Efficacy of Intrauterine Infusion Platelet-Rich Plasma on the Outcomes of IVF-ICSI cycles in Women with Recurrent IVF-ICSI Failure: A Systematic Review and Meta-Analysis

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Abstract

Background: : In the context of reproductive healthcare, repetitive implantation failures present a serious challenge (RIF). Since the implications are now unclear, more research is required to fully assess the probable benefits of platelet-rich plasma (PRP) for pregnancy outcomes. Thus, the current meta-analysis was carried out to assess the impact of intrauterine PRP injection on pregnancy results in women with RIF.

Methods: A number of databases, including Web of Science, PubMed, the Cochrane Library, and Embase, were searched for English-language studies that examined how therapy with PRP affected the success of IVF/ICSI procedures in conceiving RIF women. Fresh cycles as well as frozen-thawed cycles were examined for this impact. Case-control, case series, self-control, and cross-sectional research were not included in this set of studies; instead, they focused on randomized controlled trials (RCTs) and non-randomized experimental investigations. The Newcastle-Ottawa Scale was utilized to assess the quality of the studies. For dichotomy outcome indicators, risk ratios (RRs) were computed; for continuous outcome parameters, weighted mean difference (WMD) with 95% confidence interval (CI) was computed. Either fixed-effect or random-effect models were used for these.

Results: Fifteen publications were assessed in the published literature for this meta-analysis. PRP-treated RIF women had better pregnancy outcomes than control patients, with greater rates of implantation, clinical pregnancy, and live birth.

Conclusion: Based on the study's findings, patients with RIF and those with poor endometrium may find PRP to be an effective therapy option. To determine the subgroup of women who could benefit from PRP the most, further extensive RCTs are needed.

Keywords: Recurrent implantation failure, platelet-rich plasma, clinical pregnancy rate, IVF-ICSI.

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Introduction

For couples who are infertile, assisted reproductive technologies (ART) have shown to be successful treatments. RIF is defined differently, but generally speaking, it refers to a woman under 40 years old who fails to become clinically pregnant after transferring three good-quality embryos in two fresh or frozen cycles. Immune aspects, low embryo quality, insufficient interaction between the developing embryo and endometrium, and decreased endometrial receptivity are some of the possible causes of RIF. Aside from factors relating to embryos, the primary factor is decreased endometrial receptivity (1,2).

Purified platelet-rich plasma (PRP) is made from the entirety of blood and contains four to five times the number of platelets that are normal (3). It has been observed that intrauterine PRP injection improves embryo adhesion and endometrial development. Numerous factors that support differentiation of cells, division, and immigration have been identified to be present in platelet granules (4, 5).

PRP implications on individuals with RIF have been studied in more recent research. PRP may increase these women's chances of implantation and clinical pregnancy, based on several authors' results (6, 7, 8).

Concerning the effect of PRP injection on the prognosis of pregnancy in RIF patients, there remains disagreement. Consequently, we assessed whether intrauterine PRP infusion enhances clinical maternal outcomes in patients with recurrent failures of implantation (RIF).

Methods

Plan for data Sources, and publication Search

Following the guidance of the favorable report materials for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and the Cochrane guidelines, the current systematic review was conducted (9). The Cochrane Library, MEDLINE, PubMed, Web of Science, Google Scholar, and Embase databases were used in this search. Search terms used in the headline or abstract of English-language articles released between the database's launch and January 2023 were: "In Vitro Fertilization" (IVF), "Intracytoplasmic sperm injection" (ICSI), "Embryo transfer," and "Platelet-rich plasma" (PRP), "Recurring Implantation Failure" (RIF), and "Recurrent implantation failure" (RIF). Furthermore, a manual search was conducted through references found in candidate articles and reviews to find other pertinent reports.

Outcome Measures, Study Selection, and Data Extraction

The following endpoints have been documented in some of the papers: endometrial dimension, rate of chemical pregnancy, incidence of pregnancy loss, rate of live birth, and rate of clinical pregnancy. Studies that used quasi-experiments and randomized controlled trials (RCTs) were evaluated. Following a search using keywords of the database, one author independently reviewed each study's abstract. The other writer independently extracted the data using the entire text versions of the pertinent papers.

Inclusion and Exclusion Criteria for This Review

Research that met the following requirements was considered for inclusion in our review: (1) the research study was a randomized controlled trial, or cohort study, (2) clinically confirmed pregnancy outcomes as the endpoints; (3) the treatment involved intrauterine PRP infusion close to the date of embryo transfer; (4) the population was diagnosed with a recurrent implantation failure (RIF); (5) the control group consisted of any other therapy, no treatment, or a placebo. Research that were self-control, case-control, case series, or cross-sectional were not included. Additionally, papers were disregarded if we could not find sufficient information about the approach or findings.

