A Systematic Review

Role of Platelet-rich Plasma in Unexplained Recurrent Implantation Failure – A Systematic Review and Meta-analysis of Randomised Control Trials

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Abstract

Background: Recurrent implantation failure (RIF) is a challenging clinical situation and various strategies have been tried to improve the pregnancy rate in RIF. Platelet-rich plasma (PRP), which is obtained from the autologous blood samples of a person and is multiple times richer in platelets and other growth factors helps improve endometrial receptivity. **Objective:** This study has been conducted to summarise the evidence and quality of evidence available so far regarding the role of PRP in cases of unexplained RIF. **Materials and Methods:** An electronic database search for randomised clinical trials comparing PRP against routine care in women with unexplained RIF was performed on PubMed, EMBASE, SCOPUS and Cochrane Central. Two independent reviewers conducted a literature search and retrieved data using the predefined eligibility criteria. Bias assessment was done using the Cochrane Collaboration Network Risk of Bias Tool version 2. The quality of evidence was determined and a summary of the findings table was prepared for individual outcomes using GRADEpro software. **Results:** We identified 1146 records, and after removing duplicates, 531 records were screened. Out of these, 22 studies reached full-text screening and nine studies were included in the final review. We are uncertain about the effect of PRP due to the very low quality of evidence and we have little confidence that the administration of PRP had any significant effect on improving the live birth rate in women with RIF (odds ratio [OR]: 7.32, 95% confidence interval [CI]: 4.54–11.81, I^2 = 40%). Similarly, the quality of evidence was low for the clinical pregnancy rate, so we are uncertain if the administration of PRP had any significant effect on the clinical pregnancy rate (OR: 3.20, 95% CI: 2.38–4.28, I^2 = 0%). **Interpretation:** The current review suggests that there may be some beneficial effects of PRP in women with RIF, but the quality of evidence is very low and we are uncertain of the benefit and have little confidence in these findings. **Limitations:** Limitations are the small sample size of most studies, a short follow-up period, non-uniformity in the definition of outcomes and very low quality of evidence. **Registration:** The protocol was registered on PROSPERO (CRD42021292209).

Keywords: *In vitro fertilisation, platelet-rich plasma, recurrent implantation failure*

Introduction

The rapidly evolving field of assisted reproductive technology (ART) has allowed couples to

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attain viable pregnancies, who previously could not conceive for a variety of reasons.[1] This technique has provided new hope for struggling couples; however, it is full of challenges.[2] One of the major challenges is recurrent implantation failure (RIF) and it renders both the treating physician and couples frustrated and desperate.[3] The European Society of Human Reproduction and Embryology defines RIF as >3 failed embryo transfer cycles with high-quality embryos ('The Vienna Consensus: Report of an Expert Meeting on the Development of ART Laboratory Performance Indicators' 2017[4]). Another widely accepted definition is defined as the failure to achieve a clinical pregnancy after the transfer of at least four good-quality embryos in fresh or frozen embryo transfer (FET) cycles in a woman under 40 years of age.[5] There are many factors, which affect the outcome of the implantation process such as embryo quality, endometrial receptivity and immunological factors. Many techniques and interventions have been developed for RIF management such as blastocyst transfer, assisted hatching, endometrial scratching and immune therapy.[6] Human endometrial tissue has multiple receptors for growth factors, adhesion molecules, cytokines and other features that promote endometrial and embryonic interaction essential for implantation.[7]

Autologous platelet-rich plasma (PRP) is obtained from the autologous blood samples of a person and is multiple times richer in platelets and other growth factors such as vascular endothelial growth factor, transforming growth factor, platelet-derived growth factor and epidermal growth factor than circulating blood.[8] In recent years, PRP has been under investigation for its application in different fields such as wound healing for chronic wounds, ophthalmology, orthopaedics and dentistry.[9-12] Many studies have reported that PRP is beneficial in wound healing, regenerative medicine and tissue engineering.[8] Moreover, PRP is considered a safe and beneficial treatment in diabetic foot ulcers and in bone surgery.[13,14]

In recent years, the application of intrauterine infusion of autologous PRP to promote endometrial growth and receptivity is rising due to its positive effect on endometrial growth and pregnancy outcome.[15] PRP is used alongside routine care in fertility treatments to improve the egg quality in cases of poor ovarian reserve, uterine lining thickness and endometrial receptivity.[16,17] Some studies have demonstrated that PRP is useful in RIF patients undergoing *in vitro* fertilisation (IVF) while others have contradicted this finding. Although there is a lack of strong scientific evidence to demonstrate its overall effectiveness and safety, its clinical success is increasingly being recognised in cases of RIF.[18] Recently, few systematic reviews have highlighted the role of PRP in cases of RIF and thin endometrium, but these included either both randomised controlled trails (RCTs) and cohort studies or cases of RIF and thin endometrium[19] or the definition of RIF was not clear and some cases of one implantation failure might be included.

This systematic review has been undertaken to provide a summation of existing RCTs on the role of PRP in cases of unexplained RIF (defined as cases of two or more implantation failures with good quality oocytes and adequate endometrial development) and to assess the quality of the available evidence to provide valuable guidance to the treating clinicians.

Materials and Methods

Aim of the review

The present study aims to systematically review the effect of intrauterine infusion of PRP on live birth rate (LBR) and clinical pregnancy rate in female patients of the reproductive age group diagnosed with RIF.

Participants were the women of the reproductive age group diagnosed with RIF i.e., who had at least two previous fresh or FET failures and were planned for an IVF cycle with fresh or frozen embryos. Women in the study group had intrauterine instillation of PRP in addition to the standard treatment for embryo transfer. The control group received either a placebo or other routine treatments such as oestrogen, gonadotropins, letrozole, granulocyte colony-stimulating factor, sildenafil citrate and tamoxifen, or no treatment group.

