the review Authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
10. Did the review Authors report on the sources of funding for the studies included in the review?
11. If meta-analysis was performed did the review Authors use appropriate methods for statistical combination of results?
12. If meta-analysis was performed, did the review Authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
13. Did the review Authors account for RoB in individual studies when interpreting/discussing the results of the review?
14. Did the review Authors provide a satisfactory explanation for, and discussion of, any heterogeneity?
15. If they performed quantitative synthesis did the review Authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
16. Did the review Authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

*Np: not performed due to the paucity of available data; P: a protocol is available.

Table III - *Summary of findings table, effects of PRP for assisted reproduction on more commonly reported outcomes in systematic reviews/meta-analyses*

First Author, year [ref]	Outcome	Interventions and controls, No. trials reporting the outcome	Effect size (RR, OR or RD) and 95% CIs	GRADE assessment (reason/s for downgrading)	Comment	Effect direction
	Chemical pregnancy					
Maleki-Hajiagha, 2020[28]	RR (95% CIs)	PRP *vs* no-PRP or other active intervention, 3 trials	1.79 (1.29/2.50). p<0.001; I^2=0	⊕⊕⊕⊖ moderate (ROB)	PRP increases chemical pregnancy rates compared to controls	
Anitua, 2023[33]	RR (95% CIs)	PRP *vs* no-PRP or placebo, 5 RCTs at low ROB	1.91 (1.55/2.35); p<0.00001; I^2=0	⊕⊕⊕⊕ high	PRP increases chemical pregnancy rates compared to controls	
Deng, 2023[34]	RR (95% CIs)	PRP *vs* standard treatment, 8 trials	1.79 (1.54/2.08); p<0.00001; I^2=29	⊕⊕⊕⊖ moderate (ROB)	PRP increases chemical pregnancy rates compared to controls in RIF	
Hu, 2023[35]	RR (95% CIs)	PRP *vs* no-PRP, 4 trials	1.96 (1.58, 2.45); p<0.00001; I^2=0	⊕⊕⊕⊖ moderate (ROB)	PRP increases chemical pregnancy rates compared to controls	
Huang, 2023[36]	RD (95% CIs)	PRP *vs* no PRP or placebo, 6 trials	Favors PRP; p<0.00001; I^2=0	⊕⊕⊕⊖ moderate (ROB)	PRP increases chemical pregnancy rates compared to controls	
Soliman, 2023[41]	RD (95% CIs)	PRP *vs* standard treatment or no treatment, 6 trials	1.96 (1.61, 2.39); p<0.001; I^2=0	⊕⊕⊕⊖ moderate (ROB)	PRP increases chemical pregnancy rates compared to controls	
Kaur, 2024[47]	OR (95% CIs)	PRP *vs* standard treatment, 9 trials	1.96 (1.63/2.36); p<0.00001; I^2=0	⊕⊕⊖⊖ low (downgraded twice for serious ROB)	PRP increases chemical pregnancy rates compared to controls	
Maged, 2024[49]	OR (95% CIs)	PRP *vs* standard treatment or placebo, 7 RCTs	2.92 (2.09/4.08); p<0.0001; I^2=0	⊕⊕⊕⊕ high	PRP increases chemical pregnancy rates compared to controls, both in RIF (2 RCTs) and IF (3 RCTs)	
		PRP *vs* standard treatment or placebo, 6 non-RCTs	1.49 (0.86/2.58); p=0.16; I^2=76	⊕⊖⊖⊖ very low (ROB, indirectness, imprecision)	It is unclear if PRP increases chemical pregnancy rates compared to controls	
	Clinical pregnancy outcome					
Maleki-Hajiagha, 2020[28]	RR (95% CIs)	PRP *vs* no-PRP or other active intervention, 7 trials	1.79 (1.37/2.32). p<0.001; I^2=16	⊕⊕⊕⊖ moderate (ROB)	PRP increases clinical pregnancy rates compared to controls	
Liu, 2022[32]						
Overall	OR (95% CIs)	PRP *vs* no treatment or placebo, 8 studies (RCT and cohort)	2.24 (1.41/3.54); p=0.0006; I^2=61	⊕⊕⊖⊖ low (ROB, inconsistency)	PRP increases clinical pregnancy rates compared to controls in the overall analysis and in RCTs	
RCTs		PRP *vs* no treatment or placebo, 5 studies	3.66 (2.58/1.19); p=0001; I^2=0	⊕⊕⊕⊕ high		
Patients with RIF (recurrent implantation failure)		PRP *vs* no treatment or placebo, 3 studies	2.55 (1.49/4.38); p=0.01; I^2=69	⊕⊕⊕⊖ moderate (inconsistency)	PRP increases clinical pregnancy rates in the subset of women with RIF	
Patients with 1 or 2 IF		PRP *vs* no treatment or placebo, 3 studies	1.39 (0.73/2.66); p=0.32; I^2=69	⊕⊕⊖⊖ low (imprecision, inconsistency)	It is unclear if PRP increases clinical pregnancy rates in the subset of women with 1 or 2 IF	