Risk of Bias and Data Synthesis

Bias was evaluated using RevMan 5.3 (Cochrane Collaboration, Oxford, UK). Based on allocation concealment, random sequence generation, blinding, selected reporting, insufficient data on outcomes, and other forms of bias, they were classified as low, unclear risk, or high bias. The Newcastle–Ottawa scaling method was used to assess the caliber of cohort research. Additionally, a specific determination was made concerning the measurement of exposures and outcomes, group contrast, and choice of research group.

(Table 1): lists the studies evaluated in this review.

Author , reference	Type of study	Number of patients	Age	Blinded	Embryo stage	Comparison	Blood vol.	Outcomes
Allahveisi et al., 2020 [11]	RCT	50	<40		Blastocyst	PRP vs. Control	35	Clinical Pregnancy rate, Implantation Rate , End. Thickness
Coksuer et al., 2019 [18]	retrospective cohort	273	21-39		cleavage stage	PRP vs. Control	8	CPR, BCPR, SAR
Coksuer et al., 2019 [18	retrospective cohort	273	21-39				8	
Dawood et al., 2022 [12]	RCT	104	20-35	open label	Blastocyst	PRP vs. Control	15	Clinical Pregnancy rate, Implantation Rate , End. Thickness, biochemical pregnancy rate
Ershadi et al., 2022 [13]	RCT	85	<40		cleavage stage	PRP vs. Control	8	Clinical Pregnancy rate, Implantation Rate, biochemical pregnancy rate, live birth rate, spontaneous abortion rate, End. thickness
Mehrafza et al., 2019 [19]	retrospective cohort	123			Cleavage & blastocyst	PRP vs. GCSF	8.5	Clinical Pregnancy rate, Implantation Rate, biochemical pregnancy rate
Nazari et al., 2020 [14]	RCT	138			Blastocyst	PRP vs. GCSF	8.5	Clinical Pregnancy rate, biochemical pregnancy rate
Nazari et al., 2022 [6]	RCT	113	18-38		Blastocyst	PRP vs. GCSF	8.5	clinical pregnancy rate, biochemical pregnancy rate, live birth rate, spontaneous abortion rate

Noushin et al., 2021 [10]	retro-spective cohort	318	<40		cleav-age stage	PRP vs. Control	10	clinical pregnancy rate, biochemical pregnancy rate, live birth rate, spontane-ous abortion rate
Obidniak et al., 2017 [8]	RCT	90	28-38	open label		PRP vs. Control		Clinical Pregnancy rate, Implantation Rate
Safdarian et al., 2022 [15]	RCT	120	20-40		Blasto-cyst	PRP vs. Control	8.5	Clinical Pregnancy rate, biochemical pregnancy rate, Im-plantation Rate, live birth rate, ongoing pregnancy rate
Tehranine-jad et al., 2021 [20]	Non-RCT	85	<35		Blasto-cyst	PRP vs. Control	10	Clinical Pregnancy rate, biochemical pregnancy rate, on-going pregnancy rate
Xu et al., 2022 [21]	retro-spective cohort	410	25-40	not given	Cleav-age & blasto-cyst	PRP vs. Control	20	Clinical Pregnancy rate, Implantation Rate, biochemical pregnancy rate, live birth rate, sponta-neous abortion rate, End. Thickness
Yuan et al., 2022 [22]	retro-spective cohort	64	25-40		cleav-age stage	PRP vs. Control	8.5	Clinical Pregnancy rate, Implantation Rate
Zamaniyan et al., 2021 [16]	RCT	120	20-40	blind	Blasto-cyst	PRP vs. Control	8.5	clinical pregnancy rate, ongoing preg-nancy rate, sponta-neous abortion rate
Zargar et al., 2021 [17]	retro-spective cohort	80	<41	single blind	cleav-age stage	PRP vs. Control	8.5	clinical pregnancy rate, biochemical pregnancy rate, live birth rate, spontane-ous abortion rate

RevMan 5.3 (Cochrane Collaboration, Oxford, UK) was used to evaluate the information. The influence of the PRP therapy on results were assessed using 95% confidence interval pooled risk ratios (RRs) (95% CI). RRs were estimated using the Mantel–Haenszel fixed effects model in the lack of heterogeneity. A random effects model was applied otherwise. Cochran's Q-test was used to statistically evaluate the heterogeneity among the research studies, with I2 > 50% indicating considerable heterogeneity. To ascertain whether PRP contributed to any heterogeneity in the pregnancy outcome, subgroup analysis was done in respect to the research format (i.e., cohort vs. RCT). A sensitivity analysis was performed to evaluate the robustness of the pooled estimates. When ten trials were included, Egger's test and funnel plot visual analysis were utilized to determine potential publication bias.

Results

Study Selection

After removing repetitions, the approach to searching yielded 240 possible matches from the databases; 81 of these studies were then removed for additional review based on their abstract. A single study was put forward in a solely abstract form, and it was dropped from the analysis due to inadequate data; six papers did not meet the inclusion criteria; nine of the papers were case series, case reports, and single-arm research; and one study was omitted because the control patients were patients from the initial embryo transfer rather than RIF. Since the control group exercised self-control, three investigations were disqualified. Given that the researcher already released a study involving individuals from an identical institute at the exact same span, one study was removed. 15 articles that satisfied the selection criteria were then given additional scrutiny. Below is a flowchart that illustrates the enrollment and choice processes for studies (Fig.1).

