Review / Derleme

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How autologous platelet-rich plasma affects pregnancy and birth outcomes in women with repeated embryo implantation failure: A prisma-compliant meta-analysis

Otolog trombosit açısından zengin plazma, tekrarlayan embriyo implantasyon başarısızlığı olan kadınlarda gebelik ve doğum sonuçlarını nasıl etkiler: Prizma uyumlu bir meta-analiz

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Abstract

Repeated implantation failure refer to failure to conceive after three or more embryo transfer attempts. Several interventions were offered to improve maternal and fetal outcomes. Our objective was to investigate the impact of platelet-rich plasma (PRP) as a promising intervention to improve both pregnancy and birth outcomes. We searched PubMed, Scopus, Web of Science, and Cochrane Central, in addition to other relevant resources of grey literature. Only clinical trials were eligible to be included. We performed the meta-analysis using a random effects model. Eight randomized clinical trials, enrolling 1038 women with more than 3 implantation failure attempts, were included. We found a significant increase regarding all our prespecified primary outcomes. Chemical pregnancy rate [relative ratio (RR): 1.96, 95% confidence interval (CI): 1.61, 2.39; p<0.001], clinical pregnancy rate (RR: 4.35, 95% CI: 1.92, 2.88; p<0.001), and live birth rate (RR: 4.03, 95% CI: 1.29, 12.63; p=0.02) were found to be statistically significant and increased in patients who received PRP compared with the control group. Implantation rate (RR: 1.98, 95% CI: 1.34, 2.75; p<0.001), miscarriage rate (RR: 0.44, 95% CI: 0.23, 0.83, p=0.01), and multiple pregnancy rate (RR: 2.56, 95% CI: 1.02, 6.42, p=0.04) were also found to be significantly increased in the PRP group. We provide strong evidence on how intrauterine PRP can improve implantation, pregnancy, and birth outcomes in RIF women, which should direct clinicians to consider this intervention as a very effective tool in assisted reproductive techniques.

Keywords: Platelet-rich plasma, implantation failure, assisted reproductive techniques and in vitro fertilization

Öz

Tekrarlanan implantasyon başarısızlığı, üç veya daha fazla embriyo transferi denemesinden sonra gebe kalamamayı ifade eder. Maternal ve fetal sonuçları iyileştirmek için çeşitli müdahaleler önerildi. Bu çalışmanın amacı, trombosit açısından zengin plazmanın (PRP) hem gebelik hem de doğum sonuçlarını iyileştirmek için umut verici bir müdahale olarak etkisini araştırmaktır. Gri literatürün diğer ilgili kaynaklarına ek olarak PubMed, Scopus, Web of Science ve Cochrane Central'ı araştırdık. Yalnızca klinik araştırmalar dahil edilmeye uygun bulundu. Meta-analizi rastgele etkiler modeli kullanarak gerçekleştirdik. Üçten fazla başarısız implantasyon girişimi olan 1038 kadının dahil edildiği sekiz randomize klinik araştırma dahil edildi. Önceden belirlenmiş tüm birincil sonuçlarımızda önemli bir artış bulundu. Kimyasal gebelik oranı [risk oranı (RO): 1,96, %95 güven aralığı (GA): 1,61, 2,39; p<0,001], klinik gebelik oranı (RO: 4,35, %95 GA: 1,92, 2,88; p<0,001) ve canlı doğum oranı (RO: 4,03, %95 GA: 1,29, 12,63; p=0,02) kontrol grubuna göre PRP uygulanan hastalarda istatistiksel olarak anlamlı ve artmış bulundu. İmplantasyon oranı (RO: 1,98, %95 GA: 1,34, 2,75; p<0,001), düşük oranı (RO: 0,44, %95 GA: 0,23, 0,83, p=0,01) ve çoğul gebelik oranı (RO: 2,56, 95% GA: 1,02, 6,42, p=0,04) de PRP grubunda anlamlı olarak artmış bulundu. Rahim içi PRP'nin RIF kadınlarda

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implantasyonu, hamileliği ve doğum sonuçlarını nasıl iyileştirebileceğine dair güçlü kanıtlar sunuyoruz ve bu da klinisyenleri bu müdahaleyi yardımcı üreme tekniklerinde çok etkili bir araç olarak düşünmeye yönlendirmelidir.

Anahtar Kelimeler: Trombositten zengin plazma, implantasyon başarısızlığı, yardımcı üreme teknikleri ve tüp bebek

Introduction

The process of implantation relies on two crucial factors: a healthy embryo and a well-developed endometrium. A genetically normal zygote must attach to and invade a thoroughly decidualized endometrium, which should ideally measure 7 mm or more for successful implantation[1,2]. Hence, if implantation fails with a genetically normal zygote, it indicates endometrial insufficiency.

Repeated implantation failure (RIF) is defined as nonpregnancy after three high-quality embryo transfers or after ten or more multiple transfers. Deficient endometrial thickness is responsible for nearly 10% of failed intracytoplasmic sperm injection procedures[3]. Various fertility-enhancing modalities have been proposed to counter thin endometrial linings, including estrogen, pentoxifylline, vitamin E for expanding endometrial thickness, aspirin, local sildenafil, tamoxifen, and other factors to enhance endometrial perfusion[4,5]. Despite these multiple approaches, RIF remains a major contributing cause to the failure of assisted reproduction, whose success rate does not exceed 30%.