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Table III - *Summary of findings table, effects of PRP for assisted reproduction on more commonly reported outcomes in systematic reviews/meta-analyses (continued from previous page)*

First Author, year [ref]	Outcome	Interventions and controls, No. trials reporting the outcome	Effect size (RR, OR or RD) and 95% CIs	GRADE assessment (reason/s for downgrading)	Comment	Effect direction
	Clinical pregnancy outcome					
Jin, 2022[30]	OR (95% CIs)	PRP *vs* no intervention, 4 RCTs	3.78 (2.72/5.25)	⊕⊕⊕⊖ moderate (ROB)	PRP increases clinical pregnancy rates compared to controls	
Li, 2022[31]	RR (95% CIs)	PRP *vs* no treatment (1 study GCSF), 10 studies (6 RCTs).	1.79 (1.55/2.06); p<0.01; I^2=40	⊕⊕⊖⊖ low (ROB, inconsistency)	Heterogeneity related to PRP dosage. Infusion of 0.5-1 ml PRP better than ≥1 ml, without evidence of heterogeneity	
Anitua, 2023[33]	RR (95% CIs)	PRP *vs* no-PRP or placebo, 8 RCTs at low ROB	2.19 (1.78/2.70); p<0.00001; I^2=30	⊕⊕⊕⊕ high	PRP increases clinical pregnancy rates compared to controls	
Deng, 2023[34]	RR (95% CIs)	PRP *vs* standard treatment, 9 trials	1.96 (1.67/2.31); p<0.00001; I^2=46	⊕⊕⊕⊖ moderate (ROB)	PRP increases clinical pregnancy rates compared to controls	
Hu, 2023[35]	RR (95% CIs)	PRP *vs* no-PRP, 7 trials	2.51 (2.00, 3.13) p<0.00001; I^2=0	⊕⊕⊕⊖ moderate (ROB)	PRP increases clinical pregnancy rates compared to controls	
Huang, 2023[36]	OR (95% CIs)	PRP *vs* no PRP or placebo, 15 trials	2.34 (1.76/3.11); p<0.00001; I^2=27	⊕⊕⊕⊖ moderate (ROB)	PRP increases clinical pregnancy rates compared to controls	
Kong, 2023[37] ***(A network meta-analysis)***	OR (95% CIs)	7 trials with PRP	0.41 (0.26/0.66)	⊕⊕⊖⊖ low (ROB, indirectness)	PRP increases clinical pregnancy rates compared to controls	
Shalma, 2023[40]	RR (95% CIs)	PRP *vs* no PRP or standard treatment, 20 trials	1.84 (1.62/2.09); p<0.00001; I^2=29	⊕⊕⊕⊖ moderate (ROB)	PRP increases clinical pregnancy rates compared to controls	
Soliman, 2023[41]	RD (95% CIs)	PRP *vs* standard treatment or no treatment, 8 trials	2.35 (1.92, 2.88); p<0.001; I^2=0	⊕⊕⊕⊖ moderate (ROB)	PRP increases clinical pregnancy rates compared to controls	
Tang, 2023[42]	OR (95% CIs)	Patients with IUA. PRP *vs* conventional treatment or placebo, 5 trials	1.82 (1.19/2.78); p=0.006; I^2=0	⊕⊕⊕⊖ moderate (ROB)	PRP increases clinical pregnancy rates compared to controls	
Kaur, 2024[47]	OR (95% CIs)	PRP *vs* standard treatment, 8 trials	3.20 (2.38/4.38); p<0.00001; I^2=0	⊕⊕⊖⊖ low (downgraded twice for serious ROB)	PRP increases clinical pregnancy rates compared to controls	
Li, 2024[48]	OR (95% CIs)	PRP *vs* no treatment, 5 trials	0.06 (0.01/0.20); p<0.00001; I^2=0	⊕⊕⊕⊖ moderate (ROB)	PRP increases clinical pregnancy rates compared to controls	

