

Is it justified to offer intrauterine infusion of autologous PRP in women with repeated implantation failure?

Evangelia T. Katsika ¹, Christos A. Venetis ^{1,2}, Julia K. Bosdou ¹, and Efstratios M. Kolibianakis ^{1,*}

¹Unit for Human Reproduction, 1st Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece

²Centre for Big Data Research in Health, Faculty of Medicine & Health, University of New South Wales, Sydney, NSW, Australia

*Correspondence address. Unit for Human Reproduction, 1st Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Papageorgiou General Hospital, Agiou Pavlou 76, 56429 Thessaloniki, Greece. E-mail: stratis.kolibianakis@gmail.com  <https://orcid.org/0000-0003-0031-9460>

ABSTRACT

In recent years, an increased interest in the efficacy of intrauterine infusion of autologous platelet-rich plasma (PRP) in women with repeated implantation failure (RIF) has resulted in the publication of 13 randomized controlled trials (RCTs) and 11 meta-analyses. Although these meta-analyses support an increase in pregnancy rates after intrauterine infusion of autologous PRP, the low quality of the available original clinical studies along with concerns regarding their trustworthiness seriously questions their internal validity and does not allow for definitive conclusions to be drawn. In addition, the variability in the definition of RIF used in the individual studies limits their external validity, renders the pooling of the results problematic, and, overall, complicates the extrapolation of the results published. The variability in the definition of RIF has been recently addressed by the ESHRE, which published an evidence-based definition of RIF to facilitate the evaluation of interventions in these patients. Taking into consideration this definition, which identifies a real clinical problem, evaluation of intrauterine infusion of PRP in the published literature has not so far been performed explicitly in patients with RIF. The potential of intrauterine infusion of autologous PRP to improve outcomes for women with RIF remains an important area of research in ART. However, the current evidence is insufficient to inform clinical practice, highlighting the need for well-designed studies to provide clearer guidance.

Keywords: autologous platelet-rich plasma / PRP / repeated implantation failure / recurrent implantation failure / IVF / ICSI

The problem of repeated implantation failure

Repeated implantation failure (RIF) is generally considered a condition in which good-quality embryos fail to implant after multiple transfers (Coughlan *et al.*, 2014). RIF is a longstanding issue in reproductive medicine, impacting treatment outcomes and presenting persistent challenges in ART. This condition not only affects success rates but also leads to emotional and psychological burdens for patients. Clinically, RIF represents a complex problem for both patients and physicians, as it requires careful consideration of potential underlying causes and personalized treatment approaches. The challenge is further complicated by the lack of a standardized definition, leading to heterogeneity in how RIF is diagnosed and managed. This variation makes it difficult to extrapolate and interpret findings from various interventions that have been attempted, as data are not always applicable to the broader population.

In response to this, ESHRE has introduced good practice recommendations for managing RIF, aimed at standardizing diagnostic and therapeutic approaches and improving patient outcomes.

Interventions proposed for management of RIF

The variation in the definition of RIF makes it difficult to compare therapeutic interventions in this category of patients. Some of the interventions proposed are uterine (e.g. endometrial injury, hysteroscopy, atosiban administration, etc.) (Iakovidou *et al.*, 2023), laboratory (e.g. embryo transfer medium enriched with hyaluronic acid, assisted hatching, etc.), pharmacological treatments proposed to enhance endometrial receptivity (e.g. intramuscular growth hormone, vaginal sildenafil, etc.), technologies aimed at identifying the endometrial window of implantation (Simón *et al.*, 2020), and immunomodulatory therapies (e.g. intravenous immunoglobulin, low-molecular-weight heparin, intrauterine autologous platelet-rich plasma (PRP) infusion, etc.) (Busnelli *et al.*, 2021).

Is intrauterine infusion of autologous PRP in RIF patients the answer?

In recent years, the use of intrauterine infusion of autologous PRP in women with RIF has been the focus of interest (Shalma *et al.*, 2023). PRP is a volume of plasma, obtained by centrifugation of

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patient's blood, that has a platelet count above baseline. With the intrauterine infusion of autologous PRP, numerous proteins, growth factors (GFs), and cytokines stored in the platelet, act on the endometrium through the promotion of cell proliferation and neoangiogenesis, enhancing the probability of implantation (Bos-Mikich et al., 2019; Lin et al., 2021). The use of autologous PRP has increased in popularity during recent years in parallel with an increased understanding of the role of its GFs in tissue regeneration (Gonçalves et al., 2020).

Thirteen randomized controlled trials (RCTs) and 12 meta-analyses have so far been performed to evaluate the use of intrauterine infusion of autologous PRP in women with RIF (Tables 1 and 2).

In the most recent systematic review and meta-analysis, which pooled data from RCTs, non-RCTs, and cohort studies, significantly higher clinical pregnancy (RR: 1.83, 95% CI: 1.49–2.24, $P < 0.001$) and live birth rates (RR: 2.54, 95% CI: 1.36–4.73, $P = 0.003$) were reported in women with RIF who underwent intrauterine infusion of autologous PRP compared with those who did not (Shalma et al., 2023). The positive effect of PRP on the achievement of pregnancy in the meta-analysis by Shalma et al. (2023) was also present in all previously published meta-analyses (Table 1).

