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Original Article

Obstetrics and Gynaecology Section

Efficacy of In-utero Infusion of Autologous Platelet Rich Plasma Therapy in Women with Recurrent Implantation Failure: A Systematic Review and Meta-analysis of Randomised Controlled Trials

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ABSTRACT

Introduction: In-utero infusion of autologous Platelet Rich Plasma (PRP) is found to be a novel approach to address the thin, non receptive endometrium leading to recurrent implantation failure.

Aim: To estimate the efficacy of intrauterine PRP infusion in subfertile females affected with recurrent implantation failure via the conduction of a systematic review and meta-analysis of the available Randomised Controlled Trials (RCTs).

Materials and Methods: A systematic literature search was done in electronic databases like Medline (through PubMed), Embase, Scopus, Web of Science, and Cochrane database from January 2000 to November 2020 using keywords like "In-vitro Fertilisation" OR "IVF" OR "Intracytoplasmic sperm injection" OR "ICSI" OR "Embryo transfer" AND "Platelet rich plasma" OR "PRP" OR "Autologous platelet rich plasma" OR "Platelet rich plasma" and "recurrent implantation failure". The randomised controlled trials, comparing intrauterine infusion of PRP versus no intervention or placebo in a study population of subfertile women with recurrent implantation failure and having medically confirmed pregnancy outcomes like live birth, clinical pregnancy, chemical pregnancy, and miscarriage were included in this systematic review. Studies with inadequate details in the methodology or result section were excluded from this analysis. This meta-analysis involved a pooled data analysis of 335 participants (174 cases and 161 controls) from four RCTs.

Results: Compared with the control group, patients in the PRP group were found to have more beneficial effects in terms of implantation rate (Relative risks: 1.51, 95% Confidence interval: 0.94, 2.44; Heterogeneity: Tau^2=0.08; I^2=44%; Test for overall effect: Z=1.69, p-value=0.09) and clinical pregnancy (Relative risk: 1.88, 95% CI: 1.17, 3.03; Heterogeneity: Tau^2=0.12; I^2=51%; Test for overall effect: Z=2.62; p-value=0.009).

Conclusion: Intrauterine PRP infusion increases the implantation rate and clinical pregnancy rate in women undergoing the frozen embryo transfer cycle.

Keywords: Clinical pregnancy rate, Embryo transfer, Endometrium, Implantation rate

INTRODUCTION

In Assisted Reproductive Technique (ART) programs, the most common factors that affect implantation and pregnancy are embryo and endometrium The non functioning and non receptive endometrium are one of the inferior factors that negatively interfere with an ongoing pregnancy and are associated with recurrent implantation failure [1]. Although various treatments like estradiol valerate, acetylsalicylic acid, Sildenafil, vitamin E, Granulocyte-Colony Stimulation Factor (G-CSF), Human Chorionic Gonadotropin (HCG), L-arginine, pentoxifylline, electroacupuncture have been suggested to improve implantation, none of these therapies is quite appealing [1]. Vitagliano A et al., highlighted the success of endometrial scratch in improving implantation [2].

However, more information is required regarding the application of these treatments on a day to day practice. Recently intra-uterine infusion of autologous Platelet Rich Plasma (PRP) is found to be a new and quite promising approach to address the thin, non receptive endometrium leading to recurrent implantation failure in ART programs [3]. As the name suggests, PRP is prepared from fresh whole blood that is enriched with platelets. Platelets contain a significant amount of growth factors that stimulate proliferation and growth and have positive effects on local tissue repair [3,4]. The role of autologous PRP in the promotion of endometrial growth and improvement in pregnancy outcomes has been addressed in various studies and found PRP to be extremely useful for this condition [3,5-9]. However, most of these studies lack enough sample size, and there are only a few well-designed controlled trials that have addressed this issue. Hence, the present systematic review and meta-analysis was conducted to analyse the pooled data from the available well-organised studies {Randomised Controlled Trials (RCTs)} to estimate the efficacy of intrauterine infusion of PRP in subfertile females affected with recurrent implantation failure with a population subset of thin endometrium.

MATERIALS AND METHODS

The present systematic review and meta-analysis evaluated the efficacy of intrauterine PRP infusion compared to 'no intervention' in subfertile females undergoing Frozen Embryo Transfer (FET) cycles. The study was done according to recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [10]. This study has been registered with PROSPERO (registration ID: CRD42020223550 dated 30.12.2020).