Platelet-rich plasma (PRP) is extracted from the centrifugation process of whole blood to obtain platelets[6]. PRP contains a high concentration of growth factors that play a significant role in the process of tissue repair and regeneration. These growth factors include transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and others. These factors accelerate tissue healing, promote angiogenesis, stimulate cell proliferation and differentiation, and modulate inflammation. The efficacy of PRP has been reported in various clinical settings, including orthopaedics, and dentistry. Recently, PRP has also emerged as a promising intervention for improving pregnancy outcomes in patients with RIF, and since the autologous peripheral blood is the source of PRP, it offers a unique, cost-effective, and practical personalized medicine that is also non-immunogenic[7].

PRP has been investigated in various research fields, including ophthalmology, orthopedics, and wound healing, but its role in infertility is yet to be fully explored. Due to its proliferation and nourishment capabilities, PRP has been proposed as a new approach to promote endometrial growth and receptivity. The concept was initially proposed by Chang et al.[8] in 2015, who demonstrated that intrauterine infusion of autologous PRP 48 h before embryo transfer in IVF procedures increased endometrial growth and allowed successful implantation in RIF patients. Other studies have demonstrated that PRP can enhance clinical and chemical pregnancy outcomes in such patients, but conclusive answers to its efficacy are still in question[9]. Therefore, the aim of this systematic review and meta-analysis was to explore the value of autologous intrauterine PRP infusion through clinical trials conducted on IVF patients.

Materials and Methods

We strictly followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the guidelines of the Cochrane Handbook[10]. The review protocol was registered on PROSPERO and is available under the registration ID (CRD42022355535).

Search Strategy

We systematically searched Cochrane Central, Embase, MEDLINE (through PubMed), Scopus, and Web of Science (from inception to 31 July 2022). Also, we searched other sources of grey literature such as Google Scholar, Research Gate, clinical trials registries (e.g., clinicaltrials.gov, and WHO Clinical Trials Registry, etc.), and conference proceedings for unpublished and in-press articles. A manual search for citations and reference lists of the relevant published articles was performed to check for additional eligible studies.

To conduct our search, we used various search terms, abbreviations, and synonyms, including "implantation failure", "embryo transfer", "platelet-rich plasma", "PRP", "assisted reproductive technology", and "in vitro fertilization". We have documented our complete search terms and strategy in Supplementary File 1. We limited our search to English articles but did not specify any particular year range for publication.

Eligibility Criteria

The studies that were considered for inclusion had to meet certain criteria, which included (1) the criteria that the study participants were subfertile women who had experienced RIF. RIF was defined as a failure to achieve a clinical pregnancy after at least three attempts of embryo transfer (ET)[11], (2) the intervention consisted of the intrauterine infusion of autologous PRP before ET, (3) the comparison group must not have received any intervention or placebo, but no other active interventions were allowed, and (4) only randomized controlled trials (RCTs) were eligible for inclusion. Studies with missing data or articles that did not provide adequate information on methodology or results were excluded.

Study Selection

Two authors (AS & HMF) independently screened the exported search records to identify the potentially eligible titles and abstracts with exclusion of irrelevant results. Then, full texts of all eligible studies were retrieved to be assessed for their adherence to our inclusion criteria. In the case of an opinion

discrepancy, a third investigator (YS) was involved in the discussion.

Data Extraction

Two authors (YS & SE) independently extracted the following demographics and characteristics from the finally included articles using a standardized data extraction online form. discrepancies were solved by a discussion with a third reviewer (AS). Extracted data were (1) study characteristics (study design, sample size, country, and year of publication), (2) patient demographic criteria (average age, RIF definition, ovarian stimulation protocol), (3) intervention characteristics (preparation method, time, amount, and method to introduce to patients), (4) study endpoints and measured outcomes.

Outcome Measurements

Our main objectives were to determine the chemical pregnancy rate, clinical pregnancy rate (CPR), and live birth rate (LBR) per patient. "Chemical pregnancy" was obtained as a positive detectable serum level of β-hCG two weeks after frozen-thawed ET, while a "clinical pregnancy" was defined based on the definitive clinical signs of pregnancy or the presence of one or more intrauterine gestational sacs on transvaginal ultrasound following six weeks of ET. "Live birth" referred to the delivery of one or more living infants, as stated in reference[12].

Regarding the secondary outcomes, we included the following outcomes: Implantation rate (IR) per embryo, multiple pregnancy rate (MPR) per patient, and miscarriage rate (MR) per clinical pregnancy. We additionally assessed postinterventional endometrial thickness (PIET). The "implantation rate" was determined by dividing the number of gestational sacs identified by transvaginal ultrasound by the number of embryos transferred. If there were two or more intrauterine embryos identified by transvaginal ultrasound, it was deemed a "multiple pregnancy." The loss of the fetus before 20 weeks of gestation is commonly referred to as a miscarriage[12].

The Risk of Bias Assessment

We used the Cochrane Risk of Bias assessment tool 1 to evaluate the methodological quality of the included studies, which is suggested in the Cochrane Handbook[13]. This assessment tool considers six different factors be determined.

Statistical Analysis

We carried out statistical analysis using Cochrane Collaboration's RevMan 5.3, using a relative ratio (RR) with a 95% confidence interval (CI) as the effect estimate. We determined significance by a p-value of less than 0.05 and calculated the I^2 value to determine statistical heterogeneity. We chose to use a random effects model because of possible variations in PRP preparation and induction techniques. As our meta-analysis used a limited number of studies, we did not assess publication bias. Additionally, we conducted sensitivity analysis to account for heterogeneity in LBR outcomes between studies. We also conducted a subgroup analysis to identify the origin of heterogeneity in PIET using the time difference between PRP infusion and endometrial thickness measurements.