The latest Cochrane review evaluating the role of PRP in assisted reproduction analyzed all studies published until January 2023 (regardless of risk of bias) reporting very low-certainty evidence about the effect of intrauterine PRP compared with placebo or no intervention on live birth or ongoing pregnancy (OR 2.38, 95% CI: 1.16–4.86; $I^2 = 54\%$; six studies, 564 women) and on clinical pregnancy (OR 2.22, 95% CI: 1.50–3.27; $I^2 = 24\%$; nine studies, 824 women). When only data from RCTs judged at low risk of bias were analyzed, the results show no statistically significant benefit for either live birth or ongoing pregnancy (OR 1.10, 95% CI: 0.38–3.14; one study, 94 women) or clinical pregnancy (OR 1.55, 95% CI: 0.64–3.76; one study, 94 women) (Table 1). Authors reported that overall, the risk of bias was high for most outcomes, owing to unclear descriptions of the randomization process, inadequate management of missing outcome data, and selective reporting (Vaidakis et al., 2024).

Can the available evidence evaluating intrauterine infusion of autologous PRP in RIF patients be trusted?

Are RCTs evaluating intrauterine infusion of autologous PRP in RIF patients of adequate quality and trustworthiness?

The included studies were critically assessed, employing the Cochrane risk-of-bias tool for randomized trials (RoB 2) and the Trustworthiness in Randomized Clinical Trials (TRACT) Screening Checklist (Supplementary Figs S1 and S2, Supplementary Table S1, Supplementary Data Files S1 and S2). All the available RCTs evaluating intrauterine infusion of autologous PRP in RIF patients (Table 3) have been found to present major concerns in at least one of the domains evaluated in the TRACT Screening Checklist (governance, plausibility in the intervention usage, time-frame, drop-out rates, baseline characteristics) (Supplementary Table S1, Supplementary Data File S2).

Additionally, using the Cochrane risk-of-bias tool for randomized trials (RoB 2), it was determined that all RCTs were deemed to have an overall high risk of bias, based on the assessment of the domains of the randomization process, deviations from the intended interventions, missing outcome data, measurement of the

outcome, and selection of the reported outcome (Supplementary Figs S1 and S2, Supplementary Data File S1). A detailed methodological perusal of the available RCTs is presented in Table 3 and Supplementary Table S2.

Authors of this article attempted to seek clarification from every study but no reply was received in any instance.

Can the meta-analyses overcome quality problems of untrustworthy RCTs?

The meta-analytical synthesis of studies that are at risk of bias does not mitigate the inherent bias of individual studies and may be seriously misleading. If bias is present in each (or some) of the individual studies, meta-analysis will simply compound the errors and produce a 'wrong' result that may be interpreted as having more credibility (Higgins et al., 2024).

Therefore, the meta-analyses of RCTs evaluating the role in intrauterine PRP infusion in RIF patients may not be trustworthy due to significant biases in the included studies in several areas, such as randomization, adherence to interventions, and outcome reporting, as determined by tools like RoB 2 and the TRACT Screening Checklist.

A systematic review should always evaluate risk of bias and integrity concerns during the review process, exclude studies at significant risk, downgrade evidence if risk of bias is present, and restrict the primary analysis to trials of high quality (Vaidakis et al., 2024) (Table 1).

Are the available RCTs examining the same intervention?

The lack of uniformity in intrauterine autologous PRP infusion protocols in the RCTs published thus far, regarding differences in PRP concentration, volume, frequency of administration, and preparation techniques, hinders the ability to establish consistent and reproducible treatment methods and renders problematic the comparison of outcomes across different studies (Table 4).

Are the available RCTs examining a clinically similar population?

Different definitions of RIF have been used in the published RCTs; in 3 out of the 13 RCTs, no definition of RIF was reported (Table 5). As a result, considerable heterogeneity is present in the populations studied regarding the number of unsuccessful embryo transfers, the total number of embryos transferred and female age.

This inconsistency in the definition of RIF between studies, or its lack thereof, renders the comparison of outcomes, such as biochemical pregnancy, clinical pregnancy, or live births problematic and limits the generalizability of the results obtained as there is no clear reference population to which the produced effects might be applicable. In such cases, a meta-analysis may be meaningless (mixing 'apples and oranges'), and genuine differences in effects may be masked or spuriously detected (Higgins et al., 2024). On the other hand, if the raw data of these RCTs were analyzed in an individual participant data meta-analysis, additional insights could be provided regarding the effectiveness of autologous intrauterine PRP infusion.

To address this problem, a uniform definition of RIF has recently been the focus of interest (Kolibianakis and Venetis, 2019; Ata et al., 2021; Cimadomo et al., 2023). In this respect, ESHRE has provided clear guidelines for defining RIF, taking into consideration the euploid status of the embryos transferred directly or indirectly by adjusting the number of failed attempts according to female age (Cimadomo et al., 2023). These criteria are essential for standardizing research in RIF, ensuring that future study results are robust and comparable.

Table 1. Meta-analyses evaluating intrauterine infusion of autologous PRP in RIF patients.