The primary outcome assessed was:

1. LBR – Defined as the number of live births per started cycle.

The secondary outcomes assessed were:

1. Clinical pregnancy rate – Defined as the number of gestational sacs observed or foetal heartbeat identified
2. Biochemical pregnancy rate – Defined as cases showing positive pregnancy test
3. Miscarriage rate – Defined as pregnancy ending up in miscarriage before 12 weeks of gestation per total number of pregnancies
4. Adverse drug events or reactions to PRP.

This systematic review aimed to evaluate the effectiveness of PRP in women with RIF undergoing IVF. The protocol was registered on PROSPERO (registration number CRD42021292209). The recommendations of the Cochrane Handbook for Systematic Reviews of Interventions guidelines and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)

checklist were followed. The study did not require approval from the Institutional Ethics Committee.

Criteria for inclusion/exclusion of studies

We included randomised clinical trials with a clear definition of diagnostic criteria of RIF, a comparison of PRP against routine care or no treatment in RIF patients undergoing IVF, a detailed description of the intervention, well-defined outcome(s) and availability of full-text articles in the English language. Other studies such as observational studies, narrative reviews, case reports, case series and animal experiments, were excluded from the review. Clinical trials with multiple arms or with historical controls, quasi-randomised studies were also excluded. For this review, the operational definition of RIF-women of reproductive age group with RIF who had at least two previous fresh or FET failures and were planned for an IVF cycle with fresh or frozen embryos were used. Studies conducted on women with a thin endometrium (<7 mm) or refractory endometrium (not responding to hormonal treatment) or tubercular pathology of the endometrium or uterine malformations such as septate/bicornuate uterus or fibroid or adenomyoma distorting the endometrial cavity or presence of hydrosalpinx visible on ultrasound or Asherman's syndrome were excluded.

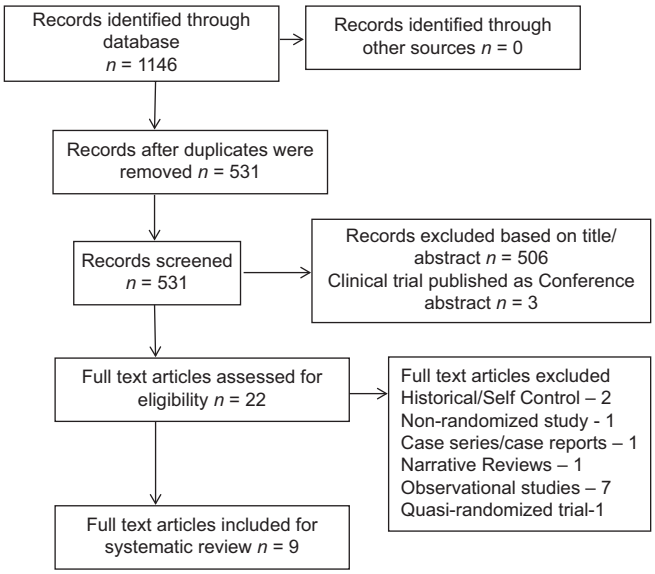

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart

Literature search and screening of data

An electronic database search of PubMed, EMBASE, SCOPUS and Cochrane Central was performed for the articles published between January 2000 and September 2022. We used the following keywords – *'In vitro* fertilisation', IVF, RIF, 'recurrent implantation failure', 'platelet-rich plasma', PRP, 'pregnancy rate', 'live birth rate' and 'adverse reactions'. Two independent primary reviewers (Dr. MM and Dr. HK) conducted a literature search using predefined eligibility criteria. Initially, title and abstract screening was done followed by full text screening in the next stage. We looked for grey literature, and conference proceedings for unpublished studies in Google Scholar, and manually searched for citations of the included studies. Duplicate studies were removed in the first stage of screening using ENDNOTE version 20.4.1. In case of any discrepancy, the opinion of the third reviewer (Dr. MS) was sought to resolve the issue. The PRISMA flowchart is depicted in Figure 1.

Data on first author's name, year of publication, sample size, study design, site and duration, intervention, control, time and mode of PRP administration, characteristics of the participants, the number and type of embryos transferred and outcome measures were extracted and crosschecked by two primary reviewers.

Our intended date to complete the review at the time of protocol registration was 31 May 2022 but could complete our search by September 2022 only. Furthermore, we planned a subgroup analysis for participants with primary or secondary infertility separately.

Risk of bias assessment

Data for the following biases, namely selection bias, performance bias, detection bias, attrition bias, reporting bias and publication bias were extracted from included studies and cross-checked by two primary reviewers using the Cochrane Collaboration Network Risk of Bias Tool version 2. In case of any discrepancy, the opinion of the third reviewer was sought to resolve the issue. For

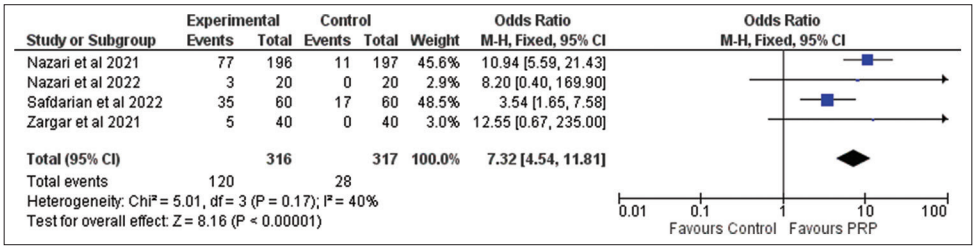

Figure 2: Forest plot of live birth rate outcome platelet-rich plasma versus control in women with recurrent implantation failure undergoing *in vitro* fertilisation. CI: Confidence interval, PRP: Platelet-rich plasma

any clarification or incomplete data, we contacted the corresponding authors using E-mail to access relevant data and/or clarification. The assessment flowchart of risk of bias and funnel plot were depicted using RevMan 5.4 software [Figures 2-9].

Adverse event

We planned to record the adverse events due to the administration of PRP like adverse drug reactions or infection following intrauterine instillation or perfusion, etc. Pregnancy-related events such as multiple pregnancies, ectopic pregnancy rate, small for gestational age at birth (defined as birth weight <10th percentile for gestational age and infant sex), abnormally adherent placenta (e.g., placenta accreta, increta or percreta) or congenital anomaly (or birth defect) rates in each study were also recorded.