Inclusion criteria:

- A Randomised Controlled Trials (RCT) that included a study population of subfertile women with recurrent implantation failure.
- The study end-points for the said RCT were medically confirmed pregnancy outcomes (live birth, clinical pregnancy, chemical pregnancy, and miscarriage).

- The study group was intervened with an intrauterine infusion of PRP around the time of Embryo Transfer (ET),
- The control group was intervened with a placebo or no intervention.

Exclusion criteria:

- Except for randomised controlled trials, all other forms of studies like cohort studies, case-control, quasi-experimental studies, small case series, cross-sectional, animal, or cell culture studies were excluded from the study.
- Studies with inadequate details in the methodology or result section were also excluded from the study.

Information sources: Literature search was done in electronic databases like Medline (through PubMed), Embase, Scopus, Web of Science and Cochrane database was done over a period from January 2000 to November 2020.

Search strategy: The search terms like: ("In-vitro fertilisation" OR "IVF" OR "Intracytoplasmic sperm injection" OR "ICSI" OR "Embryo transfer" AND "Platelet rich plasma" OR "PRP" OR "Autologous platelet rich plasma" OR "Platelet rich plasma" and "recurrent implantation failure"). Articles published in the English language were considered for this study.

Study Selection and Data Collection Process

Two authors independently carried out searching the electronic databases and then screening the titles and abstracts of these searches according to the predefined eligibility criteria. Articles were retrieved for those found to be relevant. Data were extracted from each eligible study and cross-checked by the two authors and also by a third author, who acted as a referee to sort out any differences between the first two authors.

Data management and quality appraisal: The included studies were evaluated for methodological quality in five domains, including bias arising from randomisation process, bias due to deviations from intended intervention, missing outcome data bias, bias due to the measurement of outcome, and bias owing to the selection of the reported result.

Data synthesis: Meta-analysis was performed using ReviewManager (RevMan) web 2019. Afixed-effect analysis was used for trials estimating the same treatment effect, similar intervention, and for a similar population. In cases of clinical heterogeneity, sufficient to expect that the underlying treatment effects, differed between trials, or if there was substantial statistical heterogeneity (I^2=50% or greater), a random-effects meta-analysis was used to produce an overall summary, if a mean treatment effect across trials was considered clinically meaningful.

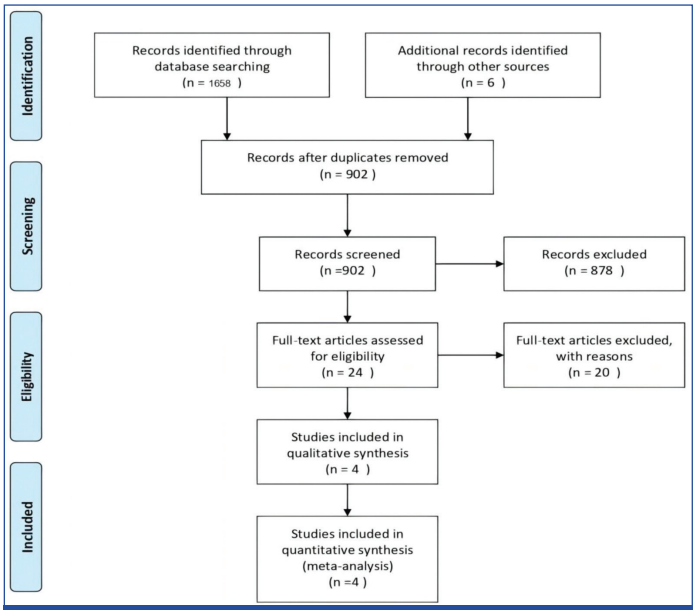
STATISTICAL ANALYSIS

The complete data was collected and descriptive statistics was used in form of frequency (n) and percentages (%). Meta-analysis was done for the complete data using ReviewManager (RevMan) web 2019.