Results

Search Results

We found 2602 search results through a comprehensive electronic computer-based database search. In addition, six articles were identified via manual screening of reference lists of relevant review articles. After removing duplicated results, we found 877 unique publications. Of these, 865 were excluded by title and abstract screening. Then, we evaluate the full texts of the 12 potentially relevant articles for their adherence to our prespecified selection criteria. Only eight articles[14-21] were eligible to be included in both qualitative and quantitative analysis. Figure 1 shows the PRISMA flow diagram for our study.

Study Characteristics

All trials were conducted between 2017 and 2022 in Iran for Obidniak et al.[21], which was conducted in Russia. The overall included participants were 1,038 (518 patients received PRP intrauterine infusion). The average age of the included patients was 34.7±6.3 years. All studies for the Russian trial reported using the GnRH antagonist protocol for ovarian stimulation.

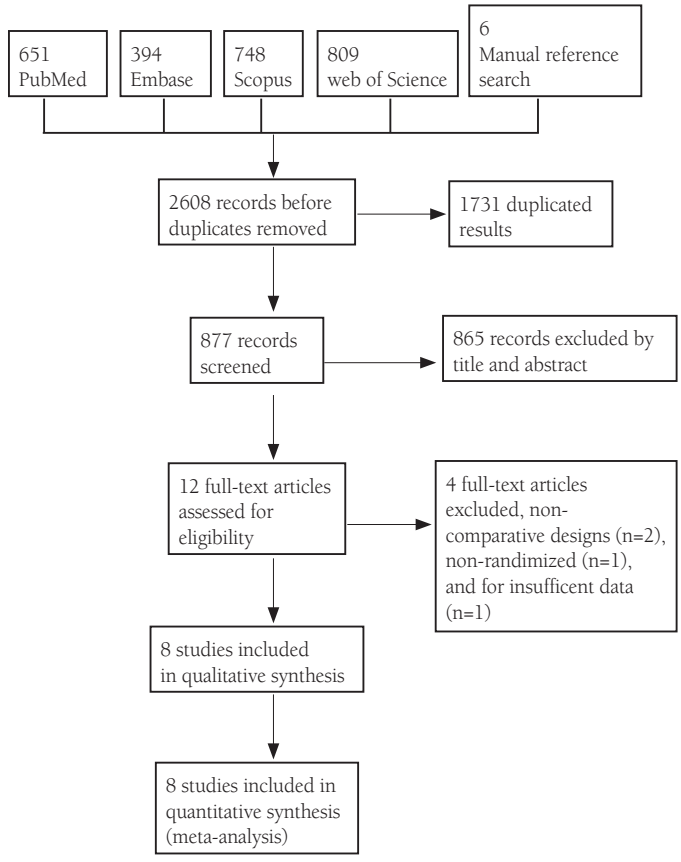

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

Five studies compared PRP versus standard treatment, two trials used no therapy in the control group, and one compared PRP versus sham catheter. All trials used the same PRP infusion protocol by administering 0.5 mL of PRP 48 h prior to the time of ET except in two studies that used a dose of 0.5-1 mL (Eftekhar et al.[15]) and 2 mL (Obidniak et al.[21]). The transfer of the embryo in frozen condition was done in all of the included studies (Table 1).

Primary Outcomes

Our 3 primary outcomes of interest were found to be significantly increased in the PRP group compared to the control group (Figure 2). CPR was mentioned in all included studies (n=981) and it was found to be significantly higher in patients who received PRP intervention compared to women in the control group [RR: 2.35, 95% CI: (1.92, 2.88), p<0.001]. The chemical pregnancy rate was evaluated in six studies (n=851). Our meta-analysis showed a significantly higher probability of chemical pregnancy in women who received PRP intervention [RR: 1.96, 95% CI: (1.61, 2.39), p<0.001]. Three RCTs (n=553) reported LBR following the intervention compared with standard treatment. They revealed a significantly higher incidence of live birth in patients treated with PRP [RR: 4.03, 95% CI: (1.29, 12.63); p=0.02]. However, substantial heterogeneity was found between the effect estimates of 3 studies (I^2=83%).

Secondary Outcomes

Regarding the secondary outcomes (Figure 3), IR was reported in 4 studies (n=391). A significantly successful and higher IR was associated with the PRP group compared to the control group [RR: 1.98, 95% CI: (1.43, 2.75), p<0.001]. Two hundred and fifty clinically pregnant women were evaluated for miscarriage in 5 studies. PRP infusion could achieve a significant reduction in MR compared to women who received standard treatment or sham catheters [RR: 0.44, 95% CI: (0.23, 0.83), p=0.01]. MPR was mentioned in three RCTs (n=511). There was a significant increase in multiple pregnant cases in the PRP group [RR: 2.56, 95% CI: (1.02, 6.42), p=0.04]. PIET was measured in 4 trials (n=617). PRP intrauterine infusion was not associated with a significant increase in endometrial thickness [MD: 1.18, 95% CI: (-0.04, 2.40), p=0.06]. Substantial heterogeneity was found between the effect estimates of 4 studies (I^2= 98%).

