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Review article

Intrauterine infusion of autologous platelet-rich plasma in women undergoing assisted reproduction: A systematic review and meta-analysis

Arezoo Maleki-Hajiagha[a], Maryam Razavi[b], Safoura Rouholamin[c], Mahroo Rezaeinejad[d], Saman Maroufizadeh[e], Mahdi Sepidarkish[f,*]

[a] Research Development Center, Arash Women's Hospital, Tehran University of Medical Sciences, Tehran, Iran
[b] Pregnancy Health Research Center, Department of Obstetrics and Gynecology, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran
[c] Department of Obstetrics and Gynecology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[d] Department of Obstetrics and Gynecology, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran
[e] School of Nursing and Midwifery, Guilan University of Medical Sciences, Rasht, Iran
[f] Department of Biostatistics and Epidemiology, Babol University of Medical Sciences, Babol, Iran

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ABSTRACT

Prior studies have provided conflicting results regarding the use of platelet-rich plasma (PRP) in women undergoing in-vitro fertilization (IVF) or intracytoplasmic injection (ICSI). The objective of this study was to evaluate the effect of the intrauterine infusion of PRP on the outcome of embryo transfer (ET) in women undergoing IVF/ICSI. We searched databases, including PubMed, Embase, Scopus, Web of Science, and the Cochrane Database of Clinical Trials (CENTRAL). Meta-analysis using a random-effects model was performed to calculate the pooled estimates. Seven studies involving 625 patients (311 cases and 314 controls) were included. The probability of chemical pregnancy (n = 3, risk ratio (RR): 1.79, 95 % confidence intervals (CI): 1.29, 2.50; P < 0.001, I^2 = 0 %), clinical pregnancy (n = 7, RR: 1.79, 95 % CI: 1.37, 2.32; P < 0.001, I^2 = 16 %), and implantation rate (n = 3, RR: 1.97, 95 % CI: 1.40, 2.79; P < 0.001, I^2 = 0 %) was significantly higher in women who received PRP compared with control. There was no difference between women who received PRP compared with control group regarding miscarriage (RR: 0.72, 95 % CI: 0.27, 1.93; P = 0.51, I^2 = 0 %). Following the intervention, endometrial thickness increased in women who received PRP compared to control group (SMD: 1.79, 95 % CI: 1.13, 2.44; P < 0.001, I^2 = 64 %). The findings of this systematic review suggest that PRP is an alternative treatment strategy in patients with thin endometrium and recurrent implantation failure (RIF). Further prospective, large, and high quality randomized controlled trials (RCTs) are needed to identify the subpopulation that would most benefit from PRP.

1. Introduction

Implantation failure can occur during any of the three stages of implantation, i.e., apposition, adhesion, and invasion (Hoozemans et al., 2004). There are several reasons for implantation failure, but it can be classified in to four main categories: altered endometrial receptivity, embryonic defects, abnormal embryo-endometrial cross-talk and impairment in the regulation of immunologic mediators (Diedrich et al., 2007).

Various interventions have been employed to increase the implantation rate and subsequently the chance of live birth in couples with RIF like hysteroscopic correction of cavity pathology (Margalioth et al., 2006), treatment of thin endometrium (Lebovitz and Orvieto, 2014), endometrial stimulation (Paulson, 2011), blastocyst transfer (Glujovsky et al., 2016), cytoplasmic transfer (Barritt et al., 2001), intrauterine administration of autologous peripheral blood mononuclear cells (Maleki-Hagiagha et al., 2019), endometrial scratching (Gibreel et al., 2015), and use of immunomodulators (D'hooghe, 2003). However, even with these new treatment approaches, many patients still are suffering from RIF. Therefore, there is a need for an alternative treatment with more success in patients with a history of treatment failure.

Recently, some progress in treating RIF and thin endometrium has been made with the use of the PRP. PRP, also known as autologous conditioned plasma, is a concentrate of PRP protein derived from fresh whole blood, centrifuged to remove red blood cells and has anti-inflammatory and pro-regenerative functions (Bos-Mikich et al., 2018). The main idea of using the PRP in patients with previous ET failures is based on the regulation of expression of growth factors and cytokines in

* Corresponding author at: Babol University of Medical Sciences, GanjAfrooz Ave., Babol, 4717647745, Iran.
E-mail address: Mahdi.sepidar@yahoo.com (M. Sepidarkish).

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the endometrium which was first presented by Chang et al., 2015 (Chang et al., 2015).

Previous studies have provided conflicting results regarding the use of PRP in patients with RIF or thin endometrium (Eftekhar et al., 2018; Chang et al., 2019; Kim et al., 2019; Mehrafza et al., 2019; Nazari et al., 2019). Based on our knowledge, there are a lack of conclusive results and a comprehensive review regarding the effect of PRP on the outcome of IVF/ICSI cycles. Therefore, in this systematic review and meta-analysis, we aimed at investigating the studies that evaluated the effect of intrauterine infusion of PRP in women undergoing IVF/ICSI cycles.

2. Methods

This systematic review and meta-analysis addressed the efficacy of intrauterine infusion of PRP compared with control (no intervention or other treatments) in sub-fertile women for improving clinical outcomes after assisted reproduction. We followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.1. Criteria for considering studies for this review

Studies were included in our review if they fulfilled the following criteria: i) the study was designed as an RCT, quasi-experimental or cohort studies in which medically confirmed pregnancy outcomes (live birth, clinical pregnancy, and miscarriage) were the endpoints, ii) the intervention was intrauterine infusion of PRP around the time of ET, iii) the control group was any other active intervention, no intervention, or placebo, iv) the population of interest was subfertile women, undergoing assisted reproduction, with any ovarian stimulation protocol. Studies were excluded if those were case-control, case series, cross-sectional, animal, or cell culture studies. Also, we excluded studies if we were unable to obtain adequate details of the study methodology or results.

