The effectiveness of immunotherapies for patients with repeated implantation failure: a systematic review and network meta-analysis

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Abstract

Background: This study compared clinical pregnancy outcomes of repeated implantation failure (RIF) patients treated with immunotherapies using a network meta-analysis.

Methods: Publications are determined by searching the Pubmed, Embase and web of science databases. The search date is from the establishment of the database till August 2021. The outcomes were clinical pregnancy rate (CPR), live birth rate (LBR) and implantation rate (IR). The Cochrane bias risk assessment tool was applied to evaluate the quality of the study, and Stata 14.0 was used for the network meta-analysis.

Results: A total of 16 RCTs including 2008 participants were included. The network meta-analysis results show that PBMC, PRP and SC-GCSF can significantly improve CPR compared with LMWH (PBMC: OR=2.15; 95% CI, 1.21-3.83; PRP: OR=2.38; 95% CI, 1.08-5.24; SC-GCSF: OR=2.46; 95% CI, 1.05-5.72). The LBR of PRP was significantly higher than IU-GCSF (OR=3.81; 95% CI, 1.22-11.86), LMWH (OR=4.38; 95% CI, 1.50-12.90) and Intralipid (OR=3.85; 95% CI, 1.03-14.29), and the LBR of PBMC was also significantly better than that of LMWH (OR=2.35; 95% CI, 1.14-4.85). Furthermore, PRP treatment significantly improved IR compared with LMWH treatment (OR=2.81; 95% CI, 1.07-7.4).

Discussion: Based on the limited evidence from existing RCTs, PBMC and PRP seem to be the best therapeutic options for RIF patients. However, due to research quantity restrictions, more top-quality researches are required in the future to obtain additional high-level evidence.

Introduction

Repeated implantation failure (RIF) is unable to achieve a clinical pregnancy after multiple cycles of fertilization *in vitro* and cumulative transfer of multiple high-quality embryos in patients undergoing assisted reproductive techniques [1]. Due to the complexity of the causes of RIF and the high diversity of patients, different academic organizations and researchers have attempted to propose clear diagnostic criteria, but no consensus has been generated to date. The current widely-used definition of RIF by Coughlan et al. is that, for a woman under the age of 40 years, the unsuccessful clinical pregnancy after at least 4 good-quality embryos transfer within minimum three fresh or frozen cycles[2, 3]. Implantation is a very complicated process and there are plenty of factors that contribute to RIF, either maternal or embryonic origin. The embryo, as a homozygous hemizygous antigen, is subject to a variety of factors for its successful implantation [1, 4]. After embryo transferred into uterus cavity, the endometrium must be receptive for the embryo synchronizely and the maternal immune system must tolerate the continued presence of the paternal alloantigen during the pregnancy [5]. In the absence of common factors as uterine abnormalities, hormonal or metabolic disorders, infections, immunological factors, thrombophilias as well as severe male factors, abnormal immunological response could result in a defected maternal-fetal immunotolerance and impaired endometrium receptivity. In order to restore the underlying immunological imbalance, some immunotherapies have been introduced to enhance clinical outcomes in women with unexplained RIF. [6–8].

The immunotherapeutic agents mainly are low-molecular-weight heparin (LMWH), intravenous immunoglobulin (IVIG), intrauterine human chorionic gonadotropin (hCG), subcutaneous (SC) or intrauterine (IU) infusion of granulocyte colony stimulating factor (G-CSF), peripheral blood mononuclear cells (PBMCs), and intrauterine autologous platelet-rich plasma (PRP) [9–12]. However, there is much conflicting evidence and the comparable effectiveness of these immunotherapies in the setting of RIF is unrevealed.

Therefore, our study uses a network meta-analysis to compare the effectiveness of the most widely used immunotherapies for RIF treatment, in order to provide an evidence basis for clinical application.

Methods

Search strategy

Publications are determined by searching the Pubmed, Embase and web of science databases. The search date is from the establishment of the database till August 2021, and the search language was limited to English. The following terms were applied for this search: repeated implantation failure, recurrent implantation failure, intravenous immunoglobulin, PBMC, G-CSF, IVIG, PRP, Intralipid, Glucocorticoid, hCG, LMWH and Aspirin.

