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Review article

Intrauterine administration of autologous peripheral blood mononuclear cells in patients with recurrent implantation failure: A systematic review and meta-analysis

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ABSTRACT

Intrauterine administration of autologous peripheral blood mononuclear cells (PBMC) has been proposed to improve implantation rates in women with recurrent implantation failure (RIF). The objective of this study was to evaluate whether intrauterine administration of PBMC improves clinical pregnancy and live birth in couples with RIF. Various databases were searched including Medline, Embase, Scopus, Web of Science and Cochrane Central Register of Controlled Trials up to April 2018. This review included all studies that compared intervention of PBMC in infertile women undergoing any form of assisted reproductive technology (ART). Two independent reviewers assessed eligibility; methodological quality; and extracted data. Meta-analysis using a random-effects model was performed to calculate the pooled estimates. Eight studies involving 886 patients were included. The probability of clinical pregnancy was significantly higher in women who received PBMC compared with control (RR: 1.92, 95% CI: 1.48–2.49; P < 0.001). No difference was observed in the studies that transmitted the embryo at blastocyst (RR: 2.44, 95% CI: 1.42–4.20; P = 0.001), or cleavage stage (RR: 2.01, 95% CI: 1.36–2.96; P < 0.001). There was no difference between studies that transmitted the embryo in fresh (RR: 2.14, 95% CI: 1.38–3.32; P < 0.001), or frozen condition (RR: 1.79, 95% CI: 1.32–2.43; P < 0.001). The probability of live birth was significantly higher in women who received PBMC compared with control (RR: 1.93, 95% CI: 1.35–2.76; P < 0.001). Administration of PBMC, irrespective of embryo stage and cycle type, increases clinical pregnancy and live birth in patients experienced RIF. However, these overall estimates should be considered with caution due to the small number, quasi-experimental design and poor quality of most included studies.

1. Introduction

RIF is generally defined as the failure to achieve a clinical pregnancy after transfer of at least four good-quality embryos in a minimum of three fresh or frozen cycles to the normal uterine cavity (Coughlan et al., 2014; Polanski et al., 2014); however, despite several studies focused on finding a universally accepted definition for RIF, still there is no consistent definition for it, and different studies have used different criteria. RIF remains a significant challenge in patients undergoing in vitro fertilization (IVF) procedures (Margalioth et al., 2006; Simon and Laufer, 2012). Embryo implantation dysfunction, as a result of insufficient trophoblast invasion and poor endometrial receptivity, is considered as one of the most important causes of RIF and early pregnancy loss (Simon and Laufer, 2012; Timeva et al., 2014). It has been mentioned in the literature that complex endocrine and immunologic interactions between the stromal and trophoblastic cells may play a critical role in the implantation process (Ferretti et al., 2007; Hammer, 2011). So, up to now, many different in-vitro and in-vivo trails have

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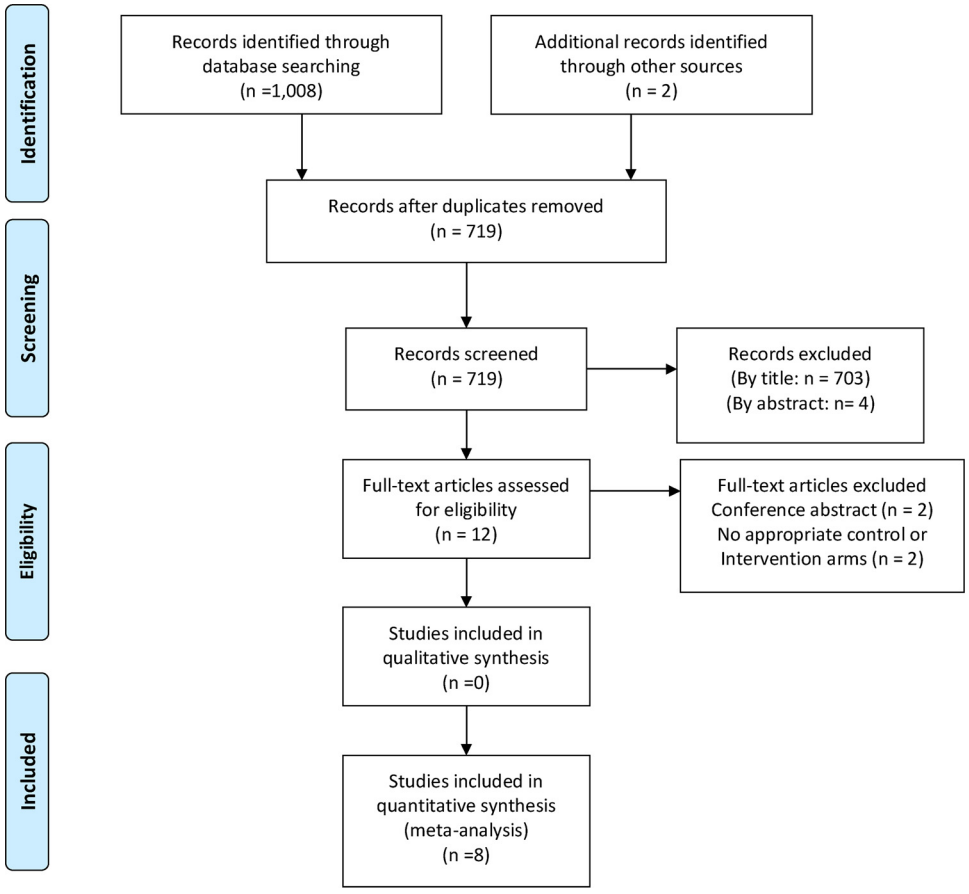