2.2. Literature search

Potential studies were identified by conducting a systematic search, using Medline (through PubMed), Embase, Scopus, Web of Science and Cochrane Central Register of Controlled Trials (from inception to 15 May 2019). Also, references and the citation lists of published articles were hand-searched to identify additional eligible studies. Also, we searched grey literature (clinical trial registries, conference proceedings) to identify unpublished and in-press studies. Search terms included: ("In Vitro Fertilization" 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 gel"). Full details of the search strategy, terms, and database-specific indexing terminology are provided in Supplementary Table 1. There were no limits on language and year of publication.

2.3. Study selection, data extraction, and quality appraisal

Two review authors (S.M. and M.R.), scrutinized the titles and abstracts of the electronic searches according to the pre-defined eligibility criteria. Full articles were retrieved for further assessment if reviewers considered the study potentially relevant. Where there was any doubt about inclusion, the study was reviewed and discussed with the third reviewer (M.R.). The following data were extracted from each eligible study and cross-checked by two reviewers (S.M. and M.R.): first author's name, year, the country where the study was conducted, study design, characteristics of the study participants, and treatment characteristics. Extracted data were abstracted directly on to previously designed standardized electronic abstraction form. The methodological quality of trials was evaluated according to the recommendation by the

Table 1
Study characteristics.

Study	Country	Study design	Population	Sample size		Intervention(s)	Control	Time of PRP Infusion	Transfer type	Outcome Measures
				Case	Control					
Eftekhar et al., 2018	Iran	Randomized Clinical trial	Women with thin endometrium (endometrium thickness <7 mm)	40	43	Intrauterine infusion of 0.5–1 ml PRP	Underwent ET without intrauterine infusion of PRP	The13th day of HRT cycle	FET	Chemical pregnancy, Clinical pregnancy, Miscarriage, Endometrial thickness
Obidniak et al., 2017	Russia	Randomized Clinical trial	RIF, normal karyotype, absence of uterine factors of infertility,absence of chromosomal abnormalities in previous pregnancy	45	45	Underwent ET with Intrauterine infusion of 2.0 ml of autologous PRP	Underwent ET without intrauterine administration	Not Mentioned	FET	Implantation Rate, Clinical pregnancy
Nazari et al., 2019	Iran	Randomized Clinical trial	RIF: three or more failures of IVF-ET therapy	49	48	Intrauterine infusion of 1 ml of platelet-rich plasma	Underwent ET without intrauterine administration	48 hrs before ET	FET	Chemical pregnancy, Clinical pregnancy
Madhavan et al., 2018	India	Cohort	RIF At least one or more failures of IVF-ET therapy	42	56	Patients who received intrauterine infusion of 0.3–0.4 ml PRP	Underwent ET without intrauterine administration	Day 8/9 of the HRT	FET	Clinical pregnancy
Chang et al., 2019	China	Cohort	Patients with cancellation history of embryo transfer due to thin endometrium	34	30	HRT + intrauterine infusion of 0.5–1 ml PRP	Underwent ET without intrauterine administration	The 10th day of HRT cycle	FET	Implantation Rate, Clinical pregnancy, Miscarriage, Endometrial thickness
Mehrafza et al., 2019	Iran	Cohort	Patients with history of more than 2 repeated failed embryo transfer cycles	67	56	Intrauterine infusion of 1 ml of PRP	Underwent ET with systemic administration of GCSF	48 hrs before ET	FET	Implantation Rate, Chemical pregnancy, Clinical pregnancy
Coksuer et al., 2019	Turkey	Cohort	RIF: one or more failures of IVF-ET therapy	34	36	Intrauterine infusion of 1 ml of PRP	Underwent ET without intrauterine administration	48 hrs before ET	FET	Clinical pregnancy, Miscarriage, Live Birth

Cochrane Handbook, including assessments of the generation of the allocation sequence (selection bias); concealment of the allocation sequence (selection bias); blinding (detection and performance bias); blinding of participants and personnel to outcome assessment; incomplete outcome data (attrition bias); selective outcome reporting (reporting bias); and other biases. Also, the quality of all cohort studies was assessed using the Newcastle–Ottawa scale. An explicit judgment regarding the following items were done: the selection of the study groups, comparability of the groups, and ascertainment of exposure and outcome.

2.4. Statistical analysis

We extracted pregnancy outcomes from each of the included studies according to treatment strata and calculated the RR with the corresponding 95 % CI for each endpoint in the PRP versus controls women. The effect size was measured as the pooled RR with corresponding 95 % CI obtained by the Mantel-Hansel method using the random-effects model. The heterogeneity of the studies was assessed graphically with forest plots and statistically by chi-square-based Q statistic and I^2 value. Heterogeneity was considered significant at a P-value of <0.10 in Q-test or $I^2>40$ %. Statistical analyses were performed using Review Manager 5.3 (Cochrane Collaboration, 2014) and Stata software (Version 13.0) (STATA Corp, College Station, Texas). Subgroup analyses were used to identify the effect of intrauterine PRP infusion on pregnancy outcomes considering relevant study characteristics including PRP dosage ($\leq$ 0.5 ml, 1 ml and $\geq$ 1 ml), study population (RIF versus thin endometrium), study design (RCT versus cohort) as possible sources of heterogeneity.

3. Results

3.1. Summary of the literature search

The initial electronic literature search yielded 2,672 publications (775 from PubMed, 239 from Embase, 1,196 from Scopus, 376 from Web of Science, 82 from Cochrane Library and 4 through other sources). All citations were saved in reference manager software (Endnote) to identify the 1,565 duplicates. The titles and abstracts of these citations were scrutinized to exclude irrelevant papers, resulting in 17 potentially eligible studies. After reading the full texts, ten articles were excluded (Supplementary Table 2). Seven were case series, one was a case report, and two didn't provide sufficient data, thus leaving seven studies to be included in the meta-analysis. The flow diagram of the literature search and selection of studies is shown in Fig. 1.