Selection criteria

Strict literature inclusion and exclusion criteria were established. The selected documents must be qualified as follows: (1) These studies are randomized controlled trials; (2) The study participants had two or more episodes of implantation failure; (3) The experimental group was treated with immunotherapy, and the control group was given with the standard care/placebo/no immunotherapy; (4) The study includes at least one outcome (clinical pregnancy rate (CPR), live birth rate (LBR) and implantation rate (IR)).

Research was excluded as any of the following conditions: (1) The data is incomplete or cannot be used for statistical analysis; (2) Non-authoritative documents such as reviews, letters, conference abstracts, and reviews.

Data extraction

Two authors independently derived the relevant data from the qualified literature, additionally, the extracted content included: the first author of the literature, publication year, research type, total number of people included, age, RIF inclusion criteria and outcome indicators, etc. The Cochrane quality evaluation system was utilized to access the quality of the involved randomized control trials. If the opinions of the two authors disagree, the third author will make the judgment.

Statistical analysis

The Stata 14.0 was used to accomplish the network meta-analysis under the consistency model. The odds ratio (OR) was analyzed for dichotomous outcomes with 95% CI. A paired meta-analysis was performed using a fixed-effects model based on the main results. I^2 is used to assess heterogeneity, and $I^2 \geq 50\%$ indicates statistical heterogeneity. The surface under the cumulative ranking (SUCRA) is to evaluate the likelihood that each intervention is the most beneficial or safest treatment. A greater SUCRA value means the higher treatment efficacy. A comparison-correction funnel chart was used to assess publication bias.

Results

Overall, 3350 documents were identified according to the searching criteria. 901 duplicate articles were eliminated, and 2379 literatures were eliminated after the title and abstract examining. The remaining 70 publications' full text was read, and 16 RCTs meeting the requirements were finally included (Figure 1).

A total of 16 RCTs including 2008 participants were included [13–28]. Among them, 3 are LMWH, 6 are GCSF, 4 are PBMC, one is hCG, one is intralipid, and 2 are PRP. Since studies of Glucocorticoid and IVIG do not meet the selection criteria, no study was included here. The age of the sample population is between 30.51 and 37.8. Table 1 demonstrates the baseline characteristics of the involved studies. Next, Figure 2 indicates the assessment of these selected studies' quality using the Cochrane risk of bias tool.

Table 1
Baseline characteristics of included studies

study	Study design	RIF criteria	Invention	No. of patients	Age (Year)	BMI (kg/m ²)	No. of transferred embryos (mean)
Urman 2009	Randomized open-labeled pilot trial	Three or more previously failed fresh embryo transfer cycles	LMWH (administered LMWH at a dose of 1 mg/kg/day starting on the day after oocyte retrieval)	75	34.0±5.0	-	2.6±0.7
			Control (received no medication besides progesterone gel on the day after oocyte retrieval)	75	34.8±5.8	-	2.6±0.8
Berker 2011	Prospective, quasi-randomized, controlled study	at least two consecutive failed cycles of intracytoplasmic sperm injection and embryo transfer (ICSI-ET)	LMWH (administered LMWH at a standard dose of 40 mg/0.4 mL per day starting on the day of oocyte retrieval)	104	31.3±4.9	-	2.4±0.6
			Control	103	31.2±5.0	-	2.5±0.6
Aleyasin 2016	Prospective randomized openlabel controlled trial	Failure of implantation in at least three consecutive IVF attempts, in which three embryos of high-grade quality are transferred in each cycle	subcutaneous GCSF (A single dose of 300 µg G-CSF administered subcutaneously 1 h before the embryo transfer)	56	33.5±4.2	-	2.3 ± 0.6
			Control (did not receive any additional treatment before the embryo transfer)	56	32.4±5.2	-	2.5 ± 0.6
Davari-Tanha 2016	Randomized double blind placebo control trial	three times implantation failure when there was history of transferring at least four good quality embryos without uterine or thrombophilic factors.	intrauterine GCSF (At the time of oocyte retrieval one ml of G-CSF (300 µg/ml) was administered by a Trans cervical Cook catheter for embryo transfer slowly into uterine cavity)	40	35.5 ± 4.32	25.2 ± 1.8	-