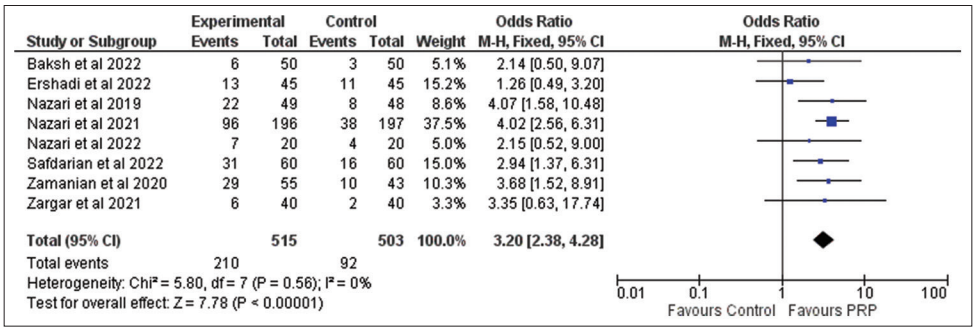

Figure3: Forest plot of clinical pregnancy rate outcome platelet-rich plasma versus control in women with recurrent implantation failure undergoing *in vitro* fertilisation. CI: Confidence interval, PRP: Platelet-rich plasm

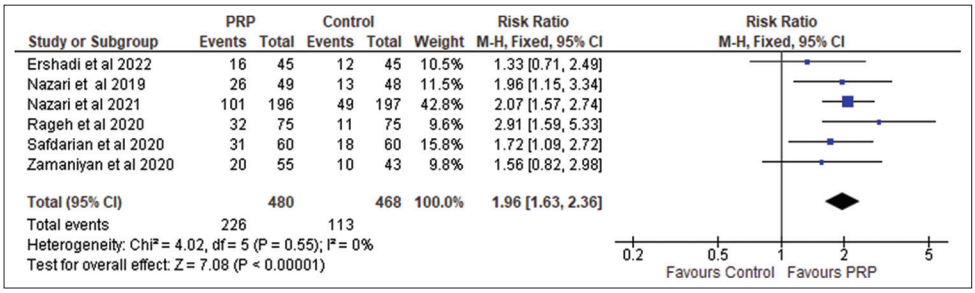

Figure 4: Forest plot of biochemical pregnancy rate outcome platelet-rich plasma versus control in women with recurrent implantation failure undergoing *in vitro* fertilisation. CI: Confidence interval, PRP: Platelet-rich plasma

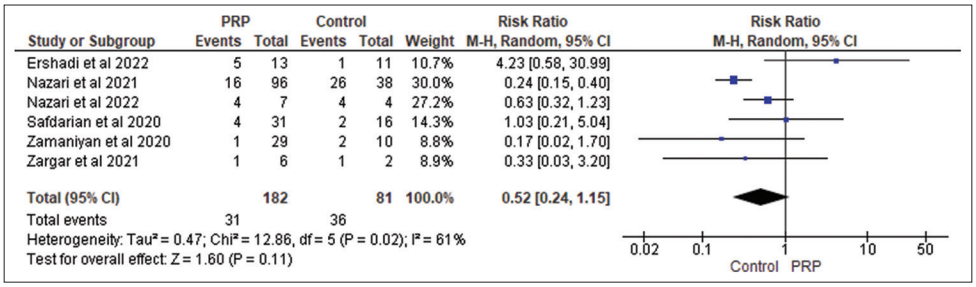

Figure 5: Forest plot of miscarriage rate outcome platelet-rich plasma versus control in women with recurrent implantation failure undergoing *in vitro* fertilisation. CI: Confidence interval, PRP: Platelet-rich plasma

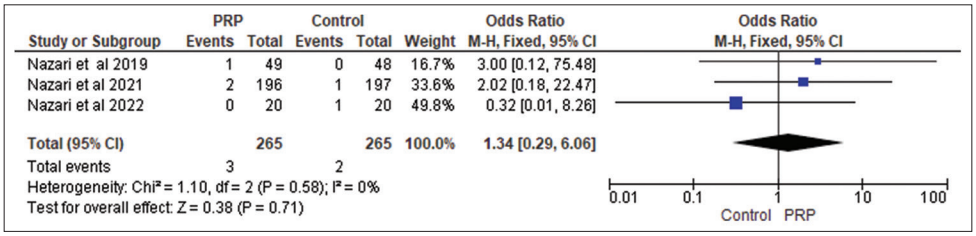

Figure 6: Forest plot of ectopic pregnancy outcome platelet-rich plasma versus control in women with recurrent implantation failure undergoing *in vitro* fertilisation. CI: Confidence interval, PRP: Platelet-rich plasma

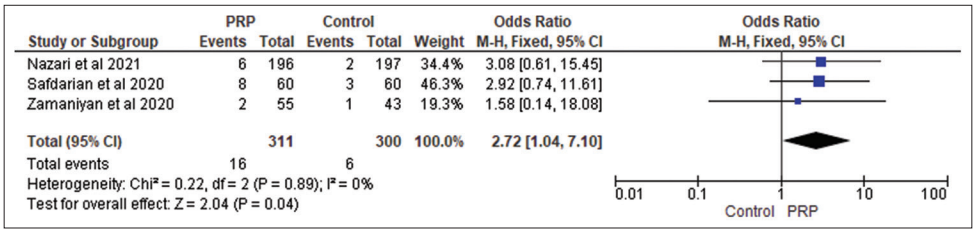

Figure 7: Forest plot of multiple pregnancy outcome platelet-rich plasma versus control in women with recurrent implantation failure undergoing *in vitro* fertilisation. CI: Confidence interval, PRP: Platelet-rich plasma