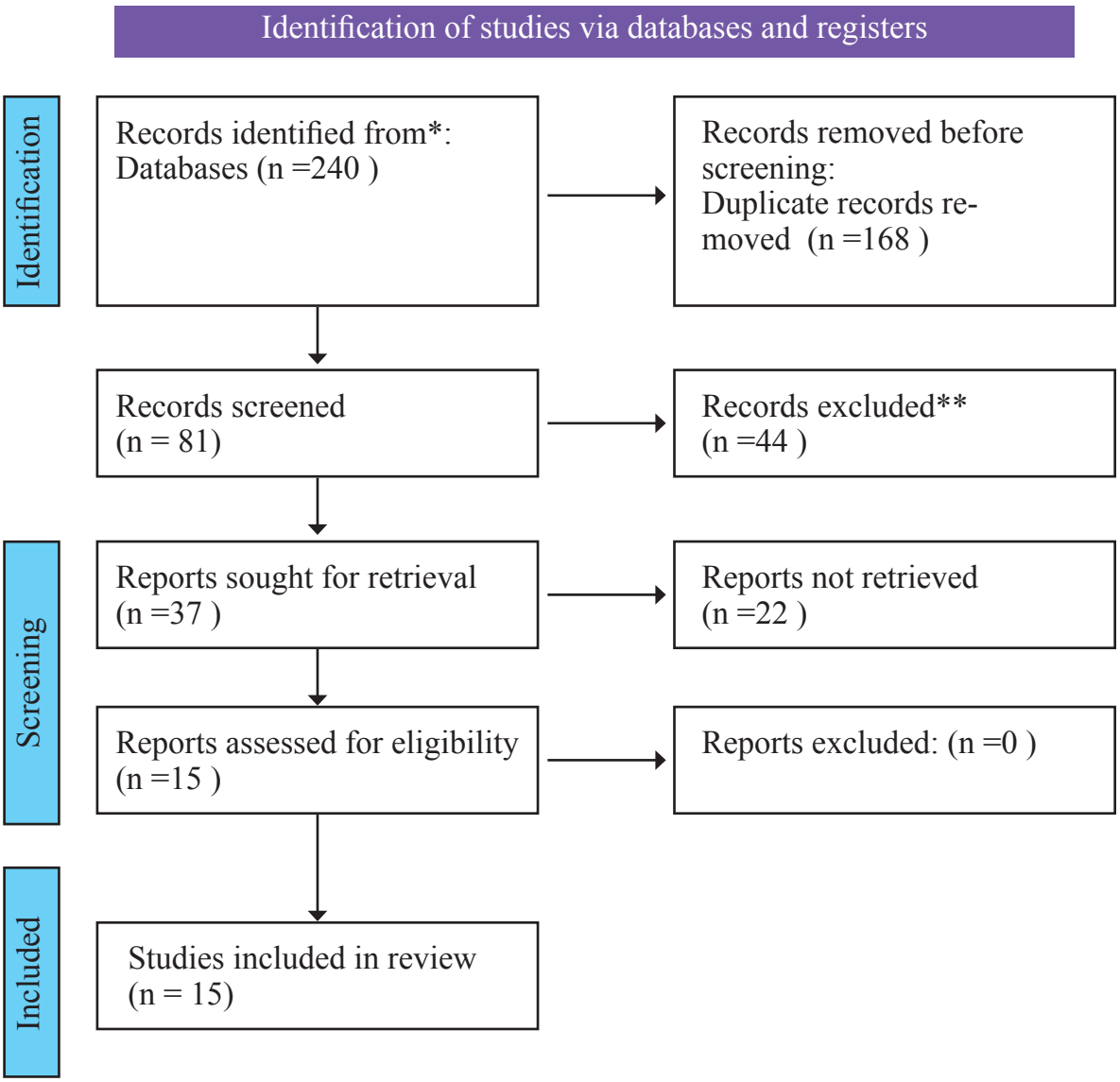

Fig.1 : PRISMA chart of Study selection.