Meta-analysis, year	RIF population: participants (studies)	Studies included in the meta-analysis		Probability of pregnancy Effect measure 95% CI n=RIF patients
		RCTs: n First author	Non RCTs: n First author	
Busnelli et al., 2021	195(2)	2 Nazari et al., 2019b ¹ , Zamaniyan et al., 2021 ¹	–	Clinical pregnancy RR 2.45 1.55–3.86 n = 195
Li et al., 2022	1629(10)	6 Nazari et al., 2019b ² , Nazari et al., 2022b ² , Safdarian et al., 2022, Zargar et al., 2021, Zamaniyan et al., 2021 ² , Ershadi et al., 2022	4 Tehraninejad et al., 2021, Noushin et al., 2021, Mehrafza et al., 2019, Xu et al., 2022	Clinical pregnancy RR 1.79 1.55–2.06 n = 1629 Live birth RR 2.92 2.22–3.85 n = 878
Liu et al., 2022	1219(8)	5 Nazari et al., 2019b ³ , Zamaniyan et al., 2021 ³ , Nazari et al., 2022b ³ , Allahveisi et al., 2020, Zargar et al., 2021	3 Madhavan et al., 2018, Tehraninejad et al., 2021, Majiyd et al., 2020	Clinical pregnancy OR 2.24 1.41–3.54 n = 1219 Live birth OR 5.76 1.55–21.44 n = 791
Kong et al., 2023	958(7)	6 Obidniak et al., 2017, Safdarian et al., 2022, Zamaniyan et al., 2021 ⁴ , Zargar et al., 2021, Nazari et al., 2019b ⁴ , Nazari et al., 2022b ⁴	1 Alhalabi et al., 2019	Clinical pregnancy OR 0.41** 0.26–0.66 n = 878 Live birth OR 0.27** 0.07–0.97 n = 593
Anitua et al., 2023	893(9)	9 Obidniak et al., 2017, Allahveisi et al., 2020, Bakhsh et al., 2022, Ershadi et al., 2022, Zamaniyan et al., 2021 ⁵ , Zargar et al., 2021, Nazari et al., 2019b ⁵ , Nazari et al., 2019a ⁵ , Nazari et al., 2022b ⁵	–	Clinical pregnancy RR 2.18 1.76–2.70 n = 893 Live birth RR 3.36 0.84–13.45 n = 523
Deng et al., 2023	1555(10)	6 Liu, 2021, Nazari et al., 2019b ⁶ , Nazari et al., 2022b ⁶ , Rageh et al., 2020, Safdarian et al., 2022, Zamaniyan et al., 2021 ⁶	4 Coksuer et al., 2019, Liu, 2020, Tehraninejad et al., 2021, Xu et al., 2022	Clinical pregnancy RR 1.96 1.67–2.31 n = 1405 Live birth RR 2.83 1.45–5.52 n = 871
Hu et al., 2023	678(4)	4 Nazari et al., 2019b ⁷ , Nazari et al., 2022b ⁷ , Obidniak et al., 2017, Zamaniyan et al., 2021 ⁷	–	Clinical pregnancy RR 2.46 1.93–3.12 n = 678 Live birth RR: 7.03 3.91–12.66 n = 433
Maged et al., 2023	Unclear* (12)	6 Allahveisi et al., 2020, Bakhsh et al., 2022, El-Samman et al., 2022, Obidniak et al., 2017, Zargar et al., 2021, Rageh et al., 2020	unclear Tehraninejad et al., 2021	Clinical pregnancy OR 2.54 1.61–4.02 n = 416 Live birth OR 2.36 0.15–36.35 n = 130
Panda et al., 2023	335(4)	4 Obidniak et al., 2017, Nazari et al., 2019a ⁸ , Allahveisi et al., 2020, Zamaniyan et al., 2021 ⁸	–	Clinical pregnancy RR: 1.88 1.17–3.03 n = 335

(continued)

Table 1. Continued

Meta-analysis, year	RIF population: participants (studies)	Studies included in the meta-analysis		Probability of pregnancy Effect measure 95% CI n=RIF patients
		RCTs: n First author	Non RCTs: n First author	
Soliman et al., 2023	1038(8)	8 Nazari et al., 2019b ⁹ Nazari et al., 2019a ⁹ Nazari et al., 2022b ⁹ Nazari et al., 2022a ⁹ Safdarian et al., 2022, Zamaniyan et al., 2021 ⁹ Eftekhar et al., 2018 Obidniak et al., 2017	–	Clinical pregnancy RR 2.35 1.92–2.88 n = 981 Live birth RR 4.03 1.29–12.63 n = 553
Shalma et al., 2023	Unclear*	6 Nazari et al., 2019b ¹⁰ Zamaniyan et al., 2021 ¹⁰ Safdarian et al., 2022 Nazari et al., 2022b ¹⁰ Baybordi et al., 2022 Pourkaveh et al., 2022	7 Tehraninejad et al., 2021, Abou-El-Naga et al., 2022 Coksuer et al., 2019, Noushin et al., 2021, Xu et al., 2022, Yuan et al., 2022, Ban et al., 2023	Clinical pregnancy RR: 1.83 1.49–2.24 n = 1772 Live birth RR: 2.54 1.36–4.73 n = 1003
Vaidakis et al., 2024	824(9)	9 Alhalabi et al., 2019 Allahveisi et al., 2020 Bakhsh et al., 2022 Baybordi et al., 2022 Ershadi et al., 2022 Obidniak et al., 2017; Safdarian et al., 2022 Zamaniyan et al., 2021 ¹¹ Zargar et al., 2021		Clinical pregnancy (for the one RCT judged at low risk of bias) OR 1.55 0.64–3.76 n = 94 Live birth or ongoing pregnancy (for the one RCT judged at low risk of bias) OR 1.10 0.38–3.14 n = 94

N; number of patients, OR; odds ratio, PRP; platelet-rich plasma, RCT; randomized controlled trial, RIF; repeated implantation failure, RR; risk ratio.