3.2. Study characteristics

Table 1 outlines the main characteristics of all included studies. Studies were conducted between 2017 and 2019, of which six studies were published after 2016. The studies were conducted in Iran (3 studies) (Eftekhar et al., 2018; Mehrafza et al., 2019; Nazari et al., 2019), Russia (1 study) (Obidniak et al., 2017), India (1 study) (Madhavan et al., 2018), Turkey (1 study) (Coksuer et al., 2019), and one in China (Chang et al., 2019). Three studies were RCTs and four were cohort. The population in all studies except two was patients with RIF. All studies compared PRP versus no intervention, except one that compared PRP versus Granulocyte Colony Stimulating Factor (GCSF) (Mehrafza et al., 2019). The sample size ranged from 64 to 123 participants. Three studies administered the PRP with dose $\leq$ 0.5 mL, two studies with a dose of 0.5–1 ml and two studies with a dose $\geq$ 1 mL. All studies transferred the embryo in frozen condition.

3.3. Risk of bias assessment

The summary of the risk of bias assessments was shown in supplementary Table 3. All the trials were judged to be at low risk of bias for random allocation. Allocation concealment was judged to be at high risk of bias for one trial. Two of the trials assessed to be at unclear risk for performance bias and blinding of participants and personnel was at high risk in one study. All trials except one judged to be at low risk of bias for attrition bias. All cohort studies selected their exposed and non-exposed participants from the same community sample. All studies provided adequate criteria for the diagnosis of the outcomes of interest and provided a proper description of how the outcomes were measured. Only in one study appropriate method adopted for control of confounding.

3.4. Clinical pregnancy

Pooling results from seven studies, which compared clinical pregnancy between PRP and control (no intervention or other active intervention), including 625 participants (311 cases and 314 controls), showed a significantly higher probability of clinical pregnancy in PRP group (RR: 1.79, 95 % CI 1.37, 2.32; $P < 0.001$, Fig. 2). In consonance, the risk difference (RD) was 21 % in favor of the PRP group compared with control (no intervention or other active intervention) intervention) (RD: 0.20, 95 % CI: 0.13, 0.27; $P < 0.001$). There was negligible heterogeneity between studies ($P = 0.31$; $I^2 = 16$ %). There was no evidence of publication bias in this regard (Egger's regression intercept: 5.35, 95 % CI: −0.54, 11.24, $P = 0.07$). Sensitivity analysis showed that the estimates of the pooled RR range from 1.73 (95 % CI: 1.27, 2.35) to 2.10 (95 % CI: 1.58, 2.78), suggesting that no one study is substantially influencing the pooled estimate. Although the effect size was stronger in clinical trials, but there was no difference in clinical pregnancy between clinical trials (n = 3, RR: 2.37, 95 % CI: 1.59, 3.52; $P < 0.001$, $I^2 = 0$ %) and cohort (n = 4, RR: 1.50, 95 % CI: 1.09, 2.06; $P = 0.01$, $I^2 = 11$ %) studies (Fig. 3). The effect size in the subset of studies that administered PRP at a dose of 0.5–1 ml (n = 2, RR: 2.26, 95 % CI: 1.25, 4.09; $P = 0.007$, $I^2 = 0$ %), were more than those administered PRP at doses of $\leq$ 0.5 ml (n = 3, RR: 1.78, 95 % CI: 1.01, 3.15; $P = 0.05$, $I^2 = 67$ %) and $\geq$ 1 ml (n = 2, RR: 1.77, 95 % CI: 1.11, 2.80; $P = 0.02$, $I^2 = 0$ %) (Fig. 4). Also, the effect size was stronger in the subset of studies that administered PRP in patients with thin endometrium (n = 2, RR: 2.26, 95 % CI: 1.25, 4.09; $P = 0.007$, $I^2 = 0$ %), rather those administered PRP in patients with RIF (n = 5, RR: 1.73, 95 % CI: 1.24, 2.41; $P = 0.001$, $I^2 = 36$ %, Fig. 5).

3.5. Chemical pregnancy

Three studies with 303 participants (156 cases and 147 controls) compared chemical pregnancy between PRP and control (no intervention or other active intervention) groups. The probability of chemical pregnancy was significantly higher in women who received PRP compared with control (RR: 1.79, 95 % CI: 1.29, 2.50; $P < 0.001$, $I^2 = 0$ %, Fig. 6). In consonance, the RD was 19 % in favor of the PRP group compared with control (no intervention or other active intervention) (RD: 0.19, 95 % CI: 0.09, 0.30; $P < 0.001$, $I^2 = 0$ %).

3.6. Implantation rate

The effect of PRP on implantation rate was evaluated in three studies involving 277 subjects (146 cases and 131 controls). Following the intervention, implantation rate significantly increased in patients who received PRP compared to controls (RR: 1.97, 95 % CI: 1.40, 2.79; $P < 0.001$, $I^2 = 0$ %, Fig. 7). In consonance, the RD was 24 % in favor of the PRP group compared with control (no intervention or other active intervention) (RD: 0.24, 95 % CI: 0.13, 0.35; $P < 0.001$, $I^2 = 0$ %).