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Table III - *Summary of findings table, effects of PRP for assisted reproduction on more commonly reported outcomes in systematic reviews/meta-analyses (continued from previous page)*

First Author, year [ref]	Outcome	Interventions and controls, No. trials reporting the outcome	Effect size (RR, OR or RD) and 95% CIs	GRADE assessment (reason/s for downgrading)	Comment	Effect direction
	Clinical pregnancy outcome					
Maged, 2023[39]	OR (95% CIs)	PRP *vs* standard treatment or placebo, 12 RCTs	2.21 (1.03/4.72); p=0.04; I^2=88	⊕⊕⊖⊖ low (ROB, inconsistency)	PRP increases clinical pregnancy rates compared to controls both in RCTs and in non-RCTs	
		PRP *vs* standard treatment or placebo, 10 non-RCTs	2.39 (1.47/3.90); p=0.0005; I^2=68	⊕⊕⊖⊖ low (ROB, inconsistency)		
		PRP *vs* standard treatment or placebo, RIF (6 RCTs)	1.95 (1.10/3.46); p=0.02, I^2=47	⊕⊕⊕⊖ moderate (ROB)	PRP increases clinical pregnancy rates compared to controls in the subset of RIF patients	
		PRP *vs* standard treatment or placebo, IF (4 RCTs)	1.88 (0.35/310.2); p=0.46, I^2=95	⊕⊖⊖⊖ very low (ROB, indirectness, imprecision)	It is unclear if PRP increases clinical pregnancy rates in the subset of IF patients (previous IF and thin endometrium)	
Vaidakis, 2024[43]	OR (95% CIs)	PRP *vs* no intervention or placebo, 9 RCTs	2.22 (1.50/3.27); p<0.0001; I^2=24	⊕⊖⊖⊖ very low (serios ROB, indirectness because only one subset of the overall population was included)	PRP increases clinical pregnancy rates compared to controls	
Xie, 2024[51] ***(A network meta-analysis)***	OR (95% CIs)	PRP *vs* controls, 13 trials	2.90 (2.15/3.90); p<0.00001; I^2=32	⊕⊕⊖⊖ low (ROB, indirectness)	PRP increases clinical pregnancy rates compared to controls	
	Implantation rate outcome					
Maleki-Hajiagha, 2020[28]	RR (95% CIs)	PRP *vs* no-PRP or other active intervention, 3 trials	1.97 (1.40/2.79). p<0.001; I^2=0	⊕⊕⊕⊖ moderate (ROB)	PRP increases implantation rates compared to controls	
Wang, 2021[29] ***(A network meta-analysis)***	OR (95% CIs)	PRP *vs* no treatment or placebo, 3 studies	1.23 (0.33/4.64)	⊕⊕⊖⊖ low (ROB, imprecision)	It is unclear if PRP increases implantation rates compared to controls	
Li, 2022[31]	RR (95% CIs)	PRP *vs* no treatment, 3 studies	1.74 (1.34/2.26); p<0.01; I^2=36	⊕⊕⊖⊖ low (ROB, inconsistency)	PRP increases implantation rates compared to controls	
Anitua, 2023[33]	RR (95% CIs)	PRP *vs* no-PRP or placebo, 4 RCTs at low ROB	1.57 (1.07/2.30); p=0.02; I^2=49	⊕⊕⊖⊖ low imprecision, (inconsistency)	PRP increases implantation rates compared to controls	
Deng, 2023[34]	RR (95% CIs)	PRP *vs* standard treatment, 4 trials	1.90 (1.50/2.41); p<0.00001; I^2=0	⊕⊕⊕⊖ moderate (ROB)	PRP increases implantation rates compared to controls	
Hu, 2023[35]	RR (95% CIs)	PRP *vs* no-PRP, 1 trial	3.27 (1,42, 7.52); p<0.005;	⊕⊕⊖⊖ low (ROB, imprecision)	PRP increases implantation rates compared to controls	
Huang, 2023[36]	RD (95% CIs)	PRP *vs* no-PRP, 6 trials	Favors PRP; p<0.00001; I^2=72	⊕⊕⊖⊖ low (ROB, inconsistency)	PRP increases implantation rates compared to controls	
Maged, 2023[39]	OR (95% CIs)	PRP *vs* standard treatment or placebo, 6 RCTs	2.62 (1.83/3.76); p<0.00001; I^2=20	⊕⊕⊕⊕ high	PRP increases implantation rates compared to controls, both in RCTs and non-RCTs	
		PRP *vs* standard treatment or placebo, 3 non-RCTs	2.88 (1.14/7.25); p=0.03; I^2=51	⊕⊕⊖⊖ low (ROB, inconsistency)		