* Unclear total number of studies and/or population included in the analysis for RIF patients.

** Better with PRP.

¹ Cited by Busnelli as Nazari et al., 2019 and Zamaniyan et al., 2021.

² Cited by Li as Nazari et al., 2020, Nazari et al., 2022, and Zamaniyan et al., 2021.

³ Cited by Liu as Nazari et al., 2019, Nazari et al., 2021, and Zamaniyan et al., 2021.

⁴ Cited by Kong as Nazari et al., 2020, Nazari et al., 2022, and Zamaniyan et al., 2021.

⁵ Cited by Anitua as Nazari et al., 2019, Nazari et al., 2020, Nazari et al., 2021, and Zamaniyan et al., 2021.

⁶ Cited by Deng as Nazari et al., 2020, Nazari et al., 2022 and Zamaniyan et al., 2021.

⁷ Cited by Hu as Nazari et al., 2020, Nazari et al., 2022 and Zamaniyan et al., 2021.

⁸ Cited by Panda as Nazari et al., 2019 and Zamaniyan et al., 2021.

⁹ Cited by Soliman as Nazari et al., 2019, Nazari et al., 2020, Nazari et al., 2022 (1), Nazari et al., 2022 (2), Zamaniyan et al., 2021.

¹⁰ Cited by Shalma as Nazari et al., 2020, Nazari et al., 2022b and Zamaniyan et al., 2021.

¹¹ Cited by Vaidakis as Zamaniyan et al., 2021.

Are the available RCTs examining a real RIF population?

In order for the results of any RCT to be credible, the intervention tested needs to have a high likelihood of biological plausibility, i. e. the RCTs should be testing an intervention in a population that is likely to benefit from this intervention. In this regard, it is important to assess whether the population examined in each RCT evaluating intrauterine PRP infusion truly satisfies the basic criteria to be considered an RIF population. In this respect, the methodology and RIF threshold proposed by ESHRE can identify a population with a real clinical problem that needs to be solved.

Although the ESHRE RIF definition has been published after the majority of the studies evaluating intrauterine infusion of PRP in RIF patients were performed, it is feasible to confirm whether the population of a specific study meets, or not, the ESHRE definition for RIF.

Currently, none of the RIF definitions used in the relevant published RCTs, evaluating the intrauterine infusion of autologous PRP, meet the minimum criteria for RIF proposed by ESHRE

(Table 5). In 2 out of the 13 RCTs (Dawood, 2022; El-Samman et al., 2022), patients evaluated were <35 years of age; however, in these studies, patients with less than three failed ETs were included, thus not complying with ESHRE's definition of RIF for this age group (three or more failed ETs).

As a consequence, intrauterine infusion of autologous PRP in these RCTs is applied to patients who do not fulfill the ESHRE criteria for RIF and therefore do not examine a real RIF population, according to ESHRE (Cimadomo et al., 2023).

Is clinical use of intrauterine infusion of autologous PRP justified in RIF patients?

Given the absence of RCTs in women with RIF, as recently proposed by ESHRE, no evidence currently exists to accept or refute a beneficial role of intrauterine infusion of autologous PRP on the probability of pregnancy in these patients. Consequently, its clinical use cannot be currently recommended and further research is needed to assess its role in patients with RIF.

Table 2. Methodological characteristics of RCTs evaluating intrauterine infusion of autologous PRP in patients with RIF.

Study, year, journal	Study period	PRP n	No PRP n	Randomization method	Allocation concealment	Blinding	Sample size calculation	Primary outcome	Effect of PRP on the probability of pregnancy: PRP vs no PRP P	Financial support
Allahveisi et al., 2020 , <i>Heliyon</i>	2018–2019	25	25	The patients were randomly assigned the numbers 1–50; those with an even number were assigned to the control group and those with an odd number were assigned to the treatment group	Not reported	Not reported	Not reported	Unclear	Chemical pregnancy rate 28.0% vs 36.0%, P = 0.830 Clinical pregnancy rate* 28.0% vs 24.0%, P = 0.830	None
Abduljabbar et al., 2022 , <i>Cureus</i>	September 2020–May 2021	35	35	Simple random sampling	Not reported	Not blinded	Performed	Endometrial thickness	Clinical pregnancy rate Odds ratio: 0.319**, P < 0.050	None
Baybordi et al., 2022 , <i>International Journal of Reproductive BioMedicine</i>	May 2017–December 2019	59	59	Sealed envelopes randomization	Sealed envelopes	Triple-blind	Performed	Unclear	Chemical pregnancy rate 43.8% vs 26.1%, P = 0.073 Clinical pregnancy rate (4 weeks) 39.6% vs 26.1%, P = 0.164 Clinical pregnancy rate (7 weeks) 35.4% vs 26.1%, P = 0.320 Ongoing pregnancy rate 16.7% vs 4.3%, P = 0.053 Live birth rate 18.8% vs 17.4%, P = 0.864	Jihad-e Daneshgahi Organization, East Azerbaijan, Iran.
Zargar et al., 2021 , <i>Clinical and Experimental Obstetrics & Gynecology</i>	Not reported	40	40	Randomization table, block size of 6	Not reported	Single-blind	Performed	Unclear	Pregnancy rate 12.5% vs 2.5%, P = 0.464 Live birth rate 12.5% vs 0.0%, P = 0.054	Ahvaz Jundishapur University of Medical Sciences
Bakhsh et al., 2022 , <i>JBRA Assisted Reproduction</i>	Not reported	50	50	Not reported	Not reported	Double-blind	Not reported	Unclear	Pregnancy rate 20.0% vs 13.3%, P = 0.620	Not reported
Ershadi et al., 2022 , <i>Journal of Family Medicine and Primary Care</i>	2019	45	45	Blocked randomization	Not concealed	Not reported	Not reported	Unclear	Chemical pregnancy rate 40.0% vs 27.0%, P = 0.192 Clinical pregnancy rate 33.0% vs 24.0%, P = 0.410	None
Nazari et al., 2019b , <i>Human Fertility</i>	2016–2017	49	48	Computer generated simple random tables in a 1:1 ratio	Not reported	Single-blind	Performed	Unclear	Chemical pregnancy rate 53.1% vs 27.1%, P = 0.009 Clinical pregnancy rate 44.9% vs 16.7%, P = 0.003	Research department of the school of medicine Shahid Beheshti University of Medical Sciences