Data about enrolled Investigations and Quality Evaluation

The key information for each of the 15 studies this review analyzed is listed in Table 1. These were released in the years 2017 through 2022. Six of the publications were cohort investigations, while nine of them described RCTs. 2478 women within the ages of 20 and 41 were enrolled in total throughout the 15 investigations. Every female participant in the PRP and placebo groups was RIF. Each study had a sample size of between 50 and 418 women. Peripheral blood in volumes ranging from 8 mL to 35 mL was used to prepare PRP. In four investigations, the embryo transfer was at the "cleavage stage," eight studies were at the "blastocyst stage," two research studies had both the cleavage and blastocyst phases, and one research did not specify the phase. In a single investigation, PRP given to the endometrial region (intrauterine, IU-PRP) or sub-endometrial (SE-PRP) were contrasted. This revealed that SE-PRP had no advantages over the less intrusive IU-PRP. Given that SE-PRP is invasive and runs the risk of harming the developing endometrium, it cannot be used during the index cycle of FET setup (10). Exclusively frozen-thawed cycles were used in twelve trials, two used fresh conditions (8, 22), and one used combined fresh and frozen conditions (17). All other studies utilized controls with no treatment, although one (19) contrasted the consumption of PRP with that of granulocyte colony stimulating factor (GCSF). Fig. 2 displays the bias risk across nine RCTs. Using the Newcastle-Ottawa Scale, the six cohort research' quality was evaluated (NOS). Two cohort investigations received an 8 while four cohort studies received a 7. The writings was of a very high caliber.

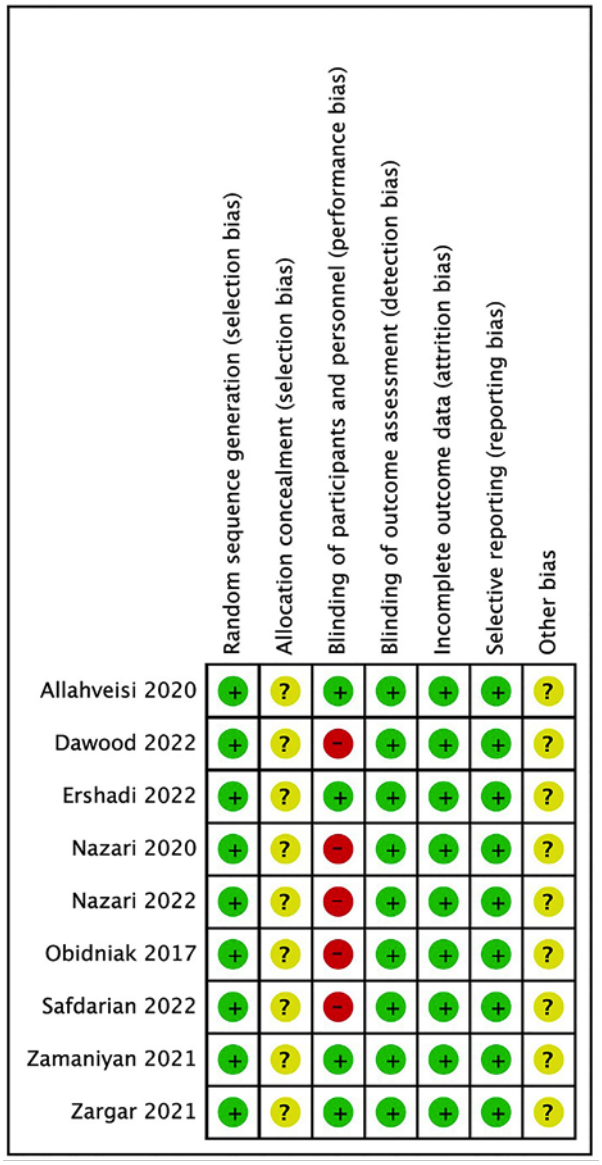

Fig.2 : An overview of the likelihood for bias in randomized controlled trials.

Clinical Results

The Clinical Pregnancy Rate

A meta-analysis of data from fourteen research investigations was carried out to ascertain the impact of PRP on the prevalence of clinical pregnancy (6, 8, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22). If we limit

our analysis to the eight RCTs [6, 8, 11, 13, 14, 15, 16, 17], we find that PRP patients significantly outperformed control patients in terms of pregnancy (risk ratios (RR) = 2.02, 95% CI: 1.56–2.61, p << 0.00001) (Fig. 3). An I22 score of 31% during the analysis of the study's heterogeneity suggested that there was no substantial heterogeneity. After the eight RCTs and the six non-RCT studies (10, 18, 19, 20, 21, 22) were taken into account, PRP patients showed a comparable rise in pregnancy (RR = 1.78, 95% CI: 1.51–2.1, p << 0.00001) (Fig. 4). Between-study heterogeneity was not found to be statistically significant (p = 0.18; I22 = 26%) (Fig. 3).