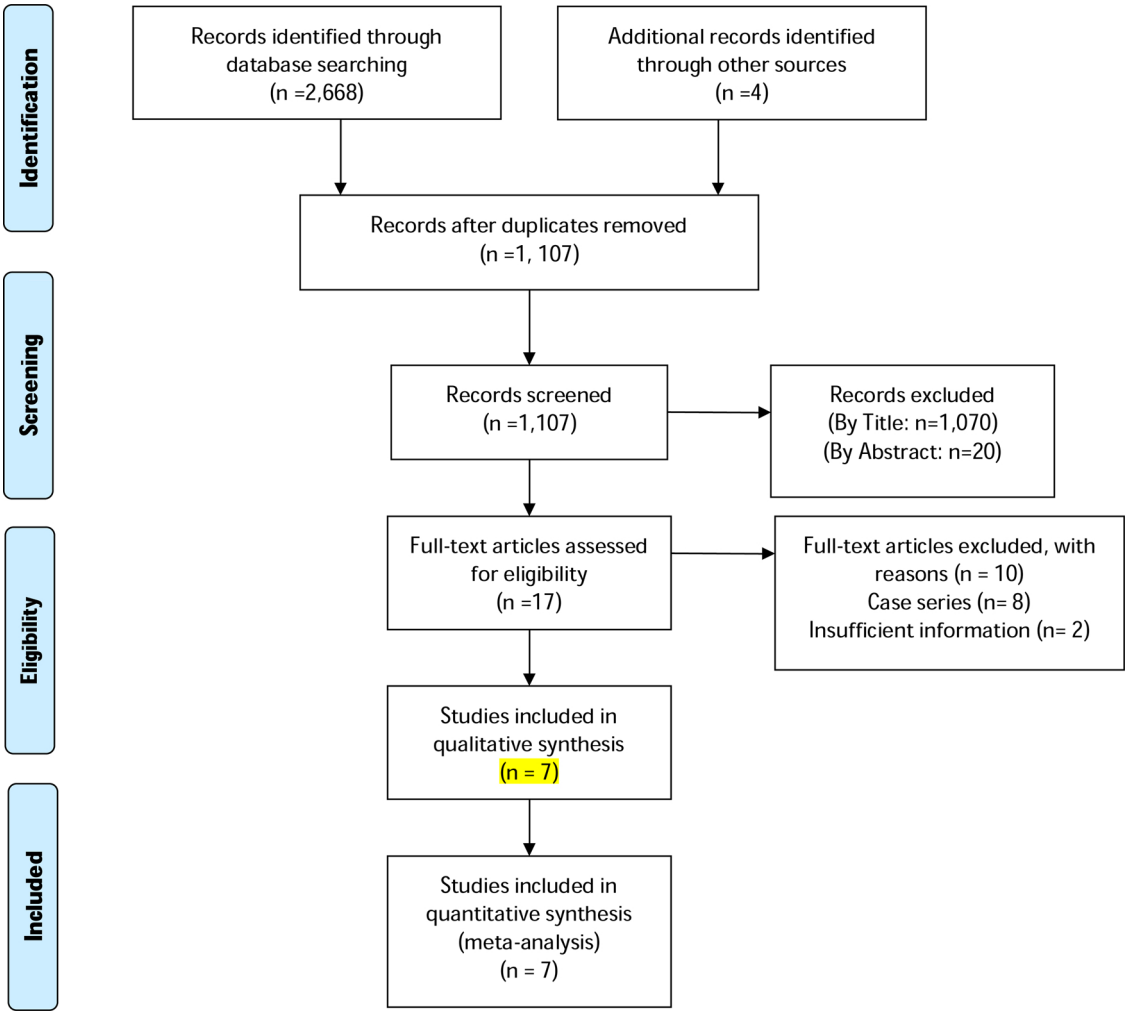

Fig. 1. PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram of study selection.

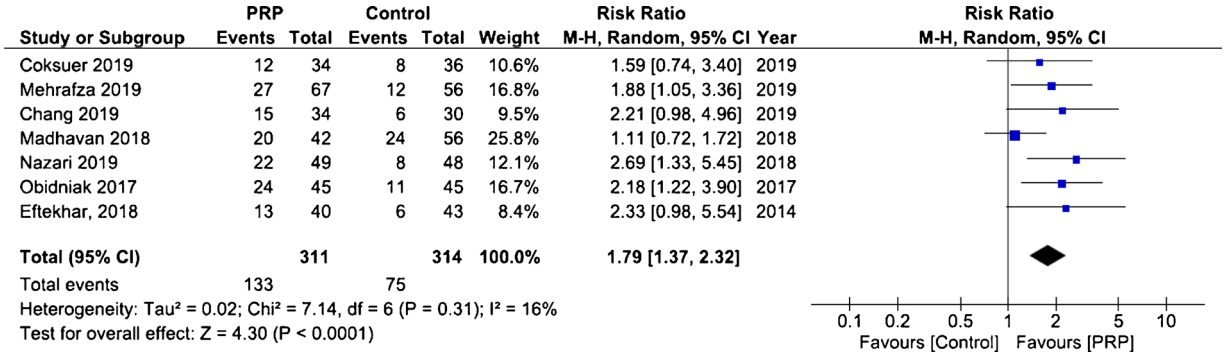

Fig. 2. Forest plot detailed risk ratio (RR) and 95 % confidence intervals for clinical pregnancy.

3.7. Miscarriage

We retrieved three studies with 217 subjects (108 cases and 109 controls) in which miscarriage was compared between PRP and no intervention. There was no difference between women who received PRP compared with no intervention regarding miscarriage (RR: 0.72, 95 % CI: 0.27, 1.93; P = 0.51, I^2 = 0 %, Fig. 8).

3.8. Endometrial thickness

Changes in endometrial thickness following PRP infusion were examined in two studies (74 cases and 73 controls). Following the intervention, endometrial thickness increased in women who received PRP compared to no intervention (SMD: 1.79, 95 % CI: 1.13, 2.44; P < 0.001, I^2 = 64 %, Fig. 9). In consonance, the MD was 0.94 mm in favor of the PRP group compared with no intervention (MD: 0.94 mm, 95 % CI: 0.44, 1.44; P < 0.001, I^2 = 88 %).