Fig. 1. PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram of study selection.

been evaluated the effect of different cell and tissue-based therapies and immunomodulatory methods to improve implantation rate and embryo transfer (ET) outcomes (Zeyneloglu and Onalan, 2014). Intrauterine insemination of autologous cultured PBMC is one of the cell-based therapies that have been widely discussed in the field of reproductive medicine. PBMC mainly consist of T lymphocytes, B lymphocytes, and monocytes and it was reported to adjust the production of several cytokines, such as IL-1α, IL-1β, and TNF-α, and can promote blastocyst spreading and invasion to the endometrium as well as endometrial receptivity in-vitro (Egawa et al., 2002; Yu et al., 2015). Also, in-vivo studies demonstrated that administration of PBMC promotes implantation and clinical pregnancy rates and might optimize IVF outcomes in patients who had suffered from the repeated failure of IVF/ICSI (Yoshioka et al., 2006; Chen et al., 2011; Feskov et al., 2016; Madkour et al., 2016; Li et al., 2017). According to our systematic searches in scientific databases, there is a lack of conclusive results and a comprehensive review regarding the effect of PBMC on the outcome of IVF/ICSI cycles. Therefore, in this systematic review and meta-analysis, we aimed to investigate the studies that evaluated the effect of intrauterine insemination of PBMC on IVF outcome in couples with RIF and shedding light on its probable role in the treatment of RIF in the future.

2. Material and methods

We adhered to the Cochrane Handbook for Systematic Reviews of Interventions and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study protocol was registered at PROSPERO (registration number CRD42018102312).

2.1. Criteria for considering studies for this review

Studies were considered in our review if they met the following criteria (1) compared intervention of PBMC in infertile women undergoing any form of ART, (2) included women undergoing ART with three or more previous implantation failures (3) being a randomized controlled trial (RCT), quasi-randomized and cohort studies in which medically confirmed pregnancy outcomes were the endpoints.

2.2. Literature search

We searched the Medline, Embase, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials (from inception to April 2018) to find potentially relevant original articles. We hand-searched the references and citation lists of all included primary studies to find more relevant articles that were not found by the initial electronic searches. Two authors (M.S. and A.A.) searched the databases independently. Searches or study selection were not restricted regarding the language, publication date or publication status. Also, we searched grey literature (clinical trials registers, conference proceedings) to identify unpublished and in press studies. The full search strategy and keywords/terms used and database-specific indexing terminology are presented in Appendix S1.

2.3. Data extraction and quality assessment

Two independent reviewers (M.S. and A.A.) screened the titles and abstracts of the electronic searches according to the predefined inclusion criteria. Any disagreements, regarding inclusion, were resolved by discussion or consultation with a third reviewer (M.R). The full manuscripts of the titles and abstracts were assessed if either, reviewers

considered the study potentially relevant. Data were extracted independently by two reviewers from each selected article on study characteristics, quality, and endpoints using a standardized data collection sheet. The risk of bias within studies was assessed using the Cochrane risk of bias tool.