(continued)

Table 2. Continued

Study, year, journal	Study period	PRP n	No PRP n	Randomization method	Allocation concealment	Blinding	Sample size calculation	Primary outcome	Effect of PRP on the probability of pregnancy: PRP vs no PRP P	Financial support
Rageh et al., 2020 , <i>Evidence Based Women's Health Journal</i>	July 2018–March 2019	75	75	Not reported	Not reported	Not reported	Not reported	Positive β -hCG rate 12 days following ET	Positive β-HCG rate 43.0% vs 15.0%, $P < 0.001$	Not reported
Zamaniyan et al., 2021 , <i>Gynecological Endocrinology</i>	February 2016–January 2019	60	60	Random number table	Not reported	Single-blind	Performed	Clinical pregnancy, implantation rates	Clinical pregnancy rate 48.3% vs 23.3%, $P \leq 0.001$ Chemical pregnancy rate 33.3% vs 16.7%, $P = 0.057$ Ongoing pregnancy rate 46.7% vs 11.7%, $P \leq 0.001$ Chemical pregnancy rate 34.6% vs 26.9%, $P = 0.400$ Clinical pregnancy rate 16.8% vs 10.9%, $P = ns$ Clinical pregnancy rate 45.8% vs 22.9%, $P = 0.011$ Chemical pregnancy rate 52.1% vs 33.3%, $P = 0.038$	Not reported
Dawood, 2022 , <i>The Egyptian Journal of Fertility of Sterility</i>	December 2018–October 2021	55	55	Computer generated simple random tables in a 1:1 ratio	Not concealed	Not-blinded	Not reported	Positive hCG, 14 days following ET	Chemical pregnancy rate 34.6% vs 26.9%, $P = 0.400$ Clinical pregnancy rate 16.8% vs 10.9%, $P = ns$ Clinical pregnancy rate 45.8% vs 22.9%, $P = 0.011$ Chemical pregnancy rate 52.1% vs 33.3%, $P = 0.038$	Not reported
El-Samman et al., 2022 , <i>Al-Azhar International Medical Journal</i>	August 2019–June 2021	52	52	Not reported	Not reported	Not reported	Not reported	Unclear	Clinical pregnancy rate 45.8% vs 22.9%, $P = 0.011$ Chemical pregnancy rate 52.1% vs 33.3%, $P = 0.038$	None
Safdarani et al., 2022 , <i>International Journal of Women's Health and Reproduction Sciences</i>	October 2017–April 2020	60	60	Block randomization	Not reported	Not blinded	Not reported	Unclear	Clinical pregnancy rate 51.7% vs 26.7%, $P = 0.005$ Chemical pregnancy rate 0.0% vs 3.3%, $P = 0.490$ Ongoing pregnancy rate 48.3% vs 25.0%, $P = 0.008$ Live birth rate 58.3% vs 28.3%, $P = 0.001$	Tehran University of Medical Sciences
Nazari et al., 2022b , <i>Reproductive Sciences</i>	2018–2020	209	209	Computer generated simple random tables in a 1:1 ratio	Not reported	Single-blind	Performed	Unclear	Clinical pregnancy rate 49.0% vs 19.3%, $P < 0.001$ Chemical pregnancy rate 51.5% vs 24.9%, $P < 0.001$ Live birth rate 39.3% vs 5.6%, $P < 0.001$	Not reported

ET, Embryo transfer; N, number of patients; P, P-value; PRP, platelet-rich plasma; RCT, randomized controlled trial; RIF, repeated implantation failure; vs, versus.

* Different results presented in tables and in abstract/main text.

** Better with PRP.

Table 3. Problems in the RCTs evaluating intrauterine infusion of autologous PRP in patients with RIF.