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Table III - *Summary of findings table, effects of PRP for assisted reproduction on more commonly reported outcomes in systematic reviews/meta-analyses (continued from previous page)*

First Author, year [ref]	Outcome	Interventions and controls, No. trials reporting the outcome	Effect size (RR, OR or RD) and 95% CIs	GRADE assessment (reason/s for downgrading)	Comment	Effect direction
	Live birth outcome					
Wang, 2021[29]	OR	PRP *vs* placebo, network meta-analysis, 3 RCTs	1.23 (0.33/4.64)	⊕⊕⊖⊖ low (ROB, imprecision)	It is unclear if PRP increases live birth rate compared to controls	
Liu, 2022[32]						
Overall	OR (95% CIs)	PRP *vs* no treatment or placebo, 3 studies	5.76 (1.55/21.44); p=0.009; I^2=85	⊕⊖⊖⊖ very low (ROB, indirectness, imprecision)	PRP increases live birth rate compared to controls both in the overall analysis and in the subset of RCTs	
RCT		PRP *vs* no treatment or placebo, 2 studies	11.02 (5.72/21.21); p<0.0001; I^2=0	⊕⊕⊖⊖ low (serious imprecision due to low number of studies and large CIs)		
Jin, 2022[30]	OR (95% CIs)	PRP *vs* no intervention, 4 RCTs	5.96 (3.38/10.52)	⊕⊕⊕⊖ moderate (ROB)	PRP increases live birth rate compared to controls	
Li, 2022[31]	RR (95% CIs)	PRP *vs* no treatment, 4 studies	2,92 (2.22/3.85); p<0.01; I^2=83	⊕⊕⊖⊖ low (ROB, inconsistency)	PRP increases live birth rate compared to controls	
Anitua, 2023[33]	RR (95% CIs)	PRP *vs* no-PRP or placebo, 4 RCTs at low ROB	2.90 (1.06/7.96); p=0.04; I^2=77	⊕⊕⊖⊖ low (imprecision, inconsistency)	PRP increases live birth rate compared to controls	
Deng, 2023[34]	RR (95% CIs)	PRP *vs* standard treatment, 4 trials	2.83 (1.45/5.52); p=0.002; I^2=87	⊕⊕⊖⊖ low (ROB, inconsistency)	PRP increases live birth rate compared to controls	
Hu, 2023[35]	RR (95% CIs)	PRP *vs* no-PRP, 2 trials	7.03 (3.9/ 12.6); p<0.00001; I^2=0	⊕⊕⊖⊖ low (ROB, imprecision)	PRP increases live birth rate compared to controls	
Kong, 2023[37] ***(A network meta-analysis)***	OR (95% CIs)	7 trials with PRP	0.15 (0.07/0.34)	⊕⊕⊖⊖ low (ROB, indirectness)	PRP increases live birth rate compared to controls	
Shalma, 2023[40]	RR (95% CIs)	PRP *vs* no PRP or standard treatment, 10 trials	1.75 (1.24/2.47); p=0.001; I^2=15	⊕⊕⊕⊖ moderate (ROB)	PRP increases live birth rate compared to controls	
Soliman, 2023[41]	RD (95% CIs)	PRP *vs* standard treatment or no treatment, 3 trials	4.03 (1.29, 12.63); p<0.02; I^2=63	⊕⊕⊖⊖ low (ROB, inconsistency)	PRP increases live birth rate compared to controls	
Tang, 2023[42]	OR (95% CIs)	Patients with IUA. PRP *vs* conventional treatment or placebo, 2 trials	1.44 (0.37/5.58); nss; I^2=33	⊕⊕⊖⊖ low (ROB, imprecision)	PRP increases live birth rate compared to controls	
Kaur, 2024[47]	OR (95% CIs)	PRP *vs* standard treatment, 4 trials	7.32 (4.54/11.81); p<0.00001; I^2=40	⊕⊕⊖⊖ low (downgraded twice for serious ROB)	PRP increases live birth rate compared to controls	
Li, 2024[48]	OR (95% CIs)	5 trials	0.02 (0.01/0.10); p<0.00001; I^2=0	⊕⊕⊕⊖ moderate (ROB)	PRP increases live birth rate compared to controls	