RESULTS

Summary of the Literature Search

The initial electronic literature search yielded 1664 publications. After excluding duplicates 902 publications were screened. Out of these 902 publications, 878 were irrelevant publications that were excluded. Thus, we found 24 potentially eligible studies. After going through these articles, 20 articles were excluded. Six were case series, two case reports; one was a case-controlled study, three were quasi-experimental studies, four were cohort studies, two were randomised controlled trials not fitting to our inclusion criteria and another two studies having insufficient data, thus leaving four studies [11-14] to be included in the meta-analysis. The flow of information through the different phases of the systematic review is shown in [Table/Fig-1].



[Table/Fig-1]: The flow of information through the different phases of the systematic review (According to PRISMA).
PRISMA: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines

Study Characteristics

In this meta-analysis, we have included four RCTs which evaluated the efficacy of platelet rich plasma in comparison to no intervention or placebo for patients with Recurrent Implantation Failure (RIF). [Table/Fig-2] outlines the important characteristics of all included studies [11-14]. All the included studies were RCTs. The population in all studies was patients with RIF. All studies compared PRP versus no intervention or placebo. The sample size ranged from 50-98 participants. In all the studies, the type of embryo transfer was FET. Outcome measures like chemical pregnancy rate, implantation rate, and clinical pregnancy rate were considered for all the studies.

Risk of Bias Assessment

The summary of the risk of bias assessment is shown in [Table/Fig-3]. Three trials [11-13], were judged to have selection bias whereas another study [14], was judged to have attrition bias.

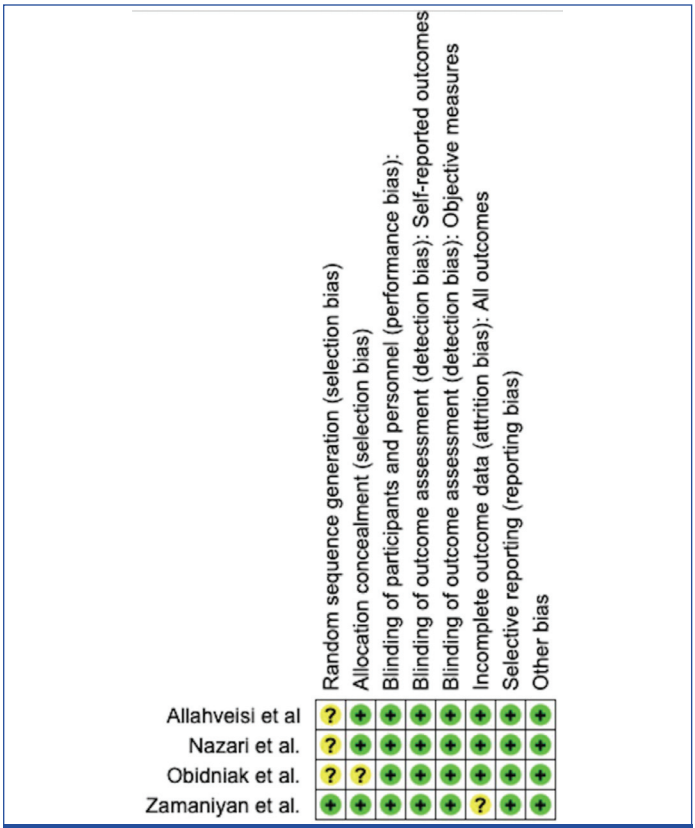
Implantation rate: The effect of PRP on implantation rate was evaluated in three RCTs [11,13,14] involving 238 subjects (125 cases and 113 controls). Following the intervention, implantation rate significantly increased in patients who received PRP compared to controls (Relative Risk: 1.51, 95% Confidence Interval: 0.94, 2.44; Heterogeneity: Tau^2=0.08; I^2=44%; Test for overall effect: Z=1.69; p-value=0.09) [Table/Fig-4]. In consonance, the Risk Difference (RD) was 18.71% in favour of the PRP group compared with control (no intervention or other active intervention (RD: 0.1871, 95% CI: 0.0653, 0.3089; p-value=0.002).

Chemical pregnancy: Two studies with 158 participants (85 cases and 73 controls) compared chemical pregnancy between PRP and control (no intervention or other active intervention) groups [12,14]. Compared to controls there was a significant increase in rate of chemical pregnancy in women who received PRP (RR: 2.65, 95% CI: 0.71, 9.98; Heterogeneity: Tau^2=0.64; I^2=67%; Test for overall effect: Z=1.44; p-value=0.15) [Table/Fig-4]. The RD was 21.21% in favour of the PRP group compared with control (no intervention or placebo) (RD: 0.2121, 95% CI: 0.0785, 0.3456; p-value <0.0019).