2.4. Statistical analysis

We extracted ET outcomes from each of the included studies according to treatment strata and calculated the risk ratio (RR) with corresponding 95% confidence intervals (CIs) for each endpoint in the cases versus controls women. Meta-analysis using Mantel-Hansel weighting was performed to calculate the random-effects pooled estimates. Heterogeneity of the studies was assessed graphically with forest plots, and statistically analyzed using the $\chi 2$ test and the degree of heterogeneity was quantified with the I^2 statistic. Statistical analyses were performed using Review Manager 5.3 (Cochrane Collaboration, 2014).

3. Results

The PRISMA flow diagram of the literature search and study selection processes for the quantitative meta-analysis is presented in Fig. 1. The search strategy yielded 1, 010 publications (51 from PubMed, 34 from Embase, 465 from Scopus, 376 from Web of Science, 82 from Cochrane Library, and 2 from other sources); of which 291 were duplicated and removed. After scrutinizing the title and abstract of remained citations, we excluded 707 studies that did not meet the predefined eligibility criteria for the systematic review and meta-analysis, so a total of 12 publications, that were suitable for full-text reading, have remained. Finally, we included eight studies which met the eligibility criteria for quantitative data synthesis.

3.1. Study characteristics

An overview of the main characteristics of the included studies is presented in Table 1. The publication date of the included studies was between 2006 and 2017. Studies were conducted in Ukraine (3 studies), Japan (2 studies), China (2 studies), and Morocco (one study). Sample sizes varied between 35 (17 cases and 18 controls) to 216 (138 cases and 78 controls). Two of the included studies were RCT, and the other six were quasi-experimental. Of the eight included studies, four studies investigated the effect of PBMC in fresh ET, three in freeze ET and one in a combination of freeze and fresh ET. Seven of the eight included studies reported the mean age of their participants. The mean age of participants in most studies was over 34 years old, and two had a lower mean age of 34 years old. Of the two clinical trials, only one study reported appropriate random sequence generation. The trials were at high risk of no allocation concealment. The analysis approach of both trials was not clear, hence classified as being at high risk for attrition bias. All studies were judged to be at low risk for performance and detection bias, as the clinical outcomes and intervention were objective. Since all possible outcomes were reported, all studies were considered as low risk for reporting bias. The methodologic quality appraisal is presented in Appendix S2.

3.2. Clinical pregnancy rate

The Clinical pregnancy rate is defined as the number of clinical pregnancies (gestational sacs observed ultrasonographically) divided by the number of embryos transfer cycles. Multiple gestational sacs are counted as one clinical pregnancy. (Zegers-Hochschild et al., 2009). There were eight studies with 886 women with RIF (493 cases and 393 controls) that compared clinical pregnancy between PBMC and control group. The probability of clinical pregnancy was significantly higher in women who received PBMC compared with the control group (RR: 1.92, 95% CI: 1.48–2.49; $P < 0.001$, Fig. 2). In consonance, the risk difference (RD) was 22% in favor of the PBMC group compared with control group (RD: 0.22, 95% CI: 0.13 to 0.30; $P < 0.001$). There was no evidence for heterogeneity between studies ($P = 0.27$; $I^2 = 20\%$). The results of the meta-analysis were not affected by studies' design. There was no difference in clinical pregnancy rate between RCT (RR: 2.32, 95% CI: 1.57–3.44; $P < 0.001$) and quasi-experimental (RR: 1.79, 95% CI: 1.27–2.50; $P < 0.001$) studies (Fig. 2). In a subgroup analysis, no significant difference was observed in the subset of studies that transmitted the embryo at the blastocyst stage (RR: 2.44, 95% CI: 1.42–4.20; $P = 0.001$), or cleavage stage (RR: 2.01, 95% CI: 1.36–2.96; $P < 0.001$) (Fig. 3). Also, there was no difference in clinical pregnancy rate between the subset of studies that transmitted the embryo in fresh (RR: 2.14, 95% CI: 1.38–3.32; $P < 0.001$), or frozen condition (RR: 1.79, 95% CI: 1.32–2.43; $P < 0.001$) (Fig. 4).

3.3. Live birth

A total of four studies (267 cases and 237 controls) were included in the live birth rate meta-analysis. One of these studies was RCT, and the remaining three studies were quasi-experimental. The probability of live birth was significantly higher in women who received PBMC compared with placebo (RR: 1.93, 95% CI: 1.35–2.76; $P < 0.001$, Fig. 5). In consonance, the risk difference (RD) was 16% in favor of the PBMC group compared with placebo (RD: 0.16, 95% CI: 0.08 to 0.23; $P < 0.001$). There was no heterogeneity ($P = 0.38$, $I^2 = 2\%$) between studies.