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Table III - *Summary of findings table, effects of PRP for assisted reproduction on more commonly reported outcomes in systematic reviews/meta-analyses (continued from previous page)*

First Author, year [ref]	Outcome	Interventions and controls, No. trials reporting the outcome	Effect size (RR, OR or RD) and 95% CIs	GRADE assessment (reason/s for downgrading)	Comment	Effect direction
	Live birth outcome					
Maged, 2024[49]	OR (95% CIs)	PRP *vs* standard treatment or placebo, 4 RCTs	4.35 (0.58/32.38); p=0.15; I^2=84	⊕⊖⊖⊖ very low (ROB, indirectness, imprecision)	It is unclear if PRP increases live birth rates compared to controls in RCTs	
		PRP *vs* standard treatment or placebo, 4 non-RCTs	4.18 (01.61/10.86); p=0.03; I^2=65	⊕⊕⊖⊖ low (ROB, inconsistency)	PRP increases live birth rate compared to controls in non-RCTs	
Vaidakis, 2024[43]	OR (95% CIs)	6 RCTs	2.38 (1.16/4.86); p=0.02; I^2=54	⊕⊖⊖⊖ very low (ROB, indirectness (only a subset of the overall population included), inconsistency)	PRP increases live birth rate compared to controls	
Xie, 2024[51] ***(A network meta-analysis)***	OR (95% CIs)	PRP *vs* control, 4 trials	4.27 (1.25/14.66); p=0.02; I^2=79	⊕⊕⊖⊖ low (ROB, inconsistency)	PRP increases live birth rate compared to controls	

PRP: platelet-rich plasma; OR: odds ratio; RR: risk ratio; RD: risk difference; SMD: standardized mean difference; ROB: risk of bias; GCSF: granulocyte colony stimulating factor; Nss: not statistically significant; RIF: repeated implantation failure; IF: implantation failure; IUA: intrauterine adhesion.

The effect size favors PRP compared to controls in a significant way	No significant differences between groups	The effect size favours controls compared to PRP in a significant way

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exception of a comparison from non-RCTs in a SR[49] showing unclear differences between groups and a very-low quality of evidence. In the remaining 8 comparisons the certainty of the evidence with the GRADE assessment was judged moderate in 5 comparisons, high in 2, and low in 1 (**Table III**).

Implantation rate was reported in 8 SRs (9 comparisons)[28-29,31,33-36,39]. An increase of implantation rate in PRP recipients compared to controls was observed in all the SRs with the exception of a network meta-analisis[29] with unclear differences between groups. The certainty of the evidence with the GRADE assessment was judged more commonly low (in 6 comparisons), moderate in 2, and high in 1.

Live birth rate (defined as the delivery of a live fetus after 20 completed weeks of gestation) was reported in 16 SRs, with 18 comparisons (**Table III**)[29-35,37,40-43,47-49,51]. An increase of live birth rate in PRP recipients compared to controls was observed in the large majority of SRs and comparisons, with the exception of two comparisons with unclear differences between groups[29,49]. The certainty of the evidence with the GRADE assessment was judged more commonly low (in 12 comparisons), very low in 3 comparisons and moderate in 3.