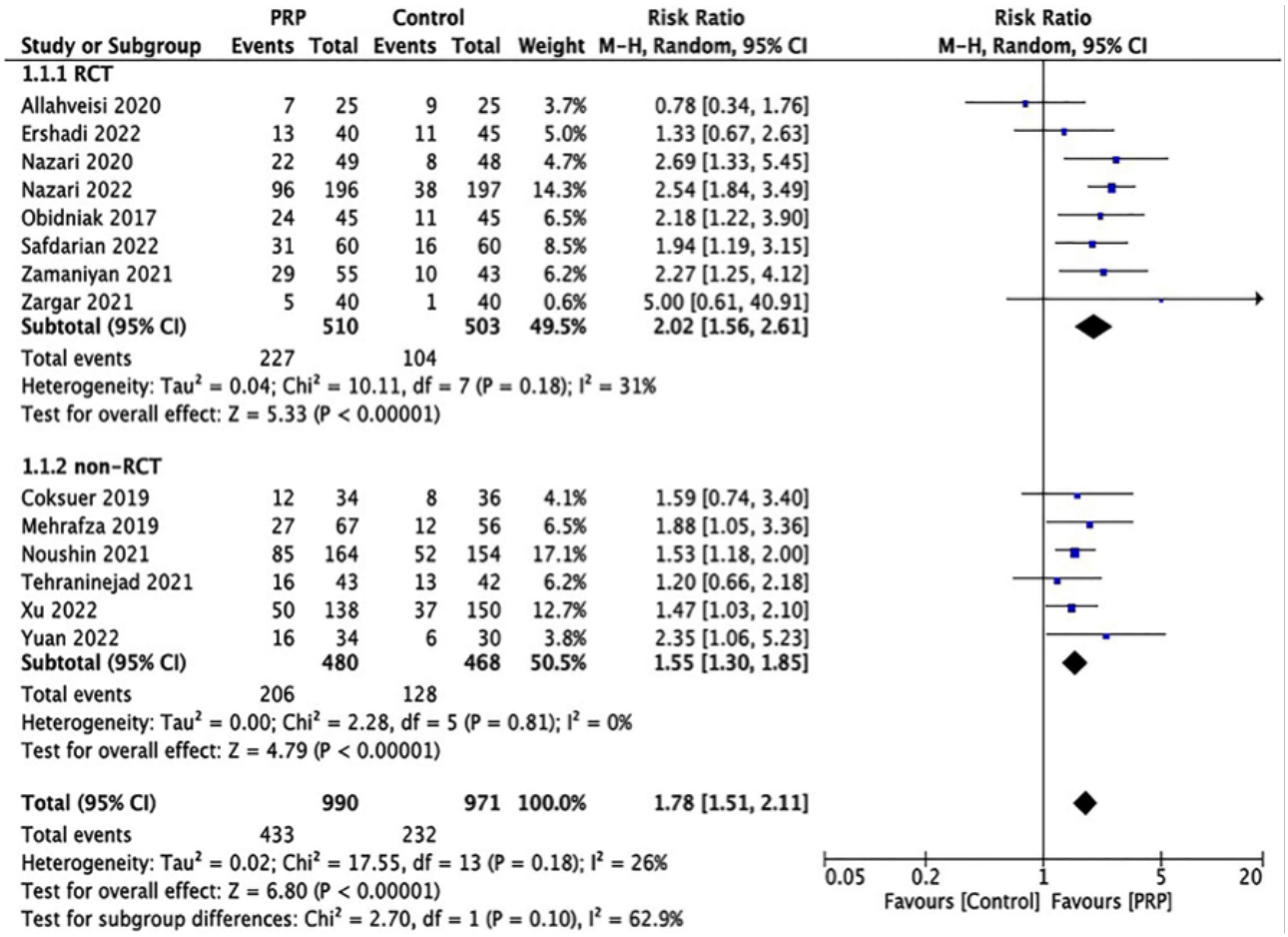

Fig.3: The forest plot displays the 95% confidence interval (CI) and risk ratios (RRs) for clinical pregnancy in both randomized controlled trials and non-RCT research.