4. Discussion

In this study, we included seven studies that evaluated the effect of intrauterine infusion of PRP for 625 women (311 cases and 314

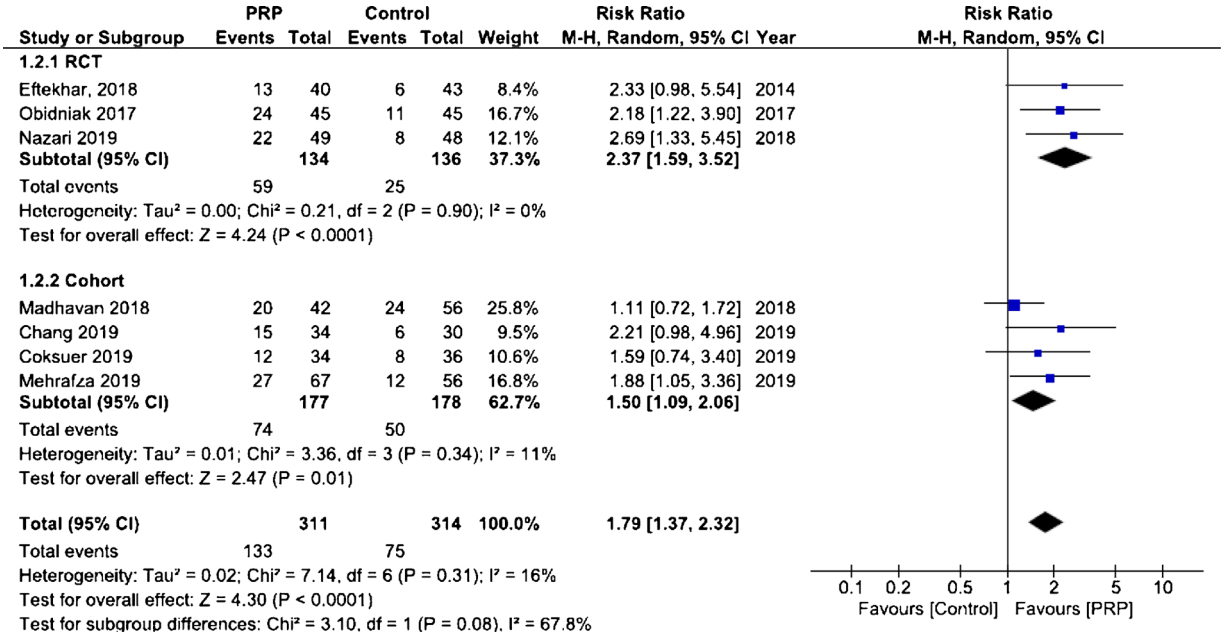

Fig. 3. Forest plot detailed risk ratio (RR) and 95 % confidence intervals for clinical pregnancy rate in the RCT and cohort studies for platelet-rich plasma and control groups.

controls) with a thin endometrium (two studies) or recurrent implantation failure (five studies) undergoing frozen-thawed ET cycle. Compared with control group, those in the PRP group exhibited better beneficial effects including clinical pregnancy, chemical pregnancy, implantation rate, and endometrial thickness, and the advantages remained after subgroup analysis regarding PRP dosage ($\leq$ 0.5 ml, 1 ml, and $\geq$ 1 ml), study population (RIF versus thin endometrium), and the study design (RCT versus cohort). Unfortunately, only one study compared the live birth between PRP and controls, which are the most important primary outcome of assisted reproduction and most of them didn't report implantation rates, miscarriage, and endometrial thickness. However, the implantation rate, chemical pregnancy, and endometrial thickness were significantly higher in women who received PRP rather control group in several studies reporting these outcomes.

Heterogeneity, the statistical measure of homogeneity, was low across all pregnancy endpoints measured, which suggests consistent

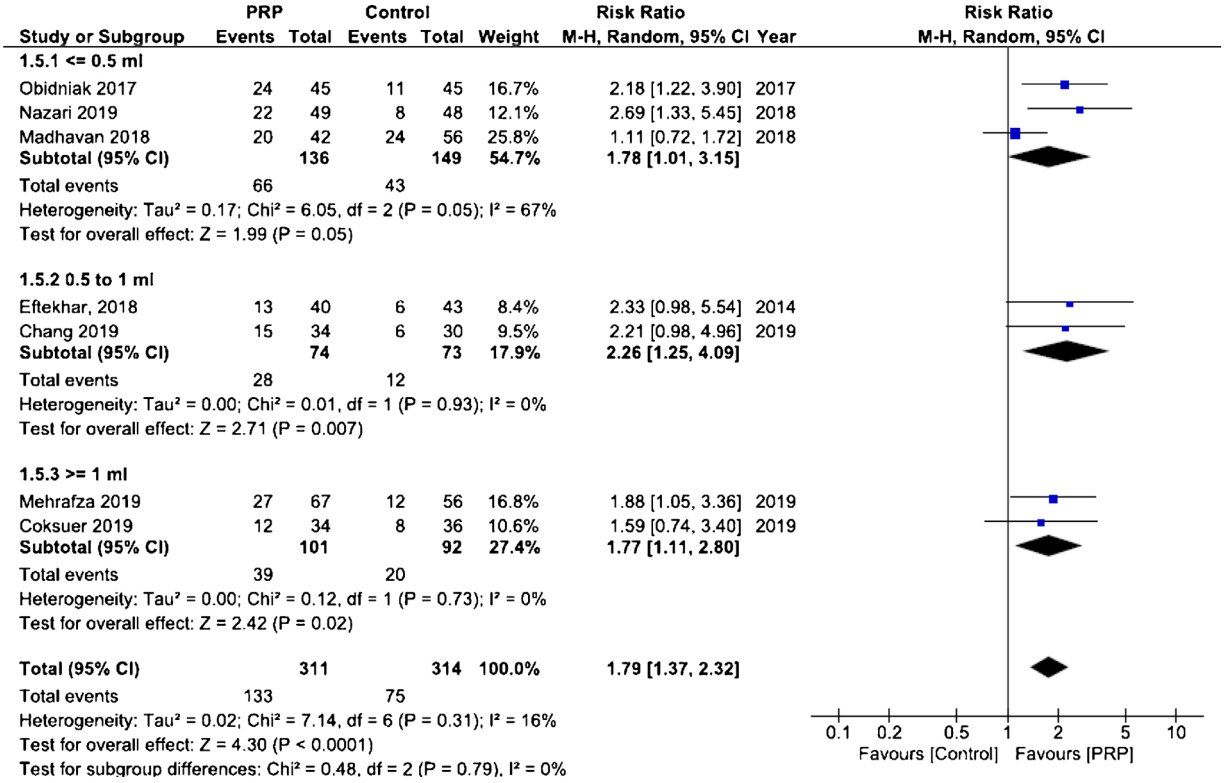

Fig. 4. Forest plot showing individual and combined effect size estimates and 95 % confidence intervals (CIs) in studies that evaluated the risk of clinical pregnancy in women who received intrauterine platelet-rich plasma versus controls regarding platelet-rich plasma dosage.