Other outcomes

Adverse events related to PRP administration (e.g., pain, infection, allergic reactions) were rarely recorded and reported.

Miscarriage rate (pregnancy loss before 20 completed weeks of gestation), ectopic pregnancy and multiple pregnancy were also among the outcomes reported in some of the SRs, but there was uncertainty about the effect of PRP infusion compared with no intervention on these outcomes (no statistically significant differences between groups).

DISCUSSION

Overviews of reviews (umbrella review) assemble several SRs on the same condition and permit to consider for inclusion the highest level of evidence available, such as SRs and meta-analyses[55]. In fact, in this umbrella review we have reappraised the results of 25 SRs, published between

2020 and 2024, on PRP use for assisted reproduction. The SRs included in this overview present data from 306 overlapping reports, based on 112 individual primary trials, both randomized and non-randomized.

The main findings of this umbrella review are the following:

1. the use of PRP increases clinical and chemical pregnancy rates, implantation rates and live birth rates compared to controls;
2. the certainty of evidence with GRADE assessment ranged from very low to high (on average low/moderate). Common reasons for downgrading the evidence in the SRs included in this overview were ROB, particularly selection bias in non-RCTs and other biases in RCTs, inconsistency (due to statistical and/or clinical heterogeneity), and indirectness (the patients studied are different from those for whom the recommendation applies);
3. the variability observed in the beneficial effects of PRP and levels of certainty of the evidence is mostly related to study design and heterogeneity across studies. For instance, the certainty in evidence with the outcome clinical and chemical pregnancy increased to high level when only RCTs at low risk of bias were included in the SRs[32,39]. However, more commonly the level decreased to low/moderate due to ROB, indirectness and inconsistency;
4. in some of the SRs the beneficial effect of PRP on clinical pregnancy was evident in the subset of women with RIF (moderate certainty of evidence), but women with 1 or 2 RIF may not benefit from the use of PRP (from low to very low certainty of the evidence)[32,34,39].
5. other outcomes were less commonly reported. Miscarriage rate, ectopic pregnancy and multiple pregnancy were reported with similar frequency among PRP recipients and controls; adverse events related to PRP administration (e.g., pain, infection, allergic reactions) were rarely recorded and reported in primary studies and SRs.

There was clinical heterogeneity among the studies included in the SRs related to variability in populations studied and interventions. There was also variability among studies in terms of the protocols for endometrial preparation, and in the endometrial thickness before PRP administration. Other limitations in the SRs and primary studies relate to the variability of PRP administration (e.g., intrauterine or intraovarian infusion/injection), time of administration of PRP and embryo transfer, and dose of PRP infused. For instance, in the meta-analysis performed by Maleki-Hajiagha *et al.*[28], a dose of 0.5-1 mL showed a higher effect in comparison to doses of <0.5 mL or >1 mL in terms of clinical pregnancy. Unfortunately, other studies did not evaluate this factor. Thus, the standardization of the PRP dose and protocol of administration should be the focus of future clinical trials.

Another limitation is that data related to safety profile are limited, although some evidence that Intrauterine PRP infusion compared with no intervention may increase considerably the risk of preterm delivery has been observed[33,43].

In conclusion, despite the aforementioned limitations of the available evidence, the results of this overview suggest that the intrauterine infusion of PRP increases the clinical pregnancy rate, chemical pregnancy rate, live birth rate, particularly among women with recurrent implantation failure (RIF) undergoing treatment with assisted reproduction technology. However, further prospective, large, and well-designed trials are required to identify the subset of women who would get most benefit from this intervention and to standardize protocols of PRP administration.

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AUTHORS' CONTRIBUTIONS

Conceptualization: MC. Methodology: MC. Data extraction: FM, IP, MC. Writing-preparation original draft: MC. Writing-review and editing: FM, IP, VP, SP, VDA. All Authors have read and agreed to the published version of the manuscript.

The Authors declare no conflicts of interest.

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