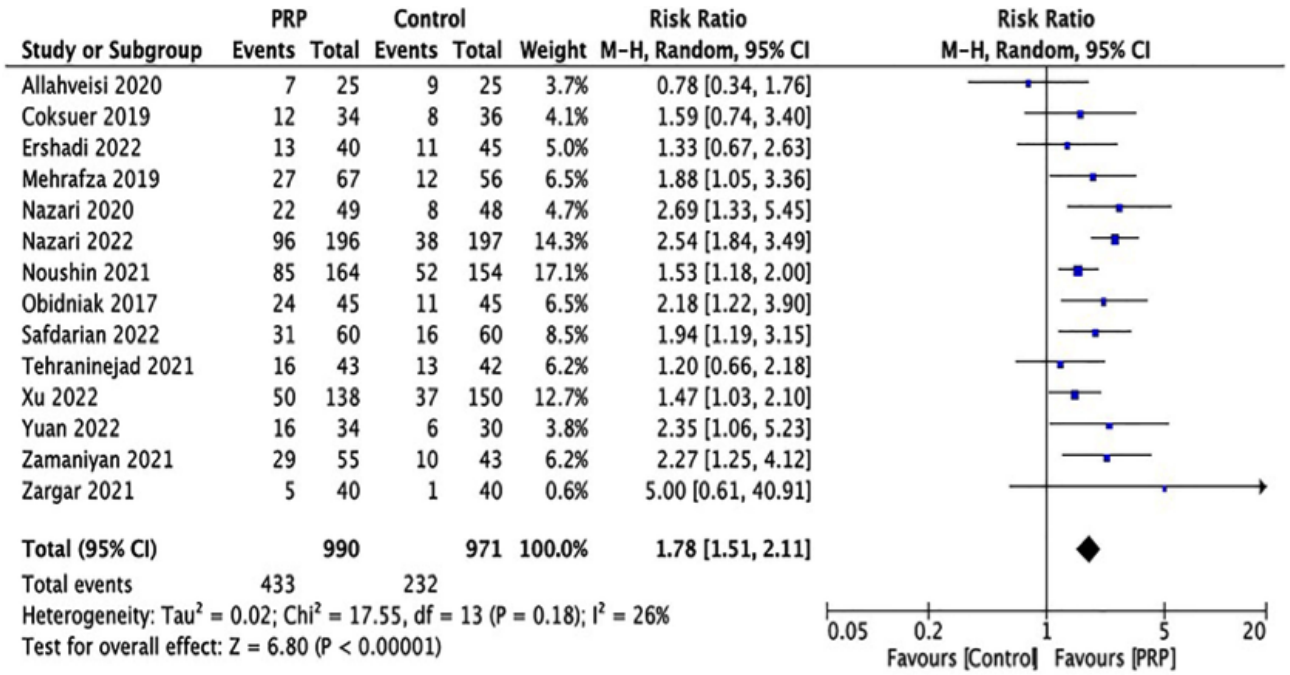

Fig.4 : Forest plot displaying RRs and 95% confidence interval (95% CI) for clinical pregnancy.

Live Birth Rate

The live birth rate has been stated in four articles (6, 11, 17, 21). Among them were 811 women with RIF, 399 of whom were PRP patients and 412 of whom were controls. There was no discernible change in the live birth rate amongst the two patient groups, according to a random-effects model (Fig. 5; RR = 2.62, 95% CI: 0.87–7.92, p = 0.09). Furthermore, for this research, an I22 of 87% was discovered. This suggests a significant degree of study heterogeneity, most likely as a result of the small sample sizes.

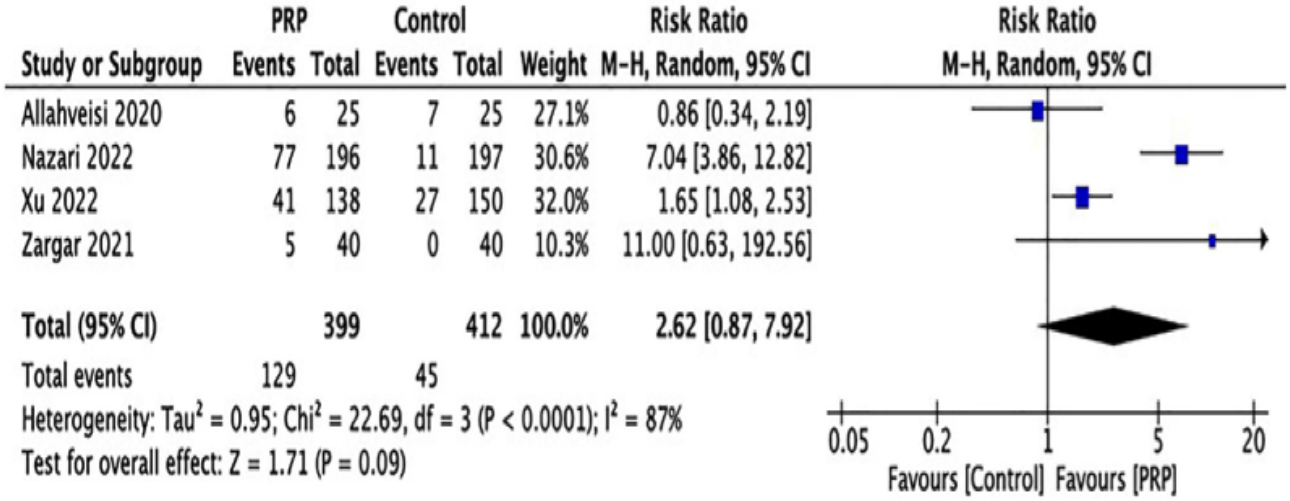

Fig.5 : Publications presenting the rate of live birth in RIF subjects are shown in a forest plot with individual and cumulative estimates of effect sizes and 95% confidence intervals.

Rate of Implantation

The rate of implantation has been documented in four research articles [15, 19, 21, 22]. There was no disparity among trials (p = 0.48; I22 = 0%), and a highly significant variance was observed comparing PRP and placebo-treated patients (RR = 1.79, 95% CI: 1.39–2.29, p << 0.00001), as illustrated in Fig. 6.