4. Discussion

In this study, we included eight studies investigated the effect of intrauterine administration of PBMC for 886 women with RIF (493 cases and 393 controls) who had experienced implantation failure after three or more ETs. Our results showed that intrauterine administration of PBMC before ET can significantly improve the ET outcomes in RIF patients and can increase the pregnancy rate by twice as much as the control group. According to our searches, this is the first systematic review and meta-analysis regarding the effect of intrauterine administration of PBMC on ET outcomes in couples experienced RIF. At the present study, we performed extensive literature search without language restrictions according to the latest guidelines for conducting and reporting of systematic reviews. Overall, in most of the studies we reviewed, the population, design, and methodology of studies and the quality of the transferred embryos, were similar. So, no statistically significant heterogeneity was observed between the studies, and results were fairly homogeneous, which it made our results more reliable. Although there is yet no universally accepted definition for RIF, the most popular proposed definition is the failure to achieve a clinical pregnancy after transfer of at least four good-quality embryos in a minimum of three fresh or frozen cycles (Coughlan et al., 2014). In the other hand, according to previous studies, it seems that patients with one or two ET failures will not benefit from using PBMC (Okitsu et al., 2011; Li et al., 2017). So, in this study, we defined RIF as three or more implantation failures or just performed the meta-analysis on the data extracted from sub-groups with three and more than three implantation failures. Unfortunately, just a few studies reported the live birth rate, which is the most important primary outcome of IVF and most of them didn't report miscarriage rates, complications, and adverse pregnancy outcomes. Also, no sufficient data were reported by most of the studies for calculating the implantation rate; therefore, we could not perform a meta-analysis on the implantation and miscarriage rates. At the present study, we analyzed the studies in two separate subgroups whether they were randomized or non-randomized. Results of subgroup analysis didn't show significant differences in pregnancy rate between two study designs.

The main idea of using the PBMC in RIF patients is based on the

Table 1
main characteristics of the included studies.

Study	Country	Study design	Population	Sample size		Intervention(s)	Control	PBMC Type	Transfer type	Stage of Embryo	Outcome Measures
				Case	Control						
Yoshioka, 2006	Japan	Non-Randomized Clinical trial	RIF: four or more failures of IVF-ET therapy without poor ovarian reserve	17	18	Underwent ET with Intrauterine PBMC	Underwent ET without intrauterine administration	Co-cultured with HCG combined with fresh PBMC	Fresh	Blastocyst Stage (Day 5)	Implantation Rate - Pregnancy Rate - Live Birth Rate
Fescove, 2011	Ukraine	Non-Randomized Clinical trial	RIF: two or more failures of IVF-ET therapy without poor ovarian reserve	80	80	Underwent ET with Intrauterine PBMC	Underwent ET without intrauterine administration	Co-cultured with HCG	Fresh and FET	Blastocyst Stage (Day 5)	Pregnancy Rate
Okitsu, 2011	Japan	Non-Randomized Clinical trial	RIF: one or more failures of IVF-ET therapy without poor ovarian reserve	19	36	Underwent ET with Intrauterine PBMC	Underwent ET without intrauterine administration	Fresh PBMC	FET	Blastocyst Stage (Day 5) and Cleavage Stage (Day 3)	Implantation Rate - Pregnancy Rate - Live Birth Rate
Sudoma, 2011	Ukraine	Randomized Clinical trial	RIF: three or more failures of IVF-ET therapy without poor ovarian reserve	42	20	Underwent ET with Intrauterine PBMC	Underwent ET without intrauterine administration	Co-cultured with HCG combined with fresh PBMC	Fresh	Blastocyst Stage (Day 5)	Pregnancy Rate
Madkour, 2015	Morocco	Randomized Clinical trial	RIF: two or more failures of IVF-ET therapy without poor ovarian reserve	27	27	Underwent ET with Intrauterine PBMC	Underwent ET without intrauterine administration	Co-cultured with HMG	Fresh	Cleavage Stage (Day 3)	Implantation Rate - Pregnancy Rate - Miscarriage Rate
Fescove, 2016	Ukraine	Non-Randomized Clinical trial	RIF: two or more failures of IVF-ET therapy without poor ovarian reserve	94	39	Underwent ET with Intrauterine PBMC	Underwent ET without intrauterine administration	Co-cultured with HCG	Fresh	Cleavage Stage (Day 3)	Pregnancy Rate
Yu, 2016	China	Randomized Clinical trial	RIF: three or more failures of IVF-ET therapy without poor ovarian reserve	93	105	Underwent ET with Intrauterine PBMC	Underwent ET without intrauterine administration	Co-cultured with HCG	FET	Cleavage Stage (Day 3)	Implantation Rate - Pregnancy Rate - Live Birth Rate - Miscarriage Rate
Li, 2017	China	Non-Randomized Clinical trial	RIF: one or more failures of IVF-ET therapy without poor ovarian reserve	138	339	Underwent ET with Intrauterine PBMC	Underwent ET without intrauterine administration	Co-cultured with HCG	FET	Blastocyst Stage (Day 5) and Cleavage Stage (Day 3)	Implantation Rate - Pregnancy Rate - Live Birth Rate