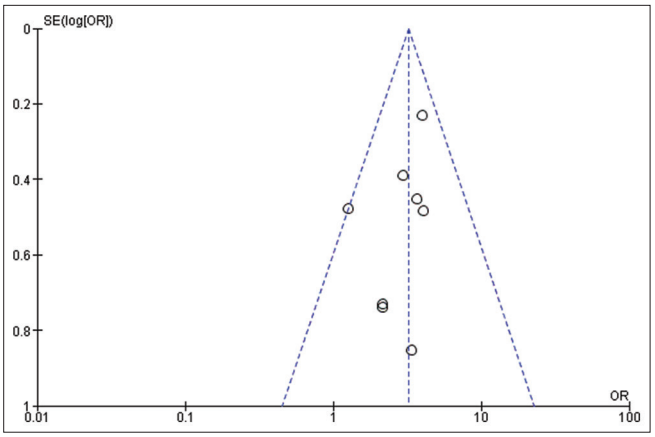

Figure 8: Funnel plot of comparison platelet-rich plasma versus control in women with recurrent implantation failure undergoing *in vitro* fertilisation for clinical pregnancy rate outcome

Data extraction

Relevant data from each article about the population studied, participants' age, body mass index, day of the cycle when PRP was administered, dose and method of PRP administration, stage and number of embryos transferred, the characteristics of the IVF cycle and the treatment offered to control group (placebo/empty catheter/standard treatment as in both groups) and whether fresh or FET was extracted. The risk ratio (RR) or odds ratio (OR) was converted to absolute numbers to get the final results in each group.

Statistical analysis

For dichotomous data, the number of events was recorded and the total number of participants randomized in each arm was used as the denominator to present the RR along with 95% confidence interval (CI) and $P < 0.05$ for statistical significance. Heterogeneity was evaluated using the I^2 statistics and visual inspection of the forest plot for overlapping CIs. Based on I^2 value, a fixed or random effect model was used for the analysis of individual outcome parameters. If the I^2 value was more than 50%, the Mantel-Haenszel method and random effect model were used. If it was below 50%, then Mantel-Hazel method and fixed effect model were used. We analysed the data for potential explanations for heterogeneity observed in the study. We planned to perform subgroup analysis to explore the reason for heterogeneity. Using the data extracted from all studies, the quality of evidence was determined and a summary of findings table was prepared for individual outcomes using GRADEpro software (GDT tool available at https://gradepro.org) assessing all the domains of GRADE assessment criteria [Table 1].

Sensitivity analysis

Sensitivity analyses were conducted for all the outcomes to assess the robustness of the results. We reversed the random effect model with the fixed effect model and vice versa and changed the summary effect measure from RR to OR to look for any change in the direction of the result or summary estimate of effect. Similarly, we planned to remove studies with an unclear or high risk of bias in any category to detect any change in the direction of the result or summary estimate of effect.

Results

The comprehensive search of PubMed, EMBASE, SCOPUS and Cochrane Central identified 1146 records. Out of the total identified records, we screened 531 records after removing the duplicates. A total of 506 records were excluded based on title/abstract as they did not meet the inclusion criteria (studies comparing PRP with placebo or standard therapy in RIF), these were either only RIF studies or PRP in IVF in general. Three studies were removed as these were exclusively published as conference abstracts. Subsequently, full texts were retrieved for 22 articles and were assessed for eligibility. Two studies used historical or self-control and one study was non-randomised, thus excluded. One study was a case report, one was a narrative review and seven articles were observational studies, hence excluded. One trial was a quasi-randomised study, so was excluded from the analysis. Nine clinical trials were included for the final review and data analysis.[20] The detailed search results are illustrated in the PRISMA flow chart [Figure 1]. Reasons for the exclusion of studies are mentioned in the flow chart.

The extracted data included study characteristics and outcome data for each study which met the inclusion criteria [Table 2]. We contacted study investigators for data on methods or results, or both, wherever required.