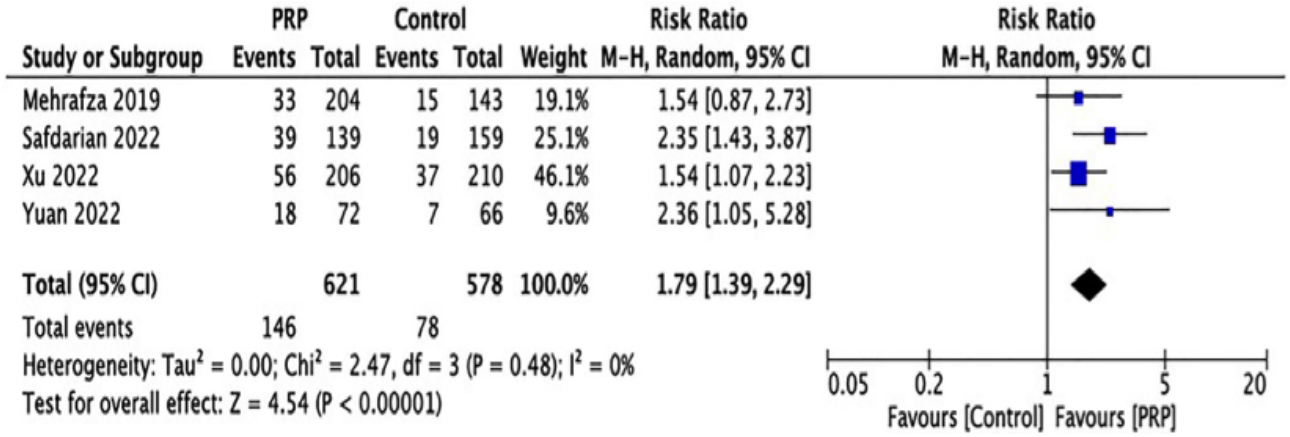

Fig.6: Forest plot from publications evaluating the rate of implantation in RIF people, displaying the individual and pooled effect size estimates and 95% confidence interval.

Spontaneous Abortion Rate

The rate of spontaneous abortions was reported in seven investigations [6, 10, 13, 16, 18, 21]. PRP versus placebo patients had significantly different spontaneous abortion rates, as seen in Fig. 7 (RR = 0.51, 95% CI: 0.30–0.81; I22 = 65%).

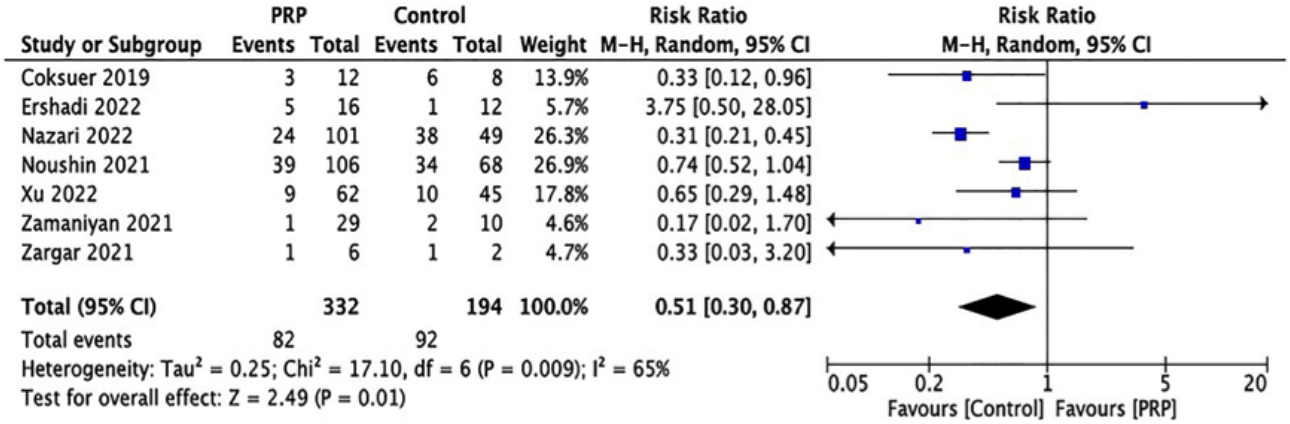

Fig.7: In research evaluating spontaneous abortion in women with reduced fetal development, a forest plot displays the individual and aggregate effect size estimates together with the 95% confidence interval.

Endometrial Thickness

Following PRP therapy, thickness of endometrium was altered in six trials [11, 13, 16, 17, 21, 23]. There were 512 controls and 506 cases in all. Endometrial thickness was higher in RIF patients treated with PRP compared to the control group, as illustrated in Fig. 8 (standardized mean difference (SMD): 0.39, 95% confidence interval (CI): –0.23 to 1.1; p = 0.22, I22 = 95%).