study	Study design	RIF criteria	Intervention	No. of patients	Age (Year)	BMI (kg/m ²)	No. of transferred embryos (mean)
			Control (a catheter pass through the cervix without any injection)	20	35.4 ± 4.01	24.8 ± 1.3	-
Eftekhari 2016	Randomised controlled trial	two or more episodes of implantation failure	intrauterine G-CSF (received uterine infusion of 300 µg (0.5ml) recombinant human G-CSF (300 µg) by the use of IUI catheter after ovarian puncture under general anesthesia)	45	32.55 ± 4.61	-	2.11 ± 0.77
			Control (the standard treatment)	45	31.75 ± 5.16	-	2.35 ± 0.71
Madkour 2016	Randomised controlled trial	at least two previous failures of implantation after IVF/intra-cytoplasmic spermatozoa injection (ICSI) (mean = 3)	PBMC (Intrauterine administration of PBMC prior to fresh embryo transfer)	27	34.74 ± 4.17	-	-
			Control	27	34.44 ± 3.86	-	-
Yu 2016	Prospective randomized study	Patients who had not experienced successful pregnancy despite three or more IVF-ET sessions	PBMC (intrauterine administration of autologous PBMC activated by HCG in vitro before ET)	93	31.08±3.95	-	-
			Control (undergoing ET without a previous intrauterine administration of autologous PBMC)	105	31.22±5.12	-	-
Arefi 2018	Randomised controlled trial	the history of more than two previous IVF/Intracytoplasmic sperm injection-embryo transfer (ET) failures despite transfer of at least two good-quality embryos in each attempt.	subcutaneous G-CSF (receive 300 µg (0.5 ml) recombinant human G-CSF subcutaneously which was injected 30 min before blastocyst embryo transfer)	32	34.53 ± 5.50	-	3.31 ± 0.85
			Control	20	34.05 ± 6.5	-	3.20 ± 0.95

study	Study design	RIF criteria	Invention	No. of patients	Age (Year)	BMI (kg/m ²)	No. of transferred embryos (mean)
Nobijari 2019	Prospective randomized study	a history of at least one RIF	PBMC (a blood sample was collected 5 days before the scheduled frozenthawed embryo transfer; PBMCs were isolated using Ficoll separation and then cultured for 72h. Two days prior to embryo transfer, 0.4 ml of cultured PBMCs were transferred into the patient's uterus)	122	35.21 ± 4.84	-	-
			Control	128	34.55 ± 5.03	-	-
Wang 2019	Prospective randomized-controlled trial	Failure of implantation in at least 4 consecutive IVF attempts, in which 1 embryos of high-grade quality are transferred in each cycle	hCG (The hCG+G2 fluid was prepared on the day of embryo transfer, and 40 µL of which was injected at an intrauterine site at 3 minutes before embryo transfer)	69	31.35±3.18	22.3±3.25	-
			Control (the G2 fluid was prepared on the day of embryo transfer, and 40 µL of which was injected at an intrauterine site at 3 minutes before embryo transfer)	68	31.7±3.56	22.7±3.61	-
Al-Zebeidi 2020	Randomised controlled trial	a history of three or more RIF undergoing ICSI cycles	Intralipid (received intralipid 20% 100 ml diluted in 500 ml normal saline for infusion therapy on the day of embryo transfer (ET) and repeated dose was administered on the day of the pregnancy test)	71	35.32 ± 4.23	28.30 ± 4.66	-

study	Study design	RIF criteria	Intervention	No. of patients	Age (Year)	BMI (kg/m ²)	No. of transferred embryos (mean)
			Control (underwent the standard ICSI cycle without intralipid infusion therapy)	71	35.21 ± 4.77	28.30 ± 4.66	-
Huang 2020	Prospective randomized single-blind study	more than two failed implantations (each time containing at least one high-quality embryo)	intrauterine G-CSF (administered a 1-ml uterine infusion of recombinant human G-CSF (150 mg, 1ml) through an intrauterine insemination catheter.)	52	32.09±4.21	21.24±2.29	
			Control (an intrauterine infusion of physiological saline before embryo transfer)	52	32.07±4.36	21.51±2.90	
Kalem 2020	Prospective randomized controlled trial	the failure to achieve a clinical pregnancy after the transfer of at least four good-quality embryos in a minimum of three fresh or frozen cycles to a woman under the age of 40 years	intrauterine G-CSF (received G-CSF once a day on hCG day, before hCG injection. The procedure involved the administration of 30 mIU of Leucostim (G-CSF 30mIU/mL) through slow infusion into the endometrial cavity using a soft embryo transfer catheter)	82	34.61 ± 4.77	25.92 ± 4.44	-
			Control (normal saline of 1 mL was infused into the endometrial cavity of patients in the same way as the study group)	75	34.92 ± 5.60	24.94 ± 4.92	-