Heterogeneity Assessment

Regarding LBR heterogeneity (I^2=83%), we performed a sensitivity analysis excluding Safdarian et al.[18] from the pooled

Table 1. characteristics of the included trials

Study ID	Location	Participants (PRP/ Control)	Age (Years) Mean ± SD	Ovarian Stimulation Protocol	PRP Infusion Protocol	Control	Reported Outcomes
Nazari et al.[14], 2022 (1)	Iran	418 (209/209)	34.1±3.7	(GnRH) Antagonist	0.5 mL, 48 h before ET	Standard treatment	CPR, Chemical pregnancy, LBR, IR, PIET, MPR, MR
Nazari et al.[17], 2022 (2)	Iran	50 (25/25)	35.7±5.1	(GnRH) Antagonist	0.5 mL, 48 h before ET	Standard treatment	CPR, LBR, MR
Safdarian et al.[18], 2022	Iran	120 (60/60)	33.4±4.9	(GnRH) Antagonist	0.5 mL, 48 h before ET	No therapy	CPR, Chemical pregnancy, LBR, IR, MPR, MR
Zamaniyan et al.[20], 2021	Iran	120 (60/60)	33.8±6.3	GnRH) Antagonist	0.5 mL, 48 h before ET	Standard treatment	CPR, Chemical pregnancy, IR, PIET, MPR, MR
Nazari et al.[19], 2020	Iran	97 (49/48)	35.7±3.4	(GnRH) Antagonist	0.5 mL, 48 h before ET	Standard treatment	CPR, Chemical pregnancy
Nazari et al.[16], 2019	Iran	60 (30/30)	33.9±2.7	(GnRH) Antagonist	0.5 mL, 48 h before ET	Sham catheter	CPR, Chemical pregnancy, PIET
Eftekhar et al.[15], 2018	Iran	83 (40/43)	31.9±2.2	(GnRH) Antagonist	0.5-1 mL on day 13th of cycle	Standard treatment	CPR, Chemical pregnancy, IR, PIET, MR
Obidniak et al.[21], 2017	Russia	90 (45/45)	35.2±6.4	N/R	2 mL before ET	No therapy	CPR, IR

PRP: Platelet-rich plasma, CPR: Clinical pregnancy rate, LBR: Live birth rate, MPR: Multiple pregnancy rate, MR: Miscarriage rate, PIET: Postinterventional endometrial thickness, IR: Implantation rate, GnRH: Gonadotropin releasing hormone, and N/R: Not reported