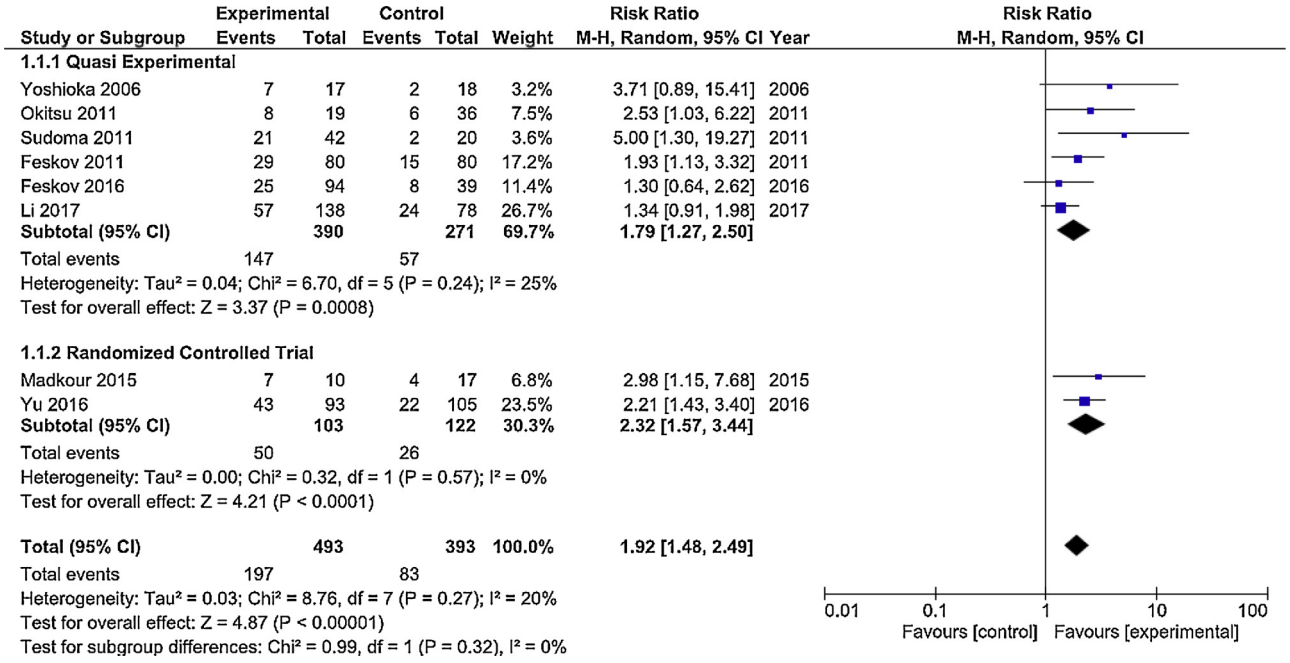

Fig. 2. Forest plot detailed risk ratio (RR) and 95% confidence intervals for clinical pregnancy rate in the randomized and non-randomized studies for peripheral blood mononuclear cells and control groups.