study	Study design	RIF criteria	Intervention	No. of patients	Age (Year)	BMI (kg/m ²)	No. of transferred embryos (mean)
Pourmoghadam 2020	Double-blind randomized control trial	at least three previous failures of IVF/ET therapy	PBMC (PBMCs (15–20×10 ⁶ cells) were suspended in 500 µl PBS and was gently administered to the uterine cavity two days before ET using an embryo transfer catheter)	50	33.42 ± 3.1	26.94 ± 2.13	-
			Control (500µl PBS was administered into the uterine cavity)	50	34.64 ± 3.0	28.53 ± 2.84	-
Salehpour 2020	Randomised controlled trial	patients who failed to conceive after 3 or more embryo transfers with high-quality embryos and candidates for frozenthawed embryo transfer (FET)	PRP (Intrauterine infusion of PRP was carried out 48 h before embryo transfer under ultrasound guidance)	49	35.73 ± 3.49	25.61 ± 3.13	1.9 ± 0.8
			Control (standard treatment)	48	34.95 ± 4.23	25.46 ± 2.68	1.7 ± 0.6
Zamaniyan 2021	Randomised controlled trial	women who unsuccessful to be pregnant after three or more high-quality embryo transfers undergoing frozen-thawed embryo transfer	PRP (Intrauterine infusion of platelet-rich plasma was performed 48 h before embryo transfer)	55	33.88 ± 6.32	26.49 ± 4.53	-
			Control	43	33.13 ± 5.00	25.03 ± 3.66	-

In Figure 3, the network of eligible comparisons is shown for each outcome. There is no closed loop between interventions, which suggests that all these pairwise comparisons are indirect. Therefore, statistical analysis is performed directly under the consistency model.

Figure 4 reveals the results of the CPR network meta-analysis. PBMC, PRP, SC-GCSF and hCG administration can significantly increase CPR when compared to the control group (PBMC: OR = 2.44; 95% CI, 1.67-3.57; PRP: OR = 2.70; 95% CI, 1.41-5.26; SC-GCSF: OR = 2.78; 95% CI, 1.35-5.88; hCG: OR = 2.44; 95% CI, 1.20-4.98). Besides, PBMC, PRP and SC-GCSF can also significantly improve CPR compared to LMWH (PBMC: OR = 2.15; 95% CI, 1.21-3.83; PRP: OR = 2.38; 95% CI, 1.08-5.24; SC-GCSF: OR = 2.46; 95% CI, 1.05-5.72).

Nine studies reported data on LBR. The network meta-analysis outcomes implied that the administration of PBMC and PRP had a higher LBR in comparison with the control group (PBMC: OR = 2.86; 95% CI, 1.64-5.00; PRP: OR = 5.26; 95% CI, 2.00-14.29) (Figure 5). The effect of PRP on LBR was significantly better than IU-GCSF (OR = 3.81; 95% CI, 1.22-11.86), LMWH (OR = 4.38; 95% CI, 1.50-12.90) and Intralipid (OR = 3.85; 95% CI, 1.03-14.29), and the efficacy of PBMC for LBR was also significantly better than that of LMWH (OR = 2.35; 95% CI, 1.14-4.85).

We conducted a network meta-analysis on nine studies that reported on IR. The results showed that IU-GCSF, PBMC, PRP, SC-GCSF and hCG were significantly associated with higher IR compared to the control (IU-GCSF: OR = 3.57; 95% CI, 1.16-11.1; PBMC: OR = 2.56;

95% CI, 1.28-5.26; PRP: OR = 3.23; 95% CI, 1.43-7.69; SC-GCSF: OR = 2.86; 95% CI, 1.30-6.25; hCG: OR = 1.86; 95% CI, 1.05-3.28) (Figure 6). Furthermore, PRP significantly improved IR compared with LMWH (OR = 2.81; 95% CI, 1.07-7.4).