Clinical pregnancy: Pooling results from four studies [11-14], which compared clinical pregnancy between PRP and control (no intervention or placebo), including 335 participants (174 cases and 161 controls), showed a significantly higher probability of clinical pregnancy in PRP group (RR: 1.88, 95% CI 1.17, 3.03); Heterogeneity: Tau^2=0.12; I^2=51%; Test for overall effect: Z=2.62;

Study	Country	Study design	Population	Age of population (study group vs control)	BMI of population (study group vs control)	Sample size		Intervention	Control	Time of PRP infusion	Outcome measures
						Cases	Controls				
Obidniak D et al., 2017 [11]	Russia	Randomised clinical trial	RIF, normal karyotype, absence of uterine factors of infertility, absence of chromosomal abnormalities in a previous pregnancy	• Age-matched women between 28-39 years	Not mentioned	45	45	Underwent Embryo Transfer (ET) with Intrauterine infusion of 2.0 mL of autologous PRP	Underwent ET without intrauterine administration	Not mentioned	Implantation rate, clinical pregnancy
Nazari L et al., 2019 [12]	Iran	Randomised clinical trial	RIF: three or more failures of IVF-ET therapy	• 33.93±2.76 vs 32.33±4.79 • p-value=0.274	• 24.3±2.24 vs 25.46±2.68 • p-value=0.262	49	48	Intrauterine infusion of 0.5 mL of platelet-rich plasma	Underwent ET without an intrauterine infusion of PRP	48 hours before ET	Chemical pregnancy, Clinical pregnancy
Allahveisi A et al., 2020 [13]	Iran	Randomised clinical trial	Infertile women (with a history of failed implantation	• 33±0.9 vs 33.8±0.54 • p-value=0.94	• 25.96±0.54 vs 25.76±0.47 • p-value=0.76	25	25	Intrauterine infusion of 0.5 mL of platelet rich plasma	Intrauterine infusion of 0.5 mg of Ringer serum	48 hours before ET	Implantation rate, clinical pregnancy rate, and live birth rate.
Zamaniyan M et al., 2020 [14]	Iran	Randomised clinical trial	Recurrent implantation failure	• 33.88±6.32 vs 33.13±5.00 • p-value=0.539	• 26.49±4.53 vs 25.03±3.66 • p-value=0.135	55	43	0.5 mL of platelet rich plasma	Underwent ET without an intrauterine infusion of PRP	48 hrs before ET	Chemical pregnancy rate, implantation rate, clinical pregnancy rate.

[Table/Fig-2]: Characteristics of the included studies.

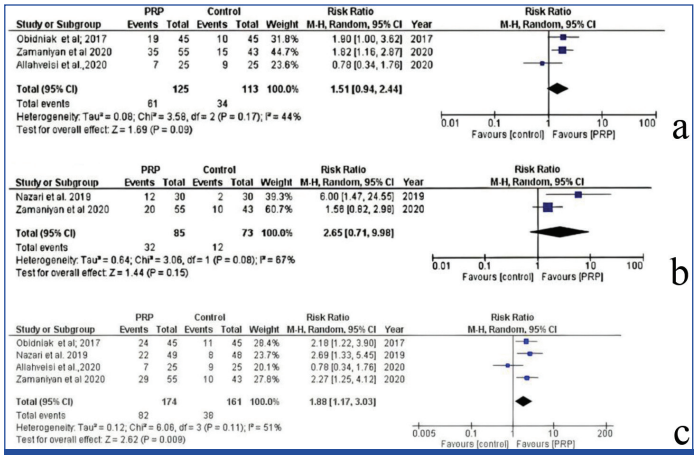


[Table/Fig-3]: Risk of bias assessment.

p-value=0.009). In agreement, RD was 23.48 % in favour of the PRP group compared with control (no intervention or placebo) (RD: 0.2348, 95% CI: 0.1314, 0.3383; p-value <0.00001). The forest plot depicting this is represented in [Table/Fig-4].