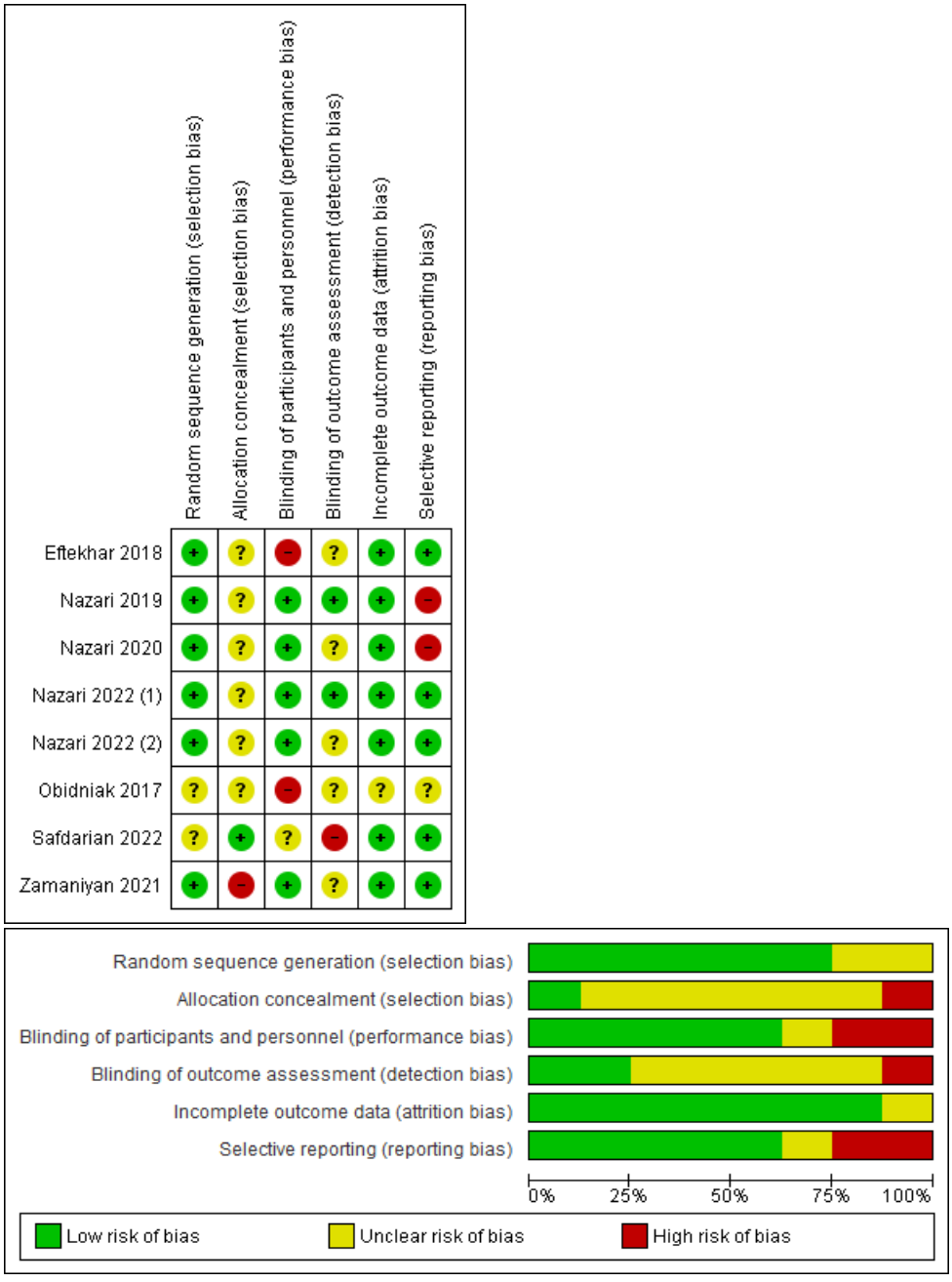

Figure 2. Risk of bias (ROB) summary and graph

analysis, which resolved heterogeneity (I^2=0%). This resulted in a significant increase in the effect estimate and CI [RR: 7.03, 95% CI: (3.91, 12.66), p<0.001]. To solve PIET heterogeneity (I^2=98%), subgrouping analysis was performed according to the period from PRP infusion to time to measure endometrial thickness and revealed a significant increase in endometrial thickness after 48 h of PRP intrauterine infusion [SMD: 0.64, 95% CI: (0.20, 1.08), p=0.005].

The Risk of Bias Assessment

The overall risk was low. However, one trial was evaluated to have some concerns due to unclear determination of the patient selection process. Another trial was judged to have a high risk of bias due to inadequate allocation concealment. Additionally, two studies had a high risk of performance bias. With regard to attrition bias, one study was deemed to have a high risk. While all trials had a low risk of reporting bias, two studies were found to have a high risk. We have provided the risk of bias summary and graph in the figures file (Figures 4-9).

Discussion

Repeated embryo implantation failure is a challenging complication in assisted reproductive techniques. Despite advancements in fertility treatment, some women continue to