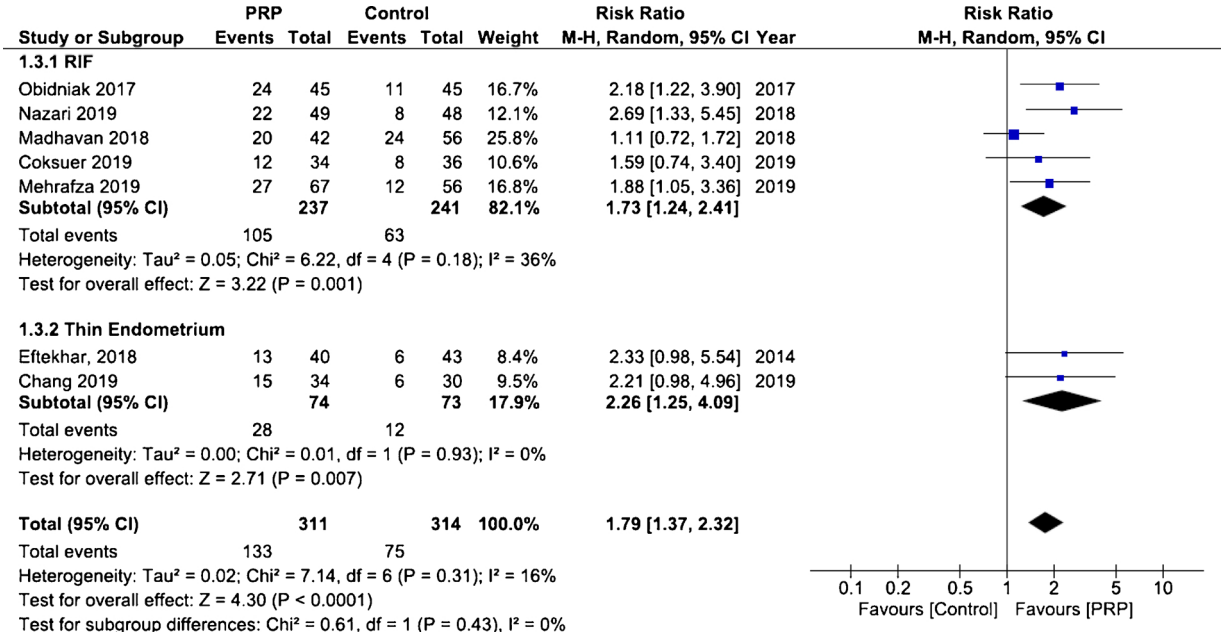

Fig. 5. Forest plot showing individual and combined effect size estimates and 95 % confidence intervals (CIs) in studies that evaluated the risk of clinical pregnancy in women who received intrauterine platelet-rich plasma versus controls regarding population type (recurrent implantation failure (RIF) and thin endometrium).

effects throughout the studies. Three of the retrieved studies were clinical trials, while the remaining were cohorts, so we analyzed the studies in two separate subgroups whether they were RCT or cohort. Results of subgroup analysis based on study design demonstrate that the effect of PRP in clinical trials is stronger rather than cohort studies. Also, after subgroup analysis, the heterogeneity between studies reduced, as it was reported zero for clinical trials and 11 percent for cohort studies.

A hierarchical system of classifying evidence in medicine, also known as the levels of evidence, is a cornerstone of evidence-based medicine (EBM). The design of the study and the outcomes measured affect the strength of the evidence. Based on the Oxford (UK) CEBM Levels of Evidence guidelines individual randomized controlled trials with narrow confidence interval classified as level 1b of evidence, while cohort studies are classified in three levels lower, 2b level (Eldredge, 2000). Therefore, we can conclude more confidently about the efficacy of PRP in women undergoing frozen-thawed ET cycle.

We found that the effect of PRP in the subset of studies that administered PRP at a dose of 0.5–1 ml was more than those administered PRP at doses of ≤ 0.5 ml and ≥ 1 mL. The interpretation of this finding is associated with a big problem. PRP also is known as autologous conditioned plasma is characterized by its absolute platelet concentration: it is a concentrate of PRP protein with any platelet concentration above that of baseline whole blood, which is 150000/μL to 450000/μL. For its autologous nature, PRP injectate may differ depending on the specific manufacturer and protocol (Alves and Grimalt, 2018).

None of the included studies reported sufficient information on the protocol for PRP preparation, processing machine, spinning parameters, platelet concentration, WBC count, growth factor analysis, and PRP activation method used. In a systematic review, a formula is proposed to compare the efficacy of PRP. The components of this formula include the PRP volume, PLP platelet concentration, whole blood volume, and whole blood platelet concentration (Fadadu et al., 2019). Since the required components to calculate this formula were not reported in the included studies, we were unable to standardize the efficiency of the PRP and compare it between studies. Therefore, merely based on the comparison of the reported dosage in the studies, it is not possible to comment on the effective range of the PRP.