Study, year, Journal	Title	Problems identified
Allahveisi et al., 2020, Heliyon	The effect of PRP on the achievement of pregnancy during frozen embryo transfer in women with a history of failed implantation	1. No registration 2. No flow diagram 3. No description of method of randomization 4. No inclusion/exclusion criteria 5. No definition of RIF
Abduljabbar et al., 2022, Cureus	The effect of autologous PRP treatment on IVF/intracytoplasmic sperm injection and its impact on the endometrium and clinical pregnancy rate	1. No registration 2. No flow diagram 3. No description of method of randomization 4. No definition of RIF 5. Discrepancy in inclusion and exclusion criteria; in inclusion criteria EMT 0.4–0.7 cm but in exclusion EMT <0.7 cm 6. No information regarding the time PRP was administered
Baybordi et al., 2022, International Journal of Reproductive BioMedicine	The effect of PRP on the improvement of pregnancy results in repeated implantation failure: a RCT	1. Retrospective registration 2. Protocol was updated twice after registration with no clear reason 3. Different methods of blinding between original protocol registered and the updates
Zargar et al., 2021, Clinical and Experimental Obstetrics & Gynecology	Effects of intrauterine autologous PRP infusions on outcomes in women with repetitive IVF failures: a prospective randomized study	1. No information regarding the recruitment period 2. Change of the inclusion criteria during the study period. Women <40 years of age with at least one failure in the IVF process were included in the registered protocol however infertile women with at least two IVF failures and age below 41 years in the manuscript 3. Discrepancy between the inclusion criteria in the flow chart (at least two IVF failures with age below 45 years) and in the main text (women with 'at least two IVF failures and age below 41 years')
Bakhsh et al., 2022, JBRA Assisted Reproduction	Effects of autologous PRP in women with repeated implantation failure undergoing assisted reproduction	1. Wrong registration ID reported 2. Discrepancy in population characteristics in inclusion criteria between the registered protocol and the published manuscript (patients with at least 2 cycle of IVF failures & at least six good-quality embryos transferred in previous cycles in the registered protocol and infertile women with a history of RIF who had failed to achieve clinical pregnancy despite having four good-quality embryos transferred, and were candidates for IVF/ICSI or freeze embryo transfer cycles, aged <40 years with BMI < 30 kg/m² in manuscript) 3. Unclear whether fresh or frozen cycles were studied 4. Although according to the protocol women with uterine abnormalities were excluded, the analysis performed incorporates patients with Asherman's syndrome 5. No flow diagram 6. No description of the method of randomization 7. Pregnancy rates reported do not match with the number of pregnancies reported
Ershadi et al., 2022, Journal of Family Medicine and Primary Care	Evaluation of the effect of intrauterine injection of PRP on the pregnancy rate of patients with a history of implantation failure in the IVF cycle	1. No information regarding patient enrolment and allocation 2. No flow chart is present
Nazari et al., 2019b, Human Fertility	The effects of autologous PRP in repeated implantation failure: a RCT	1. Discrepancy in population characteristics in inclusion criteria between the registered protocol and the published manuscript (female age below 40 years is an additional inclusion criterion in the published manuscript while patients with thin endometrium that were included in the registered protocol appeared not be included in the published study)

(continued)

Table 3. Continued

Study, year, Journal	Title	Problems identified
Rageh et al., 2020, <i>Evidence Based Women's Health Journal</i>	PRP in RIF, hope or hype? A prospective randomized controlled study	2. Discrepancy regarding randomization method between the registered protocol and the published manuscript (registered as a single center, RCT with balanced randomization but published study reported 'Randomization was carried out using computer-generated simple random tables in a 1:1 ratio'.)
Zamaniyan et al., 2021, <i>Gynecological Endocrinology</i>	Effect of PRP on pregnancy outcomes in infertile women with RIF: a RCT	3. Unclear protocol used regarding the use of sham catheter 1. Retrospective registration of the study 2. No information regarding the method of randomization used, patient allocation, enrollment, and statistical analysis 1. The study was registered as not-blinded but published as blinded 2. The number of patients lost to follow up is significantly different between the two groups compared 3. Women above 40 years of age and those with BMI > 30 were excluded as per protocol of the study but shown in the flow chart and included in the intention-to-treat analysis 1. Although the study evaluated women with RIF more than 50% of the patients (55/110) had only a single embryo transfer failure
Dawood, 2022, <i>The Egyptian Journal of Fertility of Sterility</i>	Intrauterine infusion of autologous PRP before frozen embryo transfer in patients with prior implantation failure: a randomized controlled study	1. No registration ID 2. Discrepancy regarding the number of previous failed attempts between the registered protocol and the published manuscript 3. Unclear inclusion criteria
El-Samman et al., 2022, <i>Al-Azhar International Medical Journal</i>	Autologous intrauterine PRP instillation in repeated implantation failure in assisted reproductive techniques.	1. No registration ID 2. No adequate information regarding the randomization method used
Safarian et al., 2022, <i>International Journal of Women's Health and Reproductive Sciences</i>	Efficacy of the intrauterine infusion of PRP on pregnancy outcomes in patients with repeated implantation failure: a randomized control trial	1. No registration ID 2. No adequate information regarding the randomization method used
Nazari et al., 2022b, <i>Reproductive Sciences</i>	The effects of autologous PRP on pregnancy outcomes in repeated implantation failure patients undergoing frozen embryo transfer: a RCT	1. Same registration ID with the study by Nazari et al. (2019) 2. Unclear protocol used regarding the use of sham catheter 3. No information regarding patient allocation and concealment

EMT, endometrial thickness; ID, identity document; ITT, intention-to-treat; PRP, platelet-rich plasma; RCTs, randomized controlled trials; RIF, recurrent implantation failure.