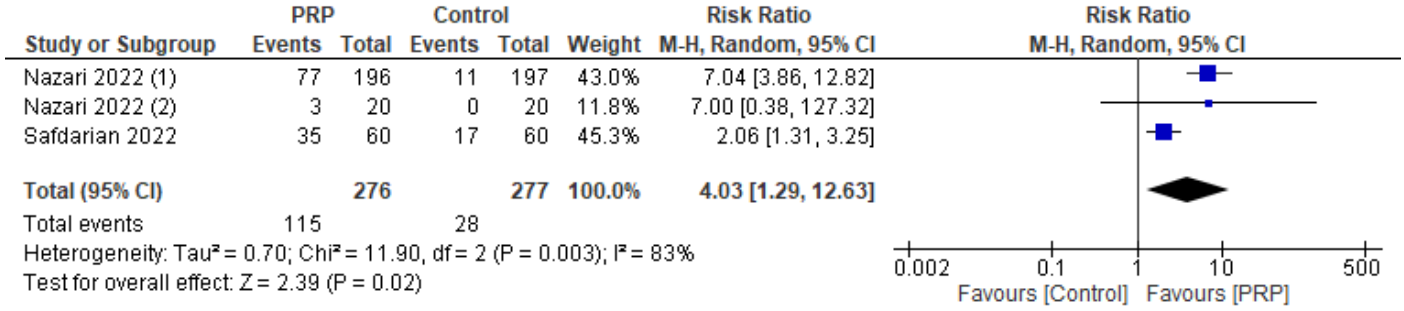

Figure 3. Meta-analysis of live birth rate (LBR) per patient

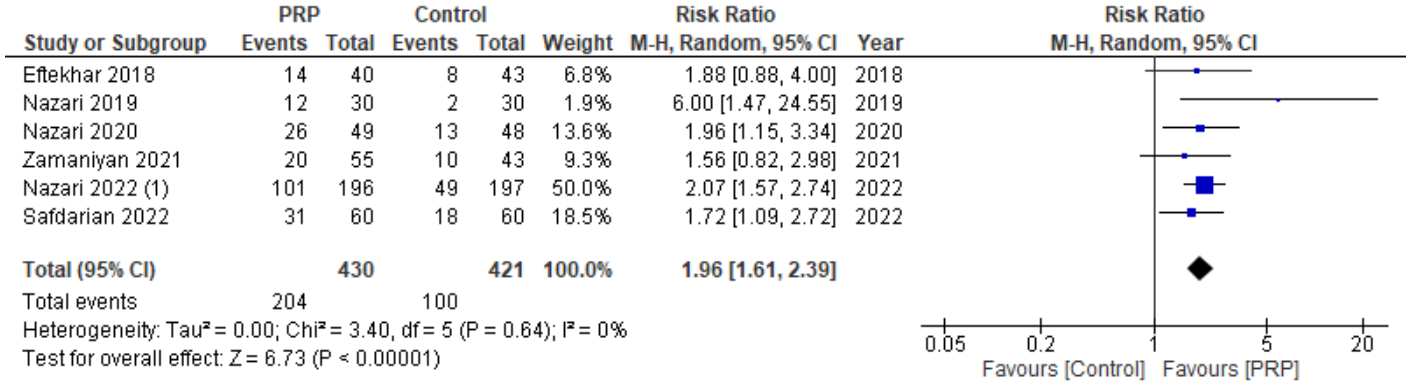

Figure 4. Meta-analysis of Chemical pregnancy rate per patient

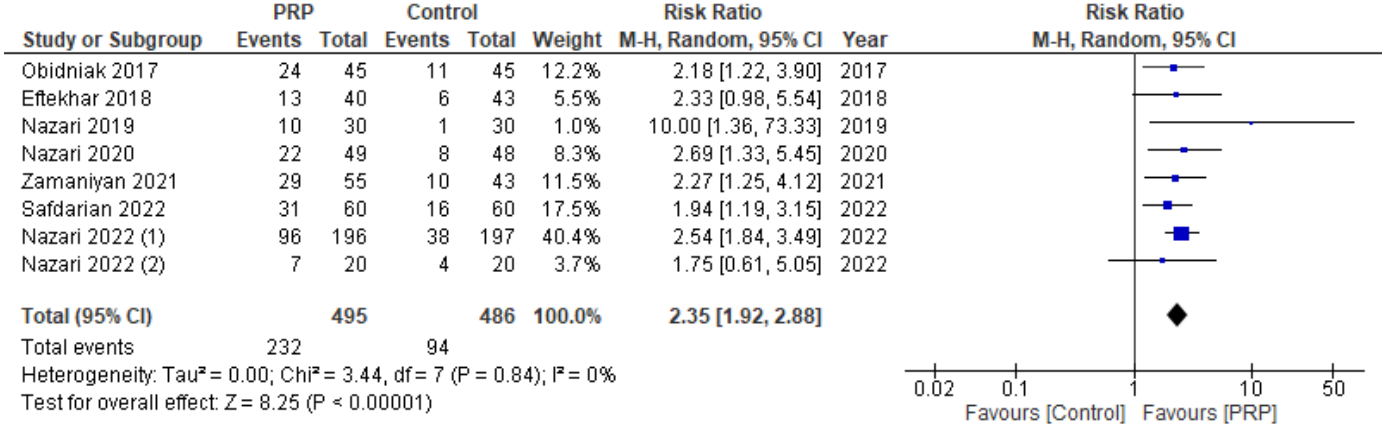

Figure 5. Meta-analysis of Clinical Pregnancy Rate (CPR) per patient

struggle with failed implantations, leading to disappointment and emotional distress. PRP has recently emerged as a promising intervention for improving pregnancy outcomes in women who have experienced RIF. PRP contains a high concentration of growth factors that have been shown to promote angiogenesis, cell proliferation, and differentiation. These mechanisms can enhance endometrial receptivity, increase IRs, and ultimately improve pregnancy rates. PRP therapy has been investigated in several studies and has shown encouraging results, particularly in patients with thin endometrium, RIF, or poor ovarian response to assisted reproductive techniques. In this way, PRP therapy can improve patient outcomes and offer hope to women struggling with RIF.

Findings Summary

Our review encompassed eight randomized clinical trials involving 1038 women who had undergone at least three unsuccessful embryo implantation attempts. We identified three main findings: first, intrauterine infusion of PRP before ET was linked to a notable increase in implantation, chemical, and CPRs and a significant rise in LBR. Second, in contrast to the control group, intrauterine PRP infusion was found to reduce the MR in patients with RIF. Third, despite a higher PIET in the PRP group,