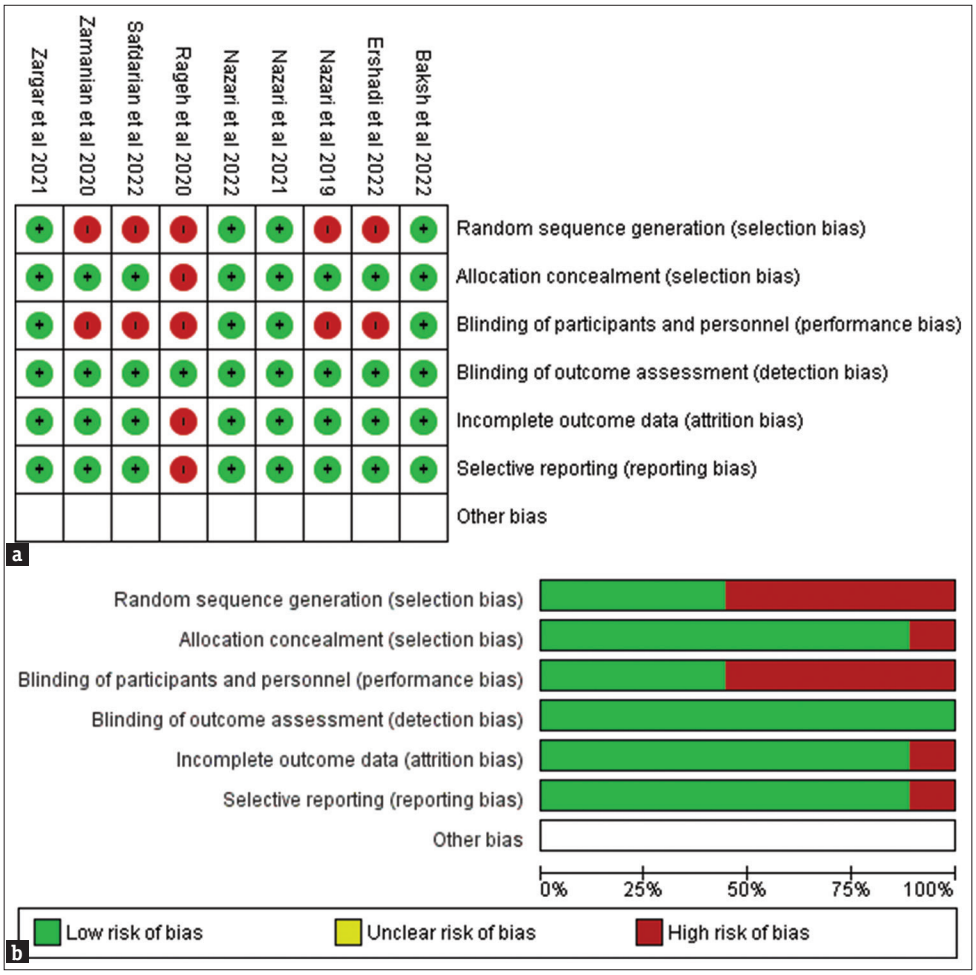

Figure 9: (a) Risk of bias summary – review authors' judgements about each risk of bias item for each included study, (b) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Description of included studies

All the included studies were RCTs. All the studies were from Iran except for the study by Rageh *et al*.,[21] which reported the data from Bahrain. All the trials excluded participants with haematological, immunological and hormonal disorders and chromosomal and genetic abnormalities. All trials included women below 40 years old with a minimum of two previously failed IVF procedures. In all trials, a single injection of intrauterine PRP was administered 48 h before embryo transfer. In eight studies, a single dose of 0.5 mL of PRP was administered, while in one study,[21] 0.5–1 mL dose of PRP was used, and in another study,[22] 1.5 mL of PRP was used and two patients needed repetition of the same dose who failed to achieve adequate endometrial size. In all studies, the intrauterine route was used for PRP administration. Except for two studies,[21,23] all studies used frozen embryos for transfer. Blastocyst transfer was done in the majority of studies except for Ershadi *et al*. 2022[24] and Zargar *et al*. 2021[22] where 'day 3' embryos were transferred. In all nine trials, the standard of care was provided in the control group. In a study by Bakhsh *et al*. 2022,[25] only an intrauterine catheter was inserted as a placebo in the control group. The standard of care was similar in all studies as per the recommendation of the American Society for Reproductive Medicine. Data from all nine included studies could be pooled for the statistical analysis.

Outcome

Live birth rate

Four studies reported the LBR as one of the outcomes, but the uniformity in definition of live birth was lacking across the studies. Gestation continuing beyond 24 weeks of pregnancy was considered as a LBR in Nazari *et al*. 2022[23] while Nazari *et al*. 2021,[26] Safdarian *et al*. 2020[27] and Zargar *et al*. 2021[22] defined LBR as delivery of a live baby after viability. We are uncertain about the effect of PRP due to the very low quality of evidence and we have little confidence that the administration of PRP had any significant effect on improving the LBR in women with RIF undergoing IVF treatment (OR: 7.32, 95% CI: 4.54–11.81, I^2 = 40%) [Figure 2 and Table 1].

Table 1: Summary of findings for all outcomes- PRP vs. Control in women with RIF undergoing IVF

Certainty assessment							№ of patients		Effect	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Control	PRP	Relative (95% CI)	
Biochemical Pregnancy[#]										
6	randomised trials	very serious[a]	not serious	serious[b]	serious[c]	strong association	226/480 (47.1%)	113/468 (24.1%)	RR 1.96 (1.63 to 2.36)	⊕◯◯◯ Very low
Clinical Pregnancy[#]										
8	randomised trials	very serious[a]	not serious	not serious	serious[c]	strong association	217/540 (40.2%)	101/528 (19.1%)	OR 3.20 (2.38 to 4.28)	⊕⊕◯◯ Low
Live Birth[##]										
5	randomised trials	serious[a]	very seriousd	not serious	very serious[c]	none	154/396 (38.9%)	42/385 (10.9%)	OR 7.32 (4.54 to 11.81)	⊕◯◯◯ Very low
Miscarriage Rate[###]										
6	randomised trials	very serious[a]	very seriousd	not serious	very serious[c]	none	31/182 (17.0%)	36/81 (44.4%)	RR 0.52 (0.24 to 1.15)	⊕◯◯◯ Very low
Ectopic Pregnancy										
3	randomised trials	very serious[a]	not serious	not serious	serious[c]	none	3/265 (1.1%)	2/265 (0.8%)	OR 1.34 (0.29 to 6.06)	⊕◯◯◯ Very low
Multiple Pregnancy[####]										
3	randomised trials	very serious[a]	not serious	not serious	serious[c]	none	16/311 (5.1%)	6/300 (2.0%)	OR 2.72 (1.04 to 7.10)	⊕◯◯◯ Very low

CI: confidence interval; OR: odds ratio; RR: risk ratio. Explanations: [a]High risk for performance and reporting bias and unclear risk for selection and other biases., [b]Chemical pregnancy is a surrogate outcome for live birth rate, [c]confidence interval does not overlap. Effect size varies between the studies. the width of CI is wide., [d]High *P* value is not significant. [#]We downgraded the evidence by two levels due to a very serious risk of bias and serious imprecision and upgraded by one level for large effect [##]The quality of evidence was downgraded by two levels due to a very serious risk of bias and substantial heterogeneity and one level for serious imprecision [###]The quality of evidence was downgraded by two levels due to very serious risk of bias and very serious inconsistency and one level for serious imprecision in the miscarriage rate. [####]The evidence was downgraded by two levels for very serious risk of bias and one level for serious imprecision