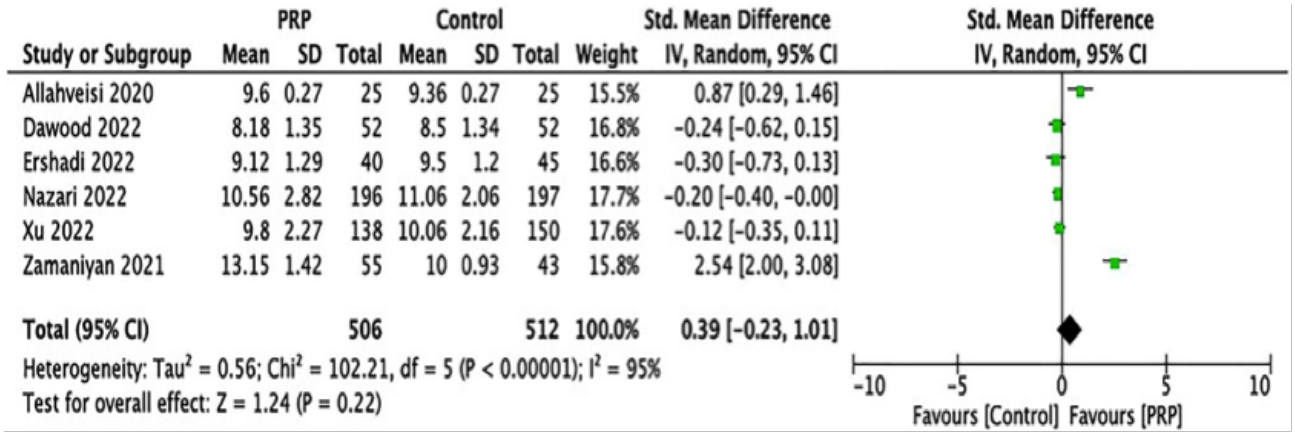

Fig.8: In research presenting normalized mean differences for thickness of the endometrium in RIF individuals, a forest plot displaying individual and cumulative effect size estimates and 95% CI is presented.

Discussion

This systematic review evaluated PRP therapies intended to enhance RIF women's pregnancy outcomes. Our analysis showed that compared to controls, women who underwent intrauterine PRP injection had significantly increased percentages of implantation, clinical pregnancy, implantation, and endometrial thickness. PRP therapy also increased endometrial thickness. Nearly all of the trials that made up this meta-analysis demonstrated benefits from PRP treatment, such as increased rates of clinical pregnancy and live delivery and decreased rates of abortion and implantation failure.

Additionally, past systematic reviews with bigger sizes are updated in this investigation (24, 25, 26, 27). The current research of PRP-treated RIF women reveals higher percentages of live births as well as biochemical, clinical, and continuing pregnancies, which aligns with the conclusions of other evaluations. RCTs are generally seen as more persuasive than cohort studies because of their objectivity. After subgroup analysis, the inclusion of nine RCTs and six cohort studies contributed to the objectivity and plausibility of this meta-analysis. A fresh embryo transfer was performed on some participants in two trials (8, 22), while a frozen-thawed transfer was performed on subjects in a single investigation (17). As a result, we did not take them out of the statistics in order to perform a subgroup analysis.

Most pregnancy outcomes had minimal statistical homogeneity, indicating similar consequences over the course of the research. In 2020, Maleki-Hajiagha et al. released the first meta-analysis (27) which supported current research by finding that IU-PRP boosted the rate of clinical pregnancy in the FET cycle. Three RCTs and four cohort investigations were incorporated in the meta-analysis by Maleki-Hajiagha et al. (27), and there was a considerable amount of heterogeneity between the studies. Further large RCTs on the routine use of PRP in RIF women are necessary in order to offer more clear results, as another prior meta-analysis (24, 25) also demonstrated that the IU-PRP has a good influence on the pregnancy outcomes for RIF patients. Additional meticulous research is necessary to validate the influence of IU-PRP in RIF.

Centrifugation is the method used for acquiring platelet concentrate, or platelet-rich plasma. By releasing platelet alpha granules, PRP provides a low-cost method of delivering large amounts of PDGF, TGF-β, and VEGF (28). A number of variables, including the embryo itself and several cytokines, growth factors, hormones, proteomic, metabolomic,

genomic and transcriptome components, are involved in defining endometrial acceptance, including platelet bioactivity (29).

The current meta-analysis has few drawbacks that need to be taken into account. First of all, it was challenging to extrapolate the results because the majority of the investigations only included data from a small number of nations and ethnic populations. The consistent pooling indices amongst studies, the meta-analysis's resilience to sensitivity testing and subgroup analysis, and the inclusion of research from various embryo transfer cycles and embryo forms are among its strong points. First, there were very few pertinent studies with evidence of excellent quality available for analysis, including only 8 RCTs that compared PRP with a placebo and studies (n = 14). Even though we took our time and performed extensive literature searches to find all pertinent research, we cannot completely rule out the chance that publication bias influenced our findings.

However, it can't go without saying that this meta-analysis is one of the very first ones to address such an essential therapeutic strategy. The novelty of the studies involved in the meta-analysis & the comprehensive analysis of aspects linked to PRP uses and efficacy.

Conclusions

According to our meta-analysis and systematic review, autologous PRP therapy administered intrauterine can improve implantation, clinical pregnancy, and live birth in patients with reduced fibrosis. However, broad knowledge about difficulties and unfavorable pregnancy outcomes was unavailable, so we were unable to draw firm conclusions. It will take more sizable, multicenter RCTs with a double-blind methodology to conclusively determine whether PRP is beneficial for these individuals.

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