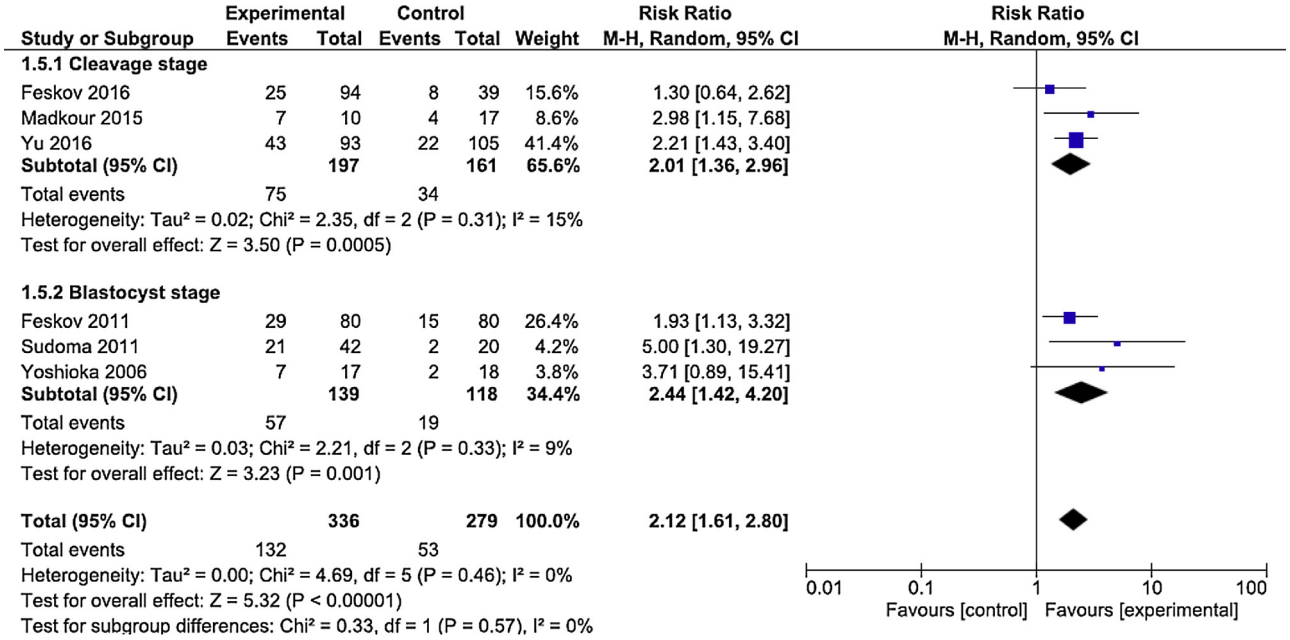

Fig. 3. Forest plot detailed risk ratio (RR) and 95% confidence intervals for clinical pregnancy rate in the blastocyst or cleavage stage for peripheral blood mononuclear cells and control groups.

regulation of cross-talk between embryo and endometrium and was first presented by Yoshioka et al. at 2006 (Yoshioka et al., 2006). Clarifying the exact role of PBMC in the process of implantation is complicated. but, several possible mechanisms have been proposed as follow: triggering the production of progesterone by luteal cells; switching the uterine local immunity from the Th-1 dominant environment to the innate (Th-2) type (Hashii et al., 1998; Bates et al., 2002); increasing the production of endometrial vascular endothelial growth factor (VEGF) and Leukemia inhibitory factor (LIF) (Yu et al., 2014); Stimulation of trophoblast cells invasion and differentiation of corpus luteum and endometrium (Yu et al., 2015); and Creation of a leading pathway through the uterine cavity as a result of the movement of locally administered PBMC toward the endometrial stromal tissue and facilitating the embryo attachment and invasion (Fujiwara et al., 2009). As a result, it seems that PBMC can be added to infertility therapies as an alternative immunological supplement for improving maternal immune recognition process (Fujiwara et al., 2016), but, in some cases with an over-activated uterine immune profile, PBMC insemination may worsen the condition and cause deleterious uterine immune over-activation. Therefore, immune profiling and personalized treatment approaches are recommended in RIF patients (Lédée et al., 2017).

It seems that some hormones can stimulate the production of chemokines and cytokines by PBMC and enhances its activity (Egawa et al., 2002; Nakayama et al., 2002; Yu et al., 2015). So, in some studies we