Table 2: Study Characteristics

Author, Year	Country	Duration of study	Randomization method of clinical trial	Participants (Number; Age; BMI)	Inclusion criteria	Exclusion criteria	Intervention	Control	Embryo transfer	Outcome
Bakhsh *et al.* 2022[25]	Iran	2020	Simple randomization	100; Age <40 years; BMI <30 Kg/m^2	Infertile women with a history of RIF who had failed to achieve a clinical pregnancy despite having at least four good- quality embryos transferred, and were now candidates for IVF/ ICSI or freeze embryo transfer cycles with and without the intrauterine infusion of PRP; age below 40 years; and body mass index (BMI) below 30kg/m^2	Hematological and immunological disorders; cancers; hormonal disorders; Hb <11g/dl & PLT <150000mm^3; chromosomal and genetic abnormalities; taking anticoagulants; taking NSAIDs for 7 days prior to the procedure; smoking; uterine abnormalities (acquired or congenital); FSH <12IU; uncontrolled underlying diseases such as diabetes, and hypertension; simultaneous administration of other drugs (prednisolone, IVIG, GCSF); and simultaneous endometrial scratch	Single intrauterine injection of 0.5 mL of PRP administered 48 h before implantation along with Routine infertility treatment	Only catheter was inserted along with routine infertility treatment	Frozen embryos, 2 blasts	Clinical pregnancy rate
Ershadi *et al.* 2022[24]	Iran	2019	Block randomization	90; Age <40 years; BMI <30 Kg/m^2	Age under 40 years and a history of two to three IVF failures	Any uterine anomalies in the performed analyses, having an underlying disease, taking any specific medication, not having proper fetus for transfer on the day of ET, insufficient endometrial thickness for ET, and reluctance toward participation in the study	Single intrauterine injection of 0.5 mL of PRP administered 48 h before implantation along with Routine infertility treatment	Routine infertility treatment	Day 3, frozen embryos, 2 blasts	Clinical pregnancy rate, Chemical pregnancy rate & Miscarriage rate
Nazari *et al.* 2019[28]	Iran	2016-2017	Computer generated simple random tables in a 1:1 ratio	97; Age <40 years; BMI <30 Kg/m^2	Age below 40 years and body mass index (BMI) below 30 kg/m^2	Uterine abnormalities (congenital or acquired), hormonal disorders, immunological and hematological disorders, azoospermia, testicular sperm extraction or aspiration, anatomical disorders of the male genital tract, varicocele and chromosomal abnormalities in the couples	Single intrauterine injection of 0.5 mL of PRP administered 48 h before implantation along with Routine infertility treatment	Routine infertility treatment	Frozen embryos, 1-2 blasts	Clinical pregnancy rate, Chemical pregnancy rate & Number of Ectopic pregnancy

Contd...

Table 2: Contd...

Author, Year	Country	Duration of study	Randomization method of clinical trial	Participants (Number; Age; BMI)	Inclusion criteria	Exclusion criteria	Intervention	Control	Embryo transfer	Outcome
Nazari *et al.* 2021[26]	Iran	2018-2020	Computer generated simple random tables in a 1:1 ratio	393; Age <40 years; BMI <30 Kg/m^2	Age between 18 and 38, body mass index (BMI) ≤30 kg/m^2, and serum FSH level ≤10 mIU/ml on day 2 or 3 of the menstrual cycle	known etiologies of implantation failure including immunological abnormalities, inflammatory conditions, hormonal or anatomical disorders, polycystic ovary syndrome (PCOS), ovarian hyperstimulation syndrome (OHSS), endometriosis, presence of space-occupying lesions, history of miscarriage or ectopic pregnancy, myomas, polyps, adhesions, previous pelvic surgeries, failed fertilization, and <2 embryos available for transfer	Single intrauterine injection of 0.5 mL of PRP administered 48 h before implantation along with Routine infertility treatment	Routine infertility treatment	Frozen embryos, 1-2 blasts	Live birth rate, Clinical pregnancy rate, Chemical pregnancy rate, Miscarriage rate, and Number of Ectopic and Multiple pregnancy
Nazari *et al.* 2022[23]	Iran	2019-2020	Computer generated simple random tables in a 1:1 ratio	40; Age <40 years; BMI <30 Kg/m^2	History of two or more pregnancy losses before 20 weeks of gestation who were candidates for ICSI, aged below 40 years, and had BMI of 20-30 Kg/m^2	immunological or hematological disorders, antiphospholipid antibody syndrome, endometriosis, testicular sperm extraction, oocyte donation, hormonal or chromosomal abnormalities, and anatomical uterine disorders	Single intrauterine injection of 0.5 mL of PRP administered 48 h before implantation along with Routine infertility treatment	Routine infertility treatment	Fresh embryos, 1-2 blasts	Live birth rate, Clinical pregnancy rate, Miscarriage rate, and Number of Ectopic pregnancy
Rageh *et al.* 2020[21]	Bahrain	2018-2019	Not clear	150; Age <40 years; BMI <30 Kg/m^2	Age <40 years; BMI <30 Kg/m^2	Hematological and immunological disorders, hormonal disorders, chromosomal and genetic abnormalities and uterine abnormalities (acquired or congenital) as confirmed by HSG and U/S to limit additional factors that may affect the results of the study	Single intrauterine injection of 1.0 mL of PRP administered 48 h before implantation along with Routine infertility treatment	Routine infertility treatment	Fresh embryos, 2-3 blasts	Chemical pregnancy rate

Contd...

Table 2: Contd...