Table 4. Intrauterine autologous PRP infusion protocols used in the available RCTs in patients with RIF.

PRP administration					
Study, year, Journal	Method of preparation	Route	Dose/mode of administration	Time	Adverse effects
Allahveisi et al., 2020, <i>Heliyon</i>	35 ml of autologous venous blood coated with 5 cc of acid citrate as the anticoagulant solution and centrifuged at 1700g for 12 min. Finally, the separated plasma was centrifuged for 7 min at 3300g.	Not reported	0.5 ml/once	48 h before ET	Not reported
Abduljabbar et al., 2022 <i>Cureus</i>	10–20 ml of autologous venous blood was drawn into a syringe that contained 2.5 ml of acid citrate anticoagulant solution and centrifuged at 1500 rpm for 10 min. The obtained plasma was then centrifuged at 3000 rpm for 5 min to extract the PRP.*	IUI catheter	0.5 ml/once	After oocyte retrieval	Not reported
Baybordi et al., 2022, <i>International Journal of Reproductive BioMedicine</i>	PRP was taken from the participant's autologous venous blood simultaneously, then prepared by centrifugal platelets and growth factors isolated and concentrated from the participant's serum.	Not reported	0.5–1 ml/once or twice per cycle	48 h before ET	None
Zargar et al., 2021, <i>Clinical and Experimental Obstetrics & Gynecology</i>	8.5 ml of autologous venous blood was drawn from the syringe pre-filled with 1.5 ml of anticoagulant solution and centrifuged immediately at 12 000g for 10 min. The plasma layer was collected to another tube and re-centrifuged at 12 000g for 10 min.	Not reported	1.5 ml/PRP (1.5 ml) was re-injected for two patients who did not have an appropriate endometrial thickness 48 h after the first injection	48 h before ET	Not reported
Bakhsh et al., 2022, <i>JBRA Assisted Reproduction</i>	8.5 cc autologous venous blood was taken, 2.5 cc acid citrate was added and was centrifuged at 1400 rpm for 10 min. The upper plasma was separated and re-centrifuged at 3500 rpm for 6 min to obtain the PRP.*	IUI catheter	0.5 cc	48 h before ET	None
Ershadi et al., 2022, <i>Journal of Family Medicine and Primary Care</i>	8 ml of autologous venous blood was taken in a syringe containing 2.5 ml of citrate acid, separated at 1200 rpm for 12 min. Then plasma was reabsorbed at 3300 rpm for 7 min to obtain the PRP.*	IUI catheter	0.5 ml	48 h before ET	Not reported
Nazari et al., 2019b, <i>Human Fertility</i>	8.5 ml of autologous venous blood was drawn in a syringe containing 1.5 ml of acid citrate and centrifuged at 1200 rpm for 10 min to separate the red blood cells. The solution was centrifuged again at 3300 rpm for 5 min to separate plasma and obtain the PRP.*	ET catheter under US guidance	0.5 ml	48 h before ET	Not reported
Rageh et al., 2020, <i>Evidence Based Women's Health Journal</i>	17.5 ml of autologous venous blood was drawn into a syringe containing 2.5 ml of acid citrate and centrifuged at 1200 rpm for 12 min to separate red blood cells, then plasma was centrifuged again at 3300 rpm for 7 min to obtain PRP.*	ET catheter	0.5–1 ml	48 h before ET	Not reported
Zamaniyan et al., 2021, <i>Gynecological Endocrinology</i>	17.5 ml of autologous venous blood was drawn into a syringe containing 2.5 ml of acid citrate and anticoagulant solution and centrifuged at 1200 rpm for 12 min to detach red blood cells, and then, plasma was centrifuged for a second time at 3300 rpm for 7 min.*	IUI catheter	0.5 ml	48 h before ET	Not reported

(continued)

Table 4. Continued

PRP administration					
Study, year, Journal	Method of preparation	Route	Dose/mode of administration	Time	Adverse effects
Dawood, 2022 <i>The Egyptian Journal of Fertility of Sterility</i>	15cc of autologous venous blood was collected in specified tubes for PRP at a temperature between 21 and 24°C and first centrifugation was performed at 1200 <i>rpm</i> for 12 min. The upper layer was transferred into another sterile tube and second centrifugation at 3300 <i>rpm</i> for 7 min was done. The upper 2/3 of the tube is discarded while the remaining 1/3 was homogenized and a total of 1 ml of PRP was obtained.* A syringe with an anticoagulant was used to draw a sample of the autologous venous blood of the patient (10 cm ³). PRP was obtained via sequential centrifugation (soft spin 200g/15 min, then hard spin 600g/6 min)	ET catheter under US guidance	1 ml	On Day 11 of menstrual cycle and may be repeated on Day 13 if endometrial thickness is still <7 mm	Not reported
El-Samman et al., 2022 , <i>Al-Azhar International Medical Journal</i>	8.5 ml of autologous venous blood was drawn from the 10-ml syringe pre-filled with 1.5 ml of acid citrate as an anticoagulant solution and was centrifuged at 1600 <i>rpm</i> for 10 min to separate red blood cells. Then, plasma was re-centrifuged at 3500 <i>rpm</i> for 6 min at room temperature (18°C) to obtain 1.5 ml lympho PRP*	IUI catheter under US guidance	0.5–0.8 ml Second sitting of PRP infusion will be performed in a few patients who fail to show desired results after 72 h 0.5 ml	72 h before ET in patients with endometrial thickness of 7 mm or more 48 h before ET	None Not reported
Safdarian et al., 2022 , <i>International Journal of Women's Health and Reproduction Sciences</i>	8.5 ml of autologous venous blood was drawn in a tube containing 1.5 ml of anticoagulant solution and centrifuged at 1200 <i>rpm</i> for 12 min to separate red blood cells. In second step, the harvested plasma was centrifuged at 3300 <i>rpm</i> for 5 min to acquire PRP.*	ET catheter under US guidance	0.5 ml	48 h before ET	Not reported