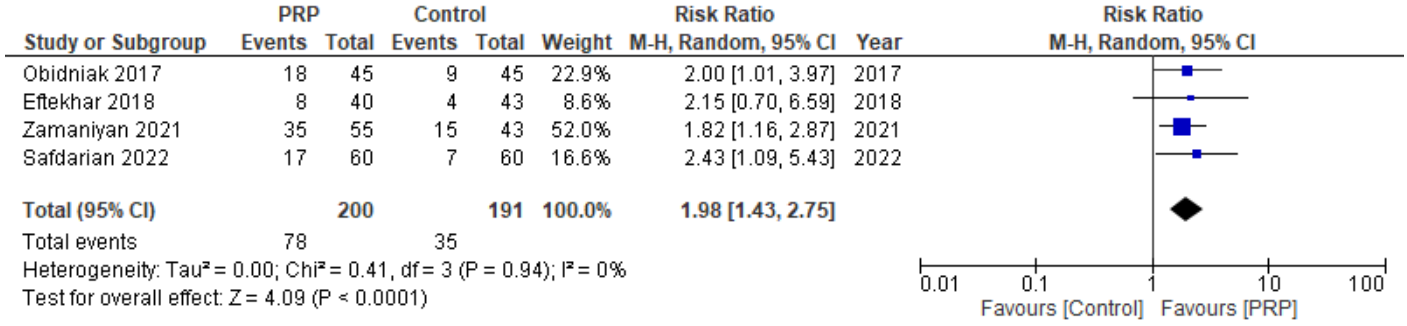

Figure 6. Meta-analysis of Implantation Rate (IR) per embryo

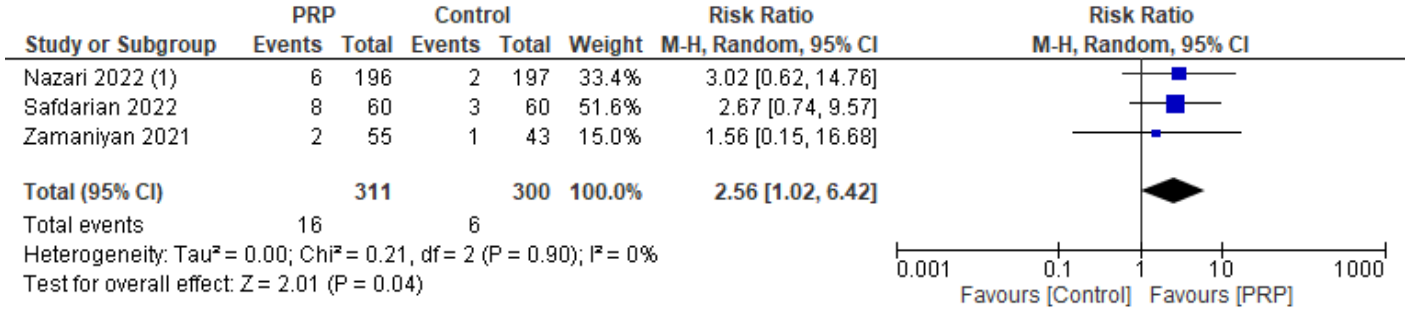

Figure 7. Meta-analysis of Multiple Pregnancy Rate (MPR) per patient

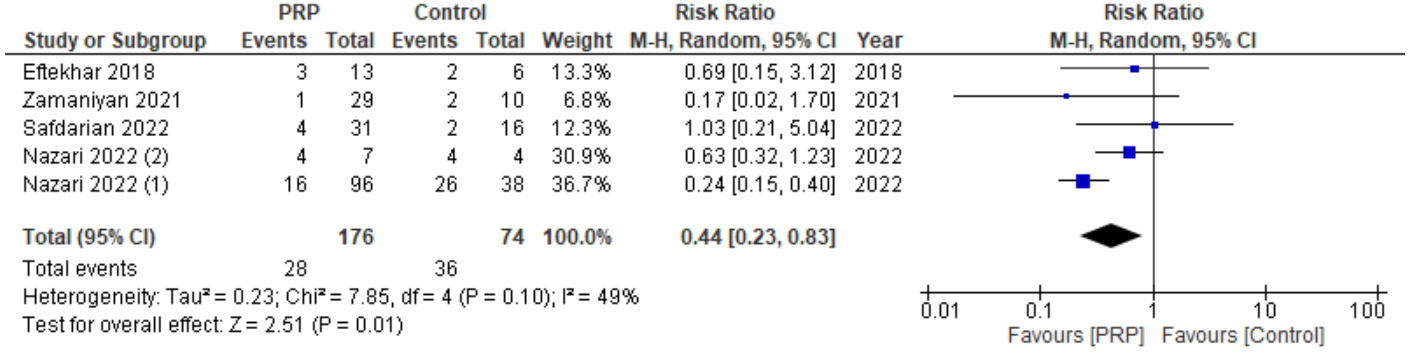

Figure 8. Meta-analysis of Miscarriage Rate (MR) per clinical pregnancy

there was no significant difference between the two groups concerning this factor. Nonetheless, based on subgroup analyses, a substantial increase in thickness was detected after 48 h.

Possible Physiological Basis

There are several physiological mechanisms by which PRP can improve pregnancy and birth outcomes in RIF women. These mechanisms include promoting angiogenesis, stimulating cell proliferation and differentiation, and modulating inflammation. One of the crucial factors for successful implantation is adequate endometrial receptivity. Studies have shown that PRP contains growth factors that can improve angiogenesis, cell proliferation, and differentiation[22]. Angiogenesis increases blood flow to the endometrium, which can improve thickness, vascularity, and receptivity, consequently facilitating embryo implantation. PRP also releases cytokines and other growth factors that have anti-inflammatory properties. Chronic inflammation plays a detrimental role in endometrial receptivity by interfering with important processes such as angiogenesis, cell proliferation, and differentiation. PRP's anti-inflammatory properties can combat this by reducing inflammation and resulting damage, therefore improving endometrial receptivity and promoting successful implantation.

Moreover, PRP has been found to contain a high concentration of growth factors such as PDGF, VEGF, and TGF-β1 that aid in the formation of a suitable endometrial microenvironment and enhance endometrial regeneration that can lead to successful embryo implantation. Overall, PRP regenerative and immunomodulatory actions prove promising for optimizing endometrial receptivity, promoting successful implantation, and improving pregnancy rates in patients with RIF.