Author, Year	Country	Duration of study	Randomization method of clinical trial	Participants (Number; Age; BMI)	Inclusion criteria	Exclusion criteria	Intervention	Control	Embryo transfer	Outcome
Safdarian *et al.* 2022[27]	Iran	2017-2020	Balanced block randomization	120; Age <40 years; BMI <30 Kg/m^2	Infertile women within the age range of 20-40 years old, failed to conceive after three or more ET with high-quality embryos and had at least one frozen good-quality blastocyst-stage embryo, and were candidates for FET	Chromosomal and genetic disorders, hematological and immunological disorders, hormonal disorders, uterine abnormality (congenital or acquired), body mass index above 30 kg/m^2, severe endometriosis, and patients with cancellation history of the previous ET due to a thin endometrium (≤7 mm) in hormone replacement therapy cycles	Single intrauterine injection of 0.5 mL of PRP administered 48 h before implantation along with Routine infertility treatment	Routine infertility treatment	Frozen embryos, 1-2 blasts	Live birth rate, Clinical pregnancy rate, Chemical pregnancy rate, Implantation rate, Miscarriage rate, and Number of Multiple pregnancy
Zamaniyan *et al.* 2020[29]	Iran	2016-2019	Random number table	98; Age <40 years; BMI <30 Kg/m^2	Age between 20–40 years, Body Mass Index (BMI) under 30 kg/m^2, and normal hysterosalpingo-graphy	Hematologic disorders (blood cancer, thrombocytopenia), immunologic disorders (anti-phospholipid syndrome, thrombophilia), hormonal disorders (diabetes, thyroid, hyperprolactinemia), chromosomal and genetic anomalies (hereditary or congenital), and renal failure	Single intrauterine injection of 0.5 mL of PRP administered 48 hours before implantation along with Routine infertility treatment	Routine infertility treatment	Frozen embryos, blasts	Ongoing pregnancy rate, Clinical pregnancy rate, Chemical pregnancy rate, Implantation rate, Miscarriage rate, and Number of Multiple pregnancy
Zargar *et al.* 2021[22]	Iran	2018	Block randomization	80; Age <40 years	infertile women with at least two IVF failures and age below 41 years old	Chromosomal, genetic, and uterine abnormalities, hematological or immunological disorders, and hormonal disorders, the embryos that arise from such maternal and paternal abnormalities	Single intrauterine injection of 1.5 mL of PRP administered 48 h before implantation along with Routine infertility treatment; two patients received two injections	Routine infertility treatment	Day 3, Frozen, embryos, 1-3 blasts	Live birth rate, Clinical pregnancy rate, Miscarriage rate

Clinical pregnancy rate

Except for one study by Rageh *et al*. 2020,[21] all studies (total of eight) reported clinical pregnancy rates. The pooled effect of eight studies showed some benefit of PRP on clinical pregnancy rate, but the quality of evidence was very low and the true effect could be substantially different from the effect estimate that administration of PRP had any significant effect on clinical pregnancy rate (OR: 3.20, 95% CI: 2.38–4.28, I^2 = 0%) [Figure 3 and Table 1].

Biochemical pregnancy rate

Out of nine clinical trials included in the meta-analysis, six studies reported a biochemical pregnancy rate. The pooled effect of these six studies showed a beneficial effect of PRP on biochemical pregnancy rate, but the quality of evidence was very low and our confidence in the effect estimate is limited (RR: 1.96, 95% CI: 1.63–2.36, I^2 = 0%) [Figure 4 and Table 2].

Miscarriage rate

Out of the nine clinical trials included in the meta-analysis, only six studies reported a miscarriage rate. There was a lack of uniformity in the definition of miscarriage rate in the studies. Safdarian *et al*. 2020[27] reported the miscarriage rate as the number of miscarriages out of the total number of pregnancies while the other trials reported the miscarriage rate as the number of miscarriages per the total number of women participants in that group. For uniformity, we considered the miscarriage rate as the number of miscarriages out of the total number of positive pregnancies and calculated from the number of events provided in the study. The pooled results demonstrated that the administration of PRP did not have a significant effect on miscarriage rate (RR: 0.52, CI: 0.24–1.15, I^2 = 61%) [Figure 5]. The quality of evidence was very low and there was likely overestimation of effect estimate [Table 1].

Adverse event

We studied any adverse events related to PRP and observed that there was no reported adverse event related to PRP administration in any of the studies. The pregnancy-related outcomes which were reported included: Ectopic pregnancy reported by three studies (Nazari *et al*. 2020a,[28] Nazari *et al*. 2021,[26] and Nazari *et al*. 2022[23]) and multiple pregnancies reported in three studies (Nazari *et al*. 2021,[26] Safdarian *et al*. 2020,[27] and Zamaniyan *et al*. 2021[29]).

Ectopic pregnancy

Out of nine clinical trials included in the meta-analysis, only three studies[23,26,28] reported ectopic pregnancy. From the pooled data of these studies, there was no significant difference in the groups concerning ectopic pregnancy rate. However, the quality of evidence was very low and it is very unlikely that the true effect lies close to the observed effect (OR: 1.34, 95% CI: 0.29–6.06, I^2 = 0%) [Figure 6].

Multiple pregnancy

Out of nine clinical trials included in the meta-analysis, only three studies[26,27,29] reported multiple pregnancies. Although pooled results showed higher odds of multiple pregnancies in the PRP group compared to the control group (OR: 2.72, 95% CI: 1.04–7.10, I^2 = 0%) [Figure 7] However, the quality of evidence was very low to draw any meaningful conclusions [Table 1].

Funnel plot

The Funnel plot and Egger test (Regression-based test for small-study effects, random effect model, P = 0.9) did not suggest strong publication bias [Figure 8].

Risk of bias

All studies were randomised clinical trials and were characterised at low risk of selection bias. None of the studies mentioned allocation concealment and assessed an unclear risk of bias. Neither the participants nor the investigator was blinded in any of the studies. Although one study (Bakhsh *et al*.) 2022,[25] mentioned the clinical trial as double-blind, it is also mentioned as a single arm and lacked any description of blinding of participants or investigators or both. The lack of blinding of investigators and participants was judged at high risk for performance bias for all studies. However, the lack of blinding of outcome assessors was reported as a low risk for detection bias due to the objective nature of the outcome. One study by Rageh *et al*. 2020[21] reported only biochemical pregnancy rates and was characterised as at high risk for detection and reporting biases. No attrition bias was detected for any of the studies and reported as a low risk of bias. All studies without LBR outcomes were assessed at high risk of reporting bias (Cochrane's Risk of bias tool version 2)[30] [Figure 9a and b].