Assessment of Quality of Evidence

Quality assessment for the evidence of the result was done according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system [15]. For the findings that implantation rate and clinical pregnancy rate was higher in the PRP intervention group, the quality of evidence was found to be of



[Table/Fig-4]: Forest plot of comparison for implantation rate (a) chemical pregnancy rate (b) and clinical pregnancy rate (c).

moderate (⊕⊕⊕◻) GRADE. However, for the outcome measure of the chemical pregnancy rate, the quality of evidence was found to be at a low (⊕⊕◻◻) GRADE [Table/Fig-5].

DISCUSSION

This meta-analysis involved a pooled data analysis of 335 participants (174 cases and 161 controls) from four randomised controlled trials [11-14]. Compared with the control group, those in the PRP group were found to have more beneficial effects in terms of implantation rate, chemical pregnancy rate and clinical pregnancy rate. These parameters were found to be significantly higher in women who received PRP instead of the control group. Three trials [11-13], were judged to have selection bias where as another study [14], was judged to have attrition bias. Although the heterogeneity was low for implantation rate, it was high for the clinical and chemical pregnancy rates. On assessment on GRADE system, the quality of evidence for the outcome of implantation rate and clinical pregnancy rate were of "moderate" GRADE (⊕⊕⊕◻) which means "we are quite confident that the effect in the study is close to the true effect, but it is also possible, it is substantially different" [15]. On the other hand, the quality of evidence for chemical pregnancy rates is low (⊕⊕◻◻) GRADE.

Summary of findings										
No of studies (Design)	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Control (n, %)	Intervention (n, %)	Relative risk (95% CI)	Risk difference (95% CI)	Quality
Implantation rate {RCT:3 (238)}	No serious limitation	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	113	125	1.51, (0.94, 2.44)	18.71% in favour of the intervention	Moderate ⊕⊕⊕□
Clinical pregnancy rate {RCT:4 (298)}	No serious limitation	Serious inconsistency (because of inconsistency in absolute effects)	No serious indirectness	No serious imprecision	Undetected	161	174	1.88, (1.17, 3.03)	23.48 % in favour of the intervention	Moderate ⊕⊕⊕□
Chemical pregnancy rate {RCT:2 (158)}	No serious limitation	Serious inconsistency (because of inconsistency in absolute effects)	No serious indirectness	Serious imprecision	Undetected	73	85	2.65, (0.71, 9.98)	21.21% in favour of intervention	Low ⊕⊕□□

[Table/Fig-5]: Assessment of quality of evidence by GRADE (Guyatt GH et al., 2008) [15].
GRADE: Grading of recommendations, assessment, development, and evaluations

The role of PRP as an enhancer of tissue repair has been witnessed in regenerative medicine. This property of tissue repairis being studied for the treatment of various disorders like alopecia, vulvar lichen sclerosus, and lichen planopilaris [16]. PRP has also been used as a treatment method for injuries to muscles, tendons, and ligaments. Panda SR et al., in their systematic review, addressed the efficacy of PRP for ovarian rejuvenation and highlighted its beneficial effects in patients with ovarian insufficiency and/or decreased ovarian reserve [17]. Chang Y et al., in 2015 first observed improvement in endometrial thickness after intrauterine infusion of PRP [3]. The immune regulatory property of PRP is believed to induce a positive effect on the endometrium in cases of recurrent implantation failure. PRP causes the downregulation of cytokines such as interleukin Interleukin-6 (IL-6) and IL-8. At the same time, IL1-β production is upregulated which is vital for implantation [18].

Although there is no standardised procedure for PRP preparation, most authors agree that a platelet concentration of approximately 1,000,000/μL (503,000-1,729,000/μL) is essential to have an optimal beneficial effect [19]. At lower and higher concentrations, the effects might be suboptimal or paradoxical low, respectively. Chang Y et al., used a double-step centrifuge technique, with 300 gm and 700 gm of RCF application respectively to concentrate the platelets [20]. In a recent meta-analysis, Maleki-Hajiagha A et al., concluded that intrauterine administration of PRP, irrespective of study design and study population, increases the clinical pregnancy rate in women who experienced frozen-thawed ET cycles [21].

In the present systematic review, the study participants using PRP intervention in women with thin endometrium found a significant increase in endometrial thickness compared to the control groups. In their study Kim H et al., also found increased endometrial thickness after intervention with PRP. However, there was no association between the endometrial thickness changes and the embryo transfer outcomes [22]. Another study also found endometrial thickness to be a poor predictor of clinical pregnancy [23]. Unfortunately, there is a lack of well-designed trials evaluating the effect of PRP on thin endometrium. Hence, it is suggested that future studies should focus on evaluating other markers of endometrial receptivity.