ET, embryo transfer; PRP, platelet-rich plasma; RCTs, randomized controlled trials; RIF, recurrent implantation failure; US, ultrasound.

* Centrifugal diameters are not stated in the published RCT(s) and therefore *g* cannot be calculated.

Table 5. Characteristics of the population studied in the RCTs evaluating intrauterine infusion of autologous PRP.

Study, year, Journal	Definition of RIF	Population age (years)	Subgroup analysis by age	Number of failed ETs	Embryo euploidy	ESHRE criteria* met/not met
Allahveisi et al., 2020, Heliyon	Not reported	Not reported	No	1–2	Unknown	Not met
Abduljabbar et al., 2022, Cureus	Not reported	18–44	No	≥1	Unknown	Not met
Baybordi et al., 2022, International Journal of Reproductive BioMedicine	Not reported	18–45	No	≥1	Unknown	Not met
Zargar et al., 2021, Clinical and Experimental Obstetrics & Gynecology	Infertile women with at least two IVF failures	≤41	No	≥2	Unknown	Not met
Bakhsh et al., 2022, JBRA Assisted Reproduction	Failure to achieve clinical pregnancy despite having four good-quality embryos transferred	≤40	No	≥2	Unknown	Not met
Ershadi et al., 2022, Journal of Family Medicine and Primary Care	History of two to three IVF failures	≤40	No	2–3	Unknown	Not met
Nazari et al., 2019b, Human Fertility	Failure to conceive after ≥3 ETs with high-quality embryos	≤40	No	1–10	Unknown	Not met
Rageh et al., 2020, Evidence Based Women's Health Journal	History of failed previous ETs attempts between 3 and 5 times	≤40	No	3–5	Unknown	Not met
Zamaniyan et al., 2021, Gynecological Endocrinology	Failure to conceive after ≥3 ETs with good-quality embryos	20–40	No	≥3	Unknown	Not met
Dawood, 2022, The Egyptian Journal of Fertility of Sterility	Failure to conceive after ≥3 ETs with good-quality embryos (four embryos) in women aged <40 years	20–35	No	1–4	Unknown	Not met
El-Samman et al., 2022, Al-Azhar International Medical Journal	Failure to conceive after ≥3 ETs with high-quality embryos and had at least one frozen good-quality blastocyst-stage embryo	18–35	No	2–5	Unknown	Not met
Safdarian et al., 2022, International Journal of Women's Health and Reproductive Sciences	Failure to conceive after ≥3 ETs with high-quality embryos	20–40	No	≥3	Unknown	Not met
Nazari et al., 2022b, Reproductive Sciences	Failure to conceive after ≥3 ETs with high-quality embryos	18–38	No	≥3	Unknown	Not met

ESHRE, European Society of Human Reproduction and Embryology; ET, embryo transfer; PRP, platelet-rich plasma; RCTs, randomized controlled trials; RIF, recurrent implantation failure.

* ESHRE criteria; when embryos of unknown euploidy are transferred, RIF is defined as the presence of three unsuccessful ETs in women under 35 years of age, four unsuccessful ETs in women aged between 35 and 39 years, or six unsuccessful ETs in women aged 40 years and above. When euploid embryos are transferred, RIF is defined as the presence of two unsuccessful ETs regardless of woman's age (Cimadomo et al., 2023).

How can future research evaluating intrauterine infusion of autologous PRP in RIF patients meaningfully guide clinical practice?

Future RCTs should be designed with strict adherence to the ESHRE criteria of RIF so that they are able to evaluate a homogeneous population of patients with a real clinical problem. Furthermore, future research should aim to identify the optimal methods for preparing and administering PRP. In this way, the resulting data can be meaningfully synthesized, leading to robust evidence on which clinicians can rely when making treatment decisions for RIF patients.

The potential of intrauterine infusion of autologous PRP to improve outcomes for women with RIF remains an important area of research in assisted reproductive technologies. However, the current evidence is insufficient to inform clinical practice, highlighting the need for well-designed studies to provide clearer guidance.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data underlying this article are available in the article and in its online [supplementary material](#).

Authors' roles

E.T.K.: conceived the idea for the study, contributed to study conception and design, performed the literature search, and contributed toward the data extraction, the analyses and interpretation of the data, and the drafting of the manuscript. E.M.K.: constructed the protocol and contributed toward the data extraction, the analyses and interpretation of the data, and the drafting of the manuscript. C.A.V.: reviewed the protocol, contributed toward the literature search, interpretation of the data, and revised the manuscript for important intellectual content. J.K.B.: reviewed the protocol and revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

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Conflict of interest

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