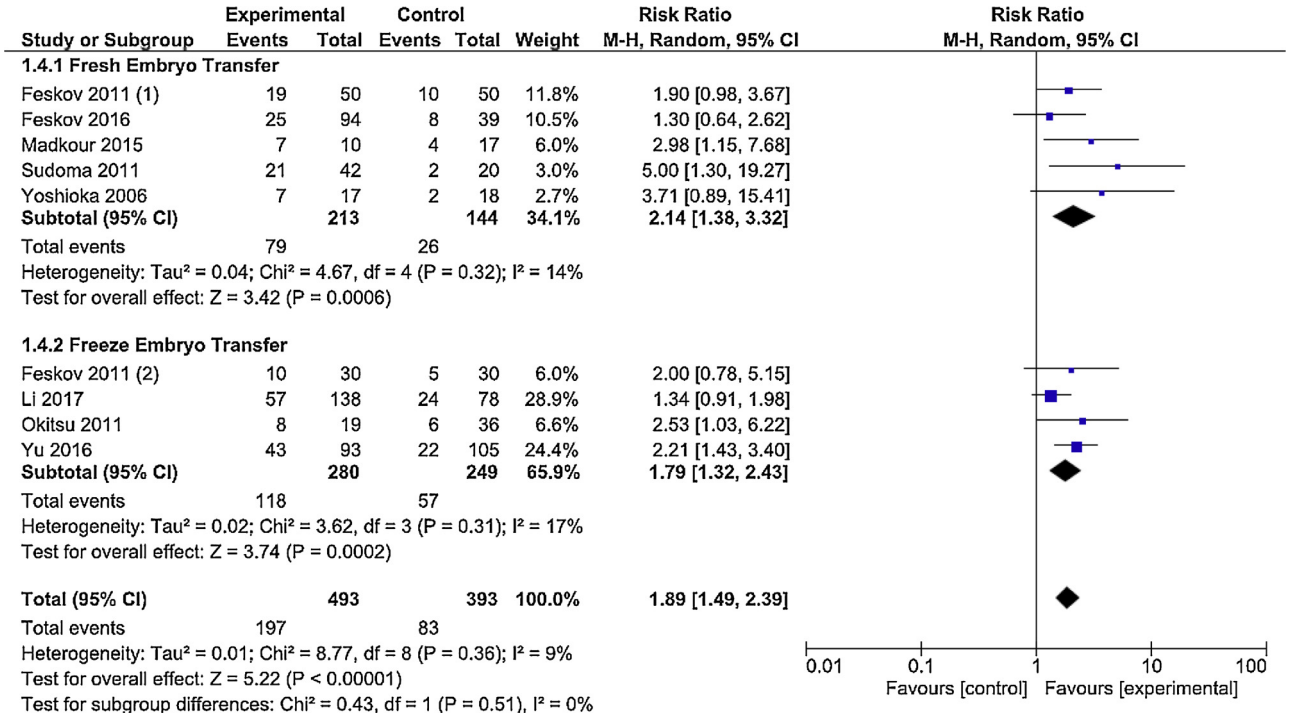

Fig. 4. Forest plot detailed risk ratio (RR) and 95% confidence intervals for clinical pregnancy rate in fresh or frozen embryo transfer for peripheral blood mononuclear cells and control groups.

investigated, PBMC was co-cultured in the presence of HCG (Feskov et al., 2016; Yu et al., 2016; Li et al., 2017), CRH (Makrigiannakis et al., 2015), HMG (Madkour et al., 2016) or even in combined form (a mixture of fresh and co-cultured PBMC) (Yoshioka et al., 2006; Feskov et al., 2011; Sudoma et al., 2011; Gultomruk et al., 2014). Unfortunately, since the number of primary studies in each subgroup was not enough, subgroup analysis was not possible, and no definitive conclusions can be drawn. More studies are still needed to investigate and compare the impact of different forms of PBC in women with RIF, in future studies. Among the studies we reviewed here, some studies used PBMC in fresh ET cycles (n = 5), and some studies enrolled patients who received frozen embryos (n = 4). Although previous studies suggested that pregnancies arising from the frozen ET seem to have better obstetric and perinatal outcomes (Maheshwari et al., 2012; Roque et al., 2013), a recently published Cochrane systematic review reported that there was no clear evidence of a difference in clinical pregnancy and cumulative live birth rate between the freeze and Fresh ET (Wong et al., 2017). Our study also showed no differences in clinical pregnancy rate between the subgroups of studies that transferred the embryo in the fresh or frozen state. Since the pregnancy rate was the only outcome reported in all of the studies, we couldn't perform subgroup analysis for the live birth rate. Another important factor that may affect the outcomes of ET is the stage of transferred embryos. ET in each stage has several advantages and disadvantages. Results of a systematic review showed that both live birth and the clinical pregnancy rate was higher in blastocyst stage (day 5) ET compared to cleavage stage (day 2–3); however failure to transfer any embryos was higher in the blastocyst transfer group (Glujovsky et al., 2016). The results of subgroup analysis showed no significant difference between the cleavage and blastocyst stage. Subgroup analysis for assessment of live birth rate was not possible. One of the fundamental problems of the studies we investigated is that none of them used a placebo or sham procedure for the control group. Recently increasing evidence has been raised that mechanical stimulation of endometrium increases implantation rate through the induction of decidualization and the release of cytokines, and may improve the implantation rate, although, robust evidence and 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 PBMC on implantation may be partially related to mechanical endometrial stimulation induced by insertion of the catheter into the uterine cavity; however, this is only a possibility, and no definitive conclusion can be drawn. It is suggested for subsequent studies to compare PBMC and endometrial scratching separately with a control group to obtain more accurate results. The inclusion and exclusion criteria were well-defined in most of the reviewed studies, but, some studies did not list the exact criteria. Additionally, the main cause of