Summary of findings

The quality of evidence was assessed and a summary of findings table was prepared for individual outcomes by assessing all the domains of GRADE assessment criteria the overall rating for the quality of evidence was assessed to be very low as shown in the GRADE summary of findings [Table 1]. The quality of evidence was downgraded by two levels due to a very serious risk of bias and substantial heterogeneity and one level for serious imprecision in the LBR. Although there was a

large effect (OR: 7.32), CI: 4.54–11.81 was not narrow enough to upgrade the level of evidence for LBR outcome. We downgraded the evidence by two levels due to a very serious risk of bias and serious imprecision and upgraded by one level for large effect (biochemical pregnancy rate OR: 1.56 [CI: 0.82–2.98] and clinical pregnancy rate OR: 3.35 [CI: 0.63-17.74]) for biochemical and clinical pregnancy rates outcomes. The quality of evidence was downgraded by two levels due to very serious risk of bias and very serious inconsistency and one level for serious imprecision in miscarriage rate. For multiple pregnancy outcomes, the evidence was downgraded by two levels for very serious risk of bias and one level for serious imprecision. Even though the effect was large, the CI was wide (OR: 2.72, CI: 1.04–7.10) and no upgradation of level was done for multiple pregnancy outcome [Table 1].

Subgroup analysis

We planned a subgroup analysis for participants with primary or secondary infertility. However, only two trials reported the number of participants in primary and secondary infertility at the baseline and none of the trials reported events in patients with primary and secondary infertility separately.

Sensitivity analysis

Upon reversing the analysis model (fixed effect or random effect) and summary effect measure (RR or OR), no change in the direction of the result or summary estimate of effect was observed. Since all studies had an unclear risk of selection bias and a high risk of performance bias, we could not do sensitivity analysis by excluding one or more trials to detect any change in the direction of the result and summary estimate of effect.

Discussion

A healthy human endometrium is crucial for a successful embryo implantation process. With the advancement in ART, pregnancy rates have markedly improved in modern times, but the success rate is modest and there are many challenges faced by both clinicians and patients. In this review, we focused on one such challenge i.e. RIF which is a real frustrating condition to manage. Many drugs currently are used to improve pregnancy outcomes in women with RIF such as oestrogen, gonadotrophins, letrozole, granulocyte colony-stimulating factor and sildenafil citrate, etc.[31-33] but none of the treatments is proven as a measure to improve pregnancy rate in RIF. The PRP is one such modality which had been tried in women with RIF in many studies[20,23,26,28,34] but with mixed results.

In this systematic review and meta-analysis, the pooled results showed some benefit of PRP in improving the LBR in RIF patients undergoing IVF. However, our confidence in the effect estimate is limited. There could be an overestimation of the treatment effect due to the very low quality of evidence. Moreover, there was a lack of reporting of LBR outcomes in many studies (only four out of ten eligible studies reported live birth), which could be due to the short follow-up period of trial participants. The definition of LBR was not uniform across the studies. Most of the studies defined live birth as the birth of a viable foetus without defining the age of viability and gestation continuing beyond 24 weeks of pregnancy considered as LBR in Nazari *et al*. 2022.[23]

Although the pooled result of this review showed some benefit in clinical and biochemical pregnancy rates, the quality of evidence was very low to make any significant recommendations. The definition of clinical pregnancy rate was not uniform in all studies, the majority (six out of nine) reported clinical pregnancy rate as the presence of a fetal heartbeat on a transvaginal scan while Nazari *et al*. 2022[25] defined clinical pregnancy rate as the presence of gestational sac and Zargar *et al*. 2021[22] did not define it.

In women with RIF planning to undergo IVF, we are uncertain whether the administration of PRP will reduce the miscarriage rate compared to no treatment or placebo due to the very low quality of evidence. However, the lack of reporting of miscarriage rate in clinical trials could be one of the contributory factors for the low quality of evidence. All studies included in this review were reported as high risk of performance bias and an unclear risk of selection bias, negatively affecting the quality of evidence.

Limitations

We conducted an extensive search to include all studies that satisfied our eligibility criteria for this review, we might have missed one (or more) studies. We also contacted authors of trials published only as abstracts and conference proceedings for complete data and clarification on the study design but did not receive any communication from the authors. None of the studies reported on the adverse events related to the PRP administration. The outcomes definition is not uniform across the studies, especially live birth has been defined as a birth beyond 24 weeks gestation[21] or defined as the birth of a live neonate after viability.[21,26,27]

Strengths

There are several strengths of this meta-analysis. To reduce the heterogeneity, we have included studies using PRP in women with unexplained RIF (where no obvious cause could be labelled and defined RIF as at least

previous two or more failed IVF cycles) and excluded studies with thin endometrium. Thin endometrium itself is a confounding factor for implantation and these cases cannot be clubbed together with those having normal endometrium. The definition of RIF has been clearly defined and only studies with RIF were included and the rest of the studies (including cases of one implantation failure) were excluded from the analysis. Furthermore, we included only RCTs available as full-text with clearly defined inclusion and exclusion criteria. A previous meta-analysis assessing the effect of PRP in women with RIF supported the use of PRP as a treatment strategy in patients with thin endometrium and RIF, but included both observational studies and RCTs and cases of thin endometrium were also included[19] or studies available only as abstracts were included which might not provide a complete report of the study findings. Implantation is a complex process which may fail to happen despite the normal endometrial thickness and normal embryos. PRP-containing proteins, cytokines and growth factors may improve endometrial receptivity and implantation in unexplained RIF.

Conclusion

The current review suggests that there may be some beneficial effects of PRP in women with RIF undergoing IVF, but the quality of evidence is very low and we are uncertain of the benefit and have little confidence in these findings. To the best of our knowledge, this is the first study, which systematically reviewed and pooled data from RCTs on the use of PRP in unexplained RIF. However, the quality of evidence is very low, the number of participants in each trial is small and the follow-up is not adequate in all the trials to conclude on the LBR. In future robustly designed and adequately powered clinical trials with a longer follow-up period are required to generate better evidence to make significant conclusions on the use of PRP in women with RIF undergoing IVF. Currently, the use of PRP should be restricted to research settings only until more data are generated.

Author's contributions

All the authors contributed significantly and are in agreement with the final content of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

Data availability statement

Only published data used.

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