The first time that PRP was used in the infertility field, the main idea of using the PRP in IVF was based on its ability in the improvement of endometrial growth and its tissue healing abilities in women with a thin endometrium (Chang et al., 2015). The latter studies also have focused on the effect of PRP on endometrial thickness as an important indicator of endometrial receptivity. In both studies that used the PRP in women with thin endometrium, the endometrial thickness was significantly increased in the PRP group compared with the control. It should be noted that in the study of Eftekhar, the endometrial thickness has reached 8.67 mm from 6.09 mm in the PRP group while in the control group it was raised to 8.04 from the 6.15 mm. In the study of Chang et al., the endometrial thickness before the PRP infusion was 6.32 mm, and it has been raised to 7.65 mm after the intervention. According to the results of these studies, these differences were statistically significant, but there is an important question that given the

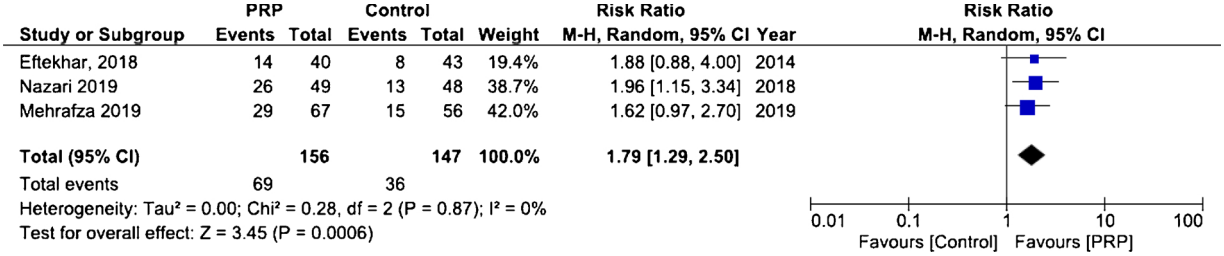

Fig. 6. Forest plot showing individual and combined effect size estimates and 95 % confidence intervals (CIs) in studies that evaluated the risk of chemical pregnancy in women who received intrauterine platelet-rich plasma versus control.

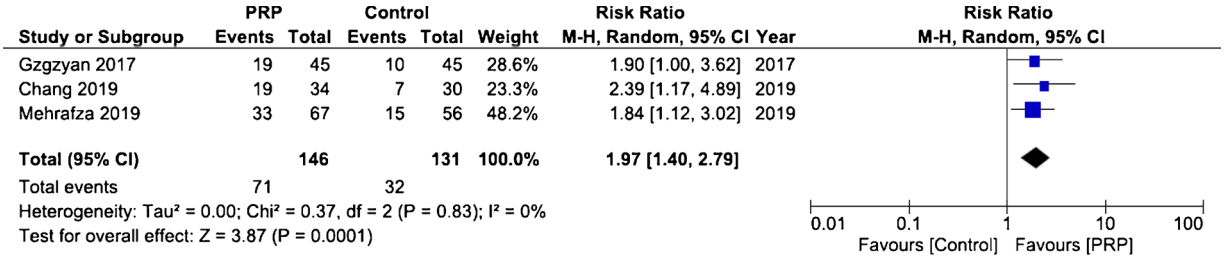

Fig. 7. Forest plot showing individual and combined effect size estimates and 95 % confidence intervals (CIs) in studies that evaluated the risk of implantation rate in women who received intrauterine platelet-rich plasma versus control.

inter-observer variation, can we consider this amount clinically significant (Karlsson et al., 1994)? In a study by Kim et al., despite the increased endometrial thickness after treatment with PRP, there was no association between the endometrial thickness changes and the ET outcomes (Kim et al., 2019). On the other hand, it has been proposed that endometrial thickness has a poor ability to predict clinical pregnancy (Craciunas et al., 2019). Unfortunately, the number of well-designed studies regarding the effect of PRP on thin endometrium is not sufficient, and we are not able to attribute the ability of the PRP to increase pregnancy rates in women with refractory endometrium exclusively to increased endometrial thickness. So, it is recommended for future studies to evaluate the other markers of endometrial receptivity.

The most accepted theory for explaining the positive effect of PRP in cases with RIF is related to the regulation of immunological interactions between embryo and endometrium at the time of the implantation window. It has been well understood that the endometrial environment should be switched to an anti-inflammatory state in the mid-secretory phase, to prevent fetal rejection (Mor et al., 2011; Griffith et al., 2017). PRP poses a downregulating effect on crucial inflammatory cytokines, such as interleukin IL-6 and IL-8 pro-inflammatory cytokines, which have an important role in the implantation process. The PRP also upregulates IL1-β production. IL1-β is a pro-inflammatory cytokine that is known to be increased in the mid-secretory phase of human endometrium, which is essential for embryo implantation (Laird et al., 2006). PRP is also known to have potential effects on soft tissue healing (Petrungaro, 2001; Tischler, 2002) as well as human endometrial and ovarian tissues (Pantos et al., 2016; Aghajanova et al., 2018). The growth factors in PRP, including TGF, PDGF, insulin-like growth factor 1, hepatocyte growth factor, vascular endothelial growth factor, and fibroblast growth factor, can influence healing and reduce inflammation (Everts et al., 2006).

In summary, the exact molecular basis of PRP action in the process of implantation is still undetermined but, several possible mechanisms have been proposed as follow: (1) activated PRP promoted the migration of human primary endometrial epithelial cells, endometrial stromal fibroblasts, endometrial mesenchymal stem cells (MSC), and bone marrow-derived MSC, (2) through their regulatory actions on proliferation, apoptosis, inflammation, cell adhesion, chemotaxis, and immune responses during blastocyst implantation (3) promotes cell regeneration, proliferation and vascularization by several growth factors including VEGF, TGF-b, PDGF, IGF1, EGF, HGF, (4) cell migration via chemo attraction, mesenchymal to epithelial trans differentiation and maybe the most importantly inflammation and (5) stimulatory effect on the expression of several pro-inflammatory cytokines (IL1A, IL1B, IL1R2), chemokines (CCL5, CCL7, CXCL13) and matrix metalloproteins (MMP3, MMP7, MMP26) (Sanchez et al., 2003; Bendinelli et al., 2010; Filardo et al., 2015; Li et al., 2016; Meheux et al., 2016; Dai et al., 2017).