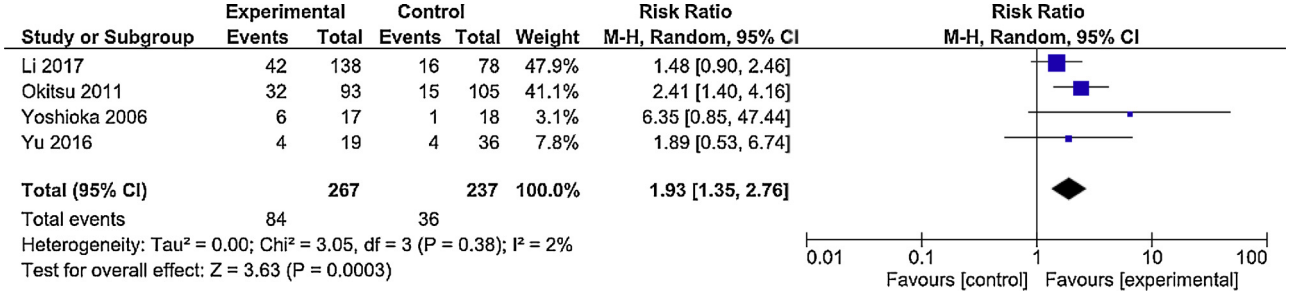

Fig. 5. Forest plot detailed risk ratio (RR) and 95% confidence intervals for live birth rate in peripheral blood mononuclear cells and control groups.

infertility of the women recruited, the laboratory protocols and techniques used for preparing PBMC, and methods for endometrial preparation were either not reported or not identical among the studies. Although we obtained homogeneous results, differences between the studies leave a number of questions unanswered. Firstly, the group of patients who are most likely to benefit from this intervention remains unclear. Also, all studies recruited young women with intact ovarian reserve and good response to ovarian stimulation, and this intervention is not still evaluated in patients with reduced ovarian reserve, thin endometrium or poor embryo quality.

5. Conclusion

Our systematic review and meta-analysis showed that intra-uterine administration of PBMC, irrespective of embryo stage at transfer and ET cycle type (fresh or frozen ET), increases the clinical pregnancy rate in patients experienced RIF and might be a beneficent option in the treatment of RIF in the future. However, given the small sample sizes and the variable quality of the studies, the current evidence does not support its use in clinical practice yet. Although, the results drawn from this study didn't show significant heterogeneity resulted by type of ET cycle (fresh or frozen ET) or stage of embryo, more randomized clinical trials with larger sample sizes are needed yet. Also, comprehensive data regarding complications, and adverse pregnancy outcomes, and the miscarriage rate was not available, so, we are not able to provide conclusive results. Still, there is a lack of a high-quality randomized controlled trial of intrauterine PBMC administration for RIF patients. Future studies should focus on subgroup analysis (cleavage versus blastocyst, fresh versus frozen, co-cultured PBMC versus fresh isolated PBMC) in order to identify the groups of patients who would benefit the most from this intervention and the most appropriate form of PBMC which would have the most positive effect on implantation and the less possible side effects. It is suggested that in future studies, the association of the use of PBMC with the level of some chemical mediators and immunological indicators should be made to clarify the mechanism of action and the ways to make it more effective. Also, complications, adverse pregnancy outcomes, miscarriage, and live birth rate should be reported in future studies.

Declaration of interest

None declared. Completed disclosure of interest forms that are available online to view as supporting information.

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Appendix A. Supplementary data

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