Additionally, some recent reports attributed these to the

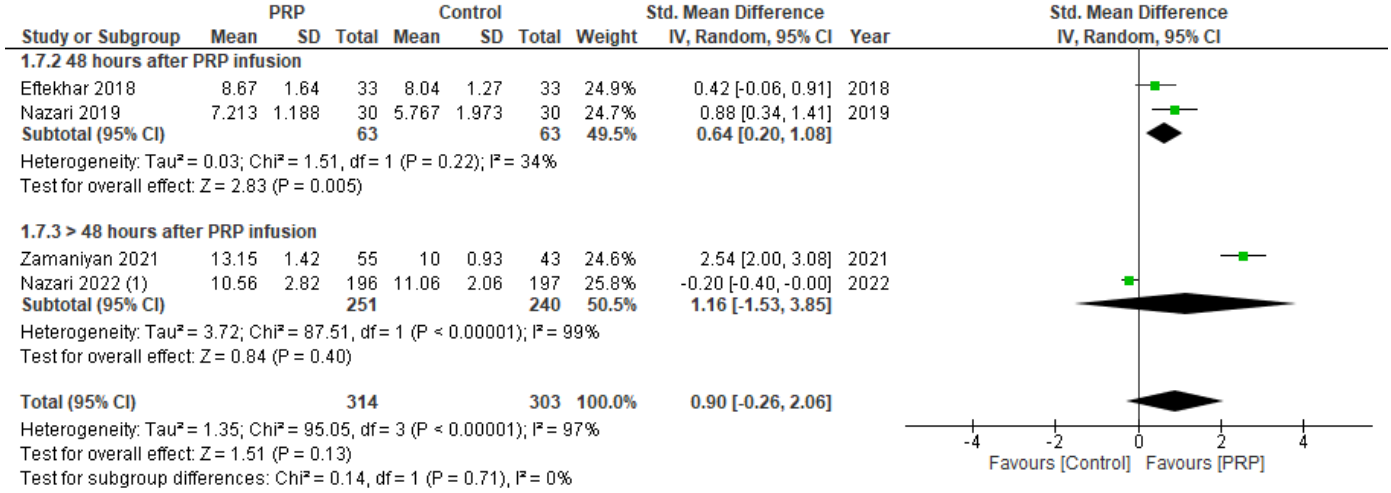

Figure 9. Meta-analysis of Post-interventional endometrial thickness (PIET), subgrouped according to the period from PRP infusion to time to measure the endometrial thickness

numerous growth factors that improve endometrial thickness and vascularity, which help tissue proliferation and differentiation, enhancing its receptivity and stabilizing pregnancy[22,23]. Additionally, platelets and extravillous trophoblast cells take the place of the endothelium and muscle layer in spiral arteries, leading to their expansion and creating sufficient blood flow to the intervillous region of the placenta[24].

Our Results in the Context of Literature

A recent meta-analysis was published by Liu et al.[25] investigating PRP efficacy on pregnancy outcomes. They included both cohort studies and clinical trials (5 RCTs and 3 Cohorts) that enrolled women with at least 2 failed attempts of ET, which may have limited generalizability when applied to RIF patients. However, our results were in the same context in pregnancy outcomes (CPR, LBR, and MR) but not in MPR. Safdarian and his colleagues recently conducted a clinical trial that evaluated the effectiveness of 0.5 mL intrauterine infusion of PRP before 48 h of ET[18]. Their results revealed that pregnancy outcomes and LBR could be improved by the effect of PRP, despite having some concerns about a significant preterm delivery detected in the PRP group compared with the control group.

Multiple studies have reported that intrauterine infusion of PRP leads to a significant increase in endometrial thickness in women with RIF[15,26]. This increase in endometrial thickness has been linked with higher pregnancy rates, suggesting that PRP impact on endometrial thickness is a crucial factor in improving pregnancy outcomes in women with RIF. PRP has been found to have a positive impact on endometrial thickness in women with RIF. Studies have shown that PRP contains a high concentration of growth factors such as PDGF and TGF-β1, which promote angiogenesis and cell proliferation. This increases blood flow and oxygenation to the endometrium, which ultimately increases endometrial thickness.

In addition to promoting endometrial angiogenesis and cell proliferation, PRP's anti-inflammatory properties can play a role in increasing endometrial thickness. Inflammation can cause fibrosis and scarring in the endometrium, which can lead to thinning of the endometrial lining.

PRP plays a key role in reducing inflammation and promoting tissue repair and regeneration. This can prevent injury and scarring, leading to thicker and more receptive endometrium. Another two recent clinical trials suggest a substantial benefit when using PRP intrauterine catheter in women with a thin endometrium (<7 mm) that interferes with successful embryo implantation[15,26]. They reported that PRP could improve endometrial growth quality in addition to increasing the chance of obtaining a clinical pregnancy in women with thin endometrium. This may be promising for patients with impaired implantation due to thin endometrium.

Study Implications

PRP is a treatment method that involves using a patients own blood, which is centrifuged to separate the plasma and platelets. In the case of RIF, PRP injections may help to improve the quality of the endometrial lining. This, in turn, may improve the chances of successful embryo implantation and reduce the risk of miscarriage. This study is the only review that pools the effect estimates of only RCTs evaluating the effectiveness of PRP on women with RIF, which generates a higher level of evidence regarding the use of PRP in resistant cases undergoing assessed reproductive techniques. Moreover, we predetermined our population to include patients who couldnot achieve a clinical pregnancy after at least 3 failed attempts of high-quality ET. This guaranties a piece of evidence that could help in decision making for RIF patients.

Study Limitations

A major limitation of this study is that 7 out of 8 are from the same research group. All trials were investigated on an Iranian population for Obidniak et al.[21], which is a strong limitation for the evidence generalizability. However, there are some

ongoing clinical trials outside Iran. Moreover, we noticed some variations regarding the PRP preparation protocols which may result in a variable composition and concentrations of its different contents. Studies have reported different centrifugation techniques for different timings and different processing[27,28].

Conclusion

We provided strong evidence on how intrauterine infusion of PRP can increase implantation and pregnancy outcomes in RIF patients, which should direct clinicians to consider this intervention as a very effective tool in assisted reproductive techniques.

Ethics

Peer-review: Internally and internally peer-reviewed.
Authorship Contributions
Concept: A.S., S.E., Y.S., D.H., H.M.F., Design: A.S., S.E., Y.S., D.H., H.M.F., Analysis or Interpretation: A.S., S.E., Y.S., D.H., H.M.F., Literature Search: A.S., S.E., Y.S., D.H., H.M.F., Writing: A.S., S.E., Y.S., D.H., H.M.F.
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study received no financial support.

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Supplementary File 1. PubMed search strategy

(((implantation failure) OR (RIF) OR (recurrent implantation failure) OR (assisted reproductive technology) OR (in vitro fertilization) OR (intracytoplasmic sperm injection) OR (embryo transfer)) AND ((platelet-rich plasma) OR (PRP)))