4.1. Strengths and limitations

This is the first systematic review presenting pooled RR of a large number of primary studies to assess the effect of intrauterine infusion of PRP in women undergoing frozen-thawed ET cycle. Strengths of the meta-analysis include homogeneity of pooled indices across studies, as well as the robustness to sensitivity and subgroup analysis. Substantial homogeneity of pooled indices across studies is indicated by the fact that in most of the studies we reviewed, the population, design, and methodology of studies were similar. Several limitations should be considered in the interpretation of the present systematic review and meta-analysis. First, the small number of included studies (n = 7) and the fact that only three of them were designed as RCT. Second, not all publications shared detailed descriptions of the PRP they used. There are variations in the ways of obtaining, preparing and applying PRP between studies. Ideally, for the meta-analysis of the cohort studies, the adjusted RR should be meta-analyzed. However, in our included studies, it was infrequent for the included primary studies to provide sufficient detail about their adjusted analysis for known confounding factors, such as age and BMI. Therefore, we were unable to perform a meta-analysis of adjusted RR. Although we conducted comprehensive and time-consuming literature searches to identify all relevant studies, and the Egger test did not suggest publication bias, we cannot exclude the possibility that publication bias might have affected our results.

In most of the included studies, the cause of implantation failure was not mentioned. Also, most of the studied used PRP in unexplained RIF cases, so we were not able to perform sub-group analysis regarding the cause of implantation failure, and still more studies are needed for a definitive conclusion. Also, among the studies that we have included at the final meta-analysis, only two studies aimed at evaluating the PRP in patients with thin endometrium that none of them reported the cause of

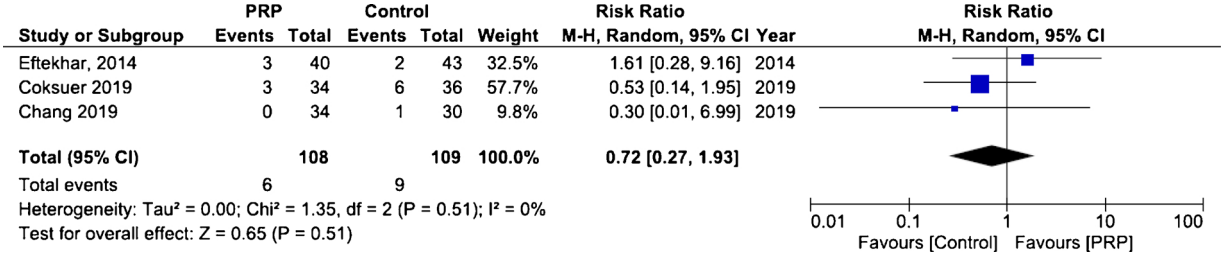

Fig. 8. Forest plot showing individual and combined effect size estimates and 95 % confidence intervals (CIs) in studies that evaluated the risk of miscarriage in women who received intrauterine platelet-rich plasma versus control.

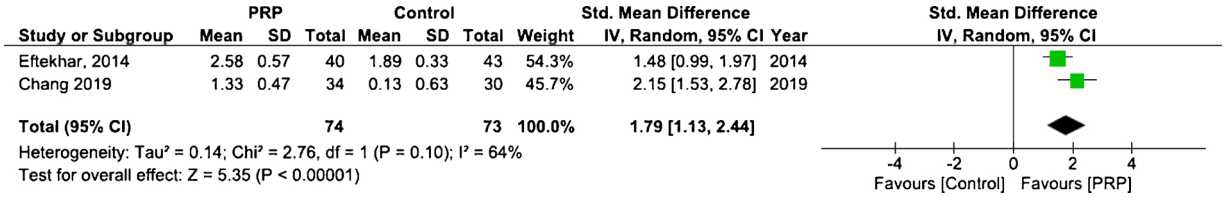

Fig. 9. Forest plot showing individual and combined effect size estimates and 95 % confidence intervals (CIs) in studies that evaluated the standardized mean difference of endometrial thickness in women who received intrauterine platelet-rich plasma versus control.

thin endometrium. So, sub-group analysis was impossible, and we were not able to show which kinds of RIF or refractory endometrium are most likely to benefit from the RPR uterine infusion.

One of the other limitations that existed in reviewed studies was the lack of sufficient data regarding the time of PRP infusion. As shown in Table 1, the time of the infusion was different between studies or even in some of them it was not reported, so we could not perform subgroup analysis, and we are not able to give a conclusive result about the best time interval between PRP infusion and ET. One of our other concerns is the lack of placebo in control groups. Since, there is growing evidence about the positive effect of endometrial mechanical stimulation on implantation success, although a conclusive result is not available yet (Gnainsky et al., 2010; El-Toukhy et al., 2012; Panagiotopoulou et al., 2015). Therefore, the positive effect of using PRP on implantation and endometrial thickness may be partially related to mechanical endometrial stimulation induced by the insertion of the catheter into the uterine cavity. So we suggest the use of placebo in subsequent studies to control the possible effect of endometrial scratching to obtain more accurate results.

5. Conclusion

Our systematic review and meta-analysis showed that intrauterine administration of PRP, irrespective of study design and study population, increases the clinical pregnancy rate in women experienced frozen-thawed ET cycle. Further prospective, large, and high quality randomized controlled trials (RCTs) are needed to identify the subpopulation that would most benefit from PRP.

Authors' roles

M.S. and A.M.H. were responsible for defining the research question. M.S. and S.R. designed the strategy for the literature search. S.M., M.R. and M.R. participated in study selection. A.M.H. and M.S. performed the quality assessment of included studies. Data extraction was carried out by S.R. and M.R. Data analysis was performed by A.M.H, M.S. and S.M. were the major contributors in manuscript writing. M.S. and A.M.H drafted the manuscript and revised content based on feedback.

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Declaration of Competing Interest

None declared.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jri.2019.103078.

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