Except for one RCT all other studies were included in the present meta-analysis, those evaluated implantation rates, and clinical pregnancy rates found a statistically significant difference, favouring intervention with platelet-rich plasma [13]. Recently Mehrafza M et al., conducted a cohort study involving 67 women, who were infused with intrauterine PRP and 56 controls with systemic administration of GCSF [24]. They found a significant increase in clinical pregnancy rate in the PRP group than the GCSF group (40.3% versus 21.4%, p-value=0.025). In line with these study results, two other studies also found an increased implantation rate favouring the PRP infusion group [21,22]. In present study, the heterogeneity for implantation rate is not a problem (I^2= 44%). However, for the clinical pregnancy rate, the I^2 value was 51% which indicates a moderate degree of heterogeneity. Similarly, the analysis of the chemical pregnancy rate carries a moderate to substantial risk of heterogeneity (I^2=67%). This is one of the reasons which prompted us to downgrade the evidence level while assessing the quality of evidence in the GRADE Working Group for the said parameters.

In the present meta-analysis, authors found a significant increase in the chemical pregnancy rate in favour of PRP infusion. Similarly, in the cohort study by Mehrafza M et al., [24], the chemical pregnancy rate was 43.3% in the PRP group and 26.8% in the GCSF group (p-value=0.057). However, in another cohort study, authors found more chemical pregnancies in the control group compared to the group that intervened with platelet-rich plasma [25]. Meta-analysis for miscarriage rate was deemed inapplicable as only two studies addressed this outcome.

Live birth rate is the most critical criterion for the assessment of any artificial reproductive technique program. However, most of the RCTs did not evaluate for live birth rate. The only RCT evaluating for live birth rate found no difference between the two groups [13]. However, the results of this study are to be interpreted cautiously as the sample size was too less. Recently two studies found increased live birth rates in the group treated with PRP [22,25]. Similarly, Colombo GVL et al., [5] and Molina M et al., [6] the strengths of this systematic review. The uniqueness of this study lies in the fact that the study trials chosen for this meta-analysis are of high quality as far as methodology is concerned.

Limitation(s)

Less number of studies (n=4) for quantitative synthesis is the major limitation. Second, we could not manage the unit analysis error arising from the meta-analysis of the implantation rate. Third, most of the studies have not described the details of PRP like its preparation, composition and the method of obtaining, preparing, and applying PRP varies across the chosen studies. A meta-analysis of adjusted RR could not be performed, as most of the included studies in the present review, did not detail the adjusted analysis for known confounding factors, such as age and BMI. In most of the included studies, the day of embryo transfer and the reasons for the failure of implantation were not detailed. In addition, as most of the studies used PRP in cases of unexplained RIF, authors could not perform a subgroup analysis for the cause of implantation failure. Another limitation of this review was that three out of four included RCTs are from a single country. So global scientific evidence may be lacking in this regard. Also, authors were not able to meta-analyse outcomes like live birth rate and miscarriage rate due to less number of RCTs addressing these outcomes.

CONCLUSION(S)

Intrauterine autologous PRP infusion increases the implantation rate, chemical pregnancy rate, and clinical pregnancy rate in women undergoing a frozen-thawed embryo transfer cycle. This simple procedure is a safe and inexpensive adjuvant treatment in optimising endometrium, especially in patients with recurrent implantation failure history. After performing the meta-analysis and the necessary assessment of quality for evidence we can conclude that PRP is

an effective method for improving atleast the clinical pregnancy rate in patients with recurrent implantation failure. Although there is insufficient evidence regarding the efficacy of PRP in terms of live birth rate, this therapy may be considered as one of the frontline measures for women undergoing FET for recurrent implantation failure given its low cost and the good quality of evidence, favouring PRP. Given the moderate degree of heterogeneity found in some of the outcome measures like clinical pregnancy rate in this review and the absence of sufficient data related to live birth rate, more high-quality randomised controlled trials are required to estimate the efficacy of PRP for these outcomes, and identify the subpopulation that would most benefit from PRP.

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