The I^2 values were 37.4% for CPR, 16.1% for LBR and 50.8% for IR (Figure S1-3). In Figure 7, the comparison-adjusted funnel plots of the network meta-analysis of each outcome suggested no publication bias.

The ranking probability of SUCRA for each treatment included in the network was shown in Table 2. In terms of CPR, SC-GCSF was the most effective therapy (78.9%), whereas LMWH was the least effective therapy (18.3%). As far as LBR is concerned, PRP is the most effective treatment (94.8%), and LMWH is the worst (29.4%). In addition, in terms of IR, the most effective treatment is IU-GCSF (77.6%), and the least effective is LMWH (16.2%).

Table 2. SUCRA of CPR, LBR and IR

Treatment	CPR	LBR	IR
IU-GCSF	37.1	39.5	77.6
LMWH	18.3	29.4	16.2
PBMC	73.1	78	63.4
PRP	77.9	94.8	75.9
SC-GCSF	78.9	60.4	68.1
control	7	11	5.1
hCG	71.4		43.7
intralipid	36.3	36.9	

Discussion

Given the fact that the pregnancy rate has increased year by year due to the development of assisted reproductive technology, but there are still a number of patients suffering from RIF [29–31]. Uterine abnormalities, spermatic factor anomalies, genetic, hormonal, and metabolic pathologies, acquired thrombophilia, and autoimmune disorders are all possible causes of RIF [32]. However, RIF remains unexplained in approximately 30% of instances, and the reasons underlying this unexplained infertility are not fully understood [33]. It has been reported that immune factors are crucial in the process of embryo implantation, thus immunotherapies can improve the pregnancy outcome of some patients with RIF [33]. Recently, there have been many studies on the pathogenesis of RIF immune factors and immunotherapeutic methods, but there are differences in efficacy due to the different mechanisms of action of different preparations. Therefore, this study evaluated the efficacy of immunotherapies in improving the CPR and LBR of RIF patients through network meta-analysis. According to the outcomes of treated RIF patients, it was found that PBMC and PRP are effective in boosting CPR and LBR. In comparison to the control group, PBMC, PRP, SC-GCSF and hCG treatment significantly increased CPR and IR, and PBMC and PRP were significantly related with greater LBR.

Previous research has demonstrated that RIF patients can benefit with immunotherapies, but there are still no direct or indirect comparisons of the efficacy of different immunotherapies [12, 34–37]. This study evaluated the efficacy of five immunotherapies through a network meta-analysis system, and found that SC-GCSF is the best in improving CPR, while IU-GCSF is the best in improving IR. Our results confirmed the conclusions of Zhao et al., and Xie et al. Zhao et al. showed that the administration of G-CSF may have a favorable clinical effect on pregnancy outcomes. In addition, the best way to administer G-CSF may be the subcutaneous injection [38]. Xie et al. found that intrauterine perfusion of G-CSF could significantly improve IR compared with control group [39]. G-CSF, as a glycoprotein, belongs to the growth factor family. It has been discovered to regulate the growth of the endometrium and involve in the occurrence of early endometriosis [40]. G-CSF has been shown to promote endometrial stem cells, mobilize bone marrow stem cells, and enhance endometrial development [41]. However, there is still controversy about the ideal route of G-CSF administration, and the reasons for the difference between the two administration effects have not yet been fully clarified. Therefore, more and higher-quality studies are needed to clarify these phenomena.

For LBR, PRP has the best efficacy among the five immunotherapies. We also discovered that PRP had a significantly better effect on LBR than IU-G-CSF, LMWH, and Intralipid. Moreover, PRP can also increase the CPR and IR of RIF patients compared with the control group. PRP is made up of a high concentration of autologous platelets, normally 5-7 times greater compared to the platelet concentration in peripheral blood, which was collected by centrifuging peripheral whole blood [42]. PRP contains a variety of growth factors and cytokines, which may help regulate endometrial cell migration, attachment, proliferation, differentiation and neovascularization, thereby having a beneficial effect on endometrial receptivity [43, 44]. Amable et al. shows that compared with whole blood plasma or platelet-poor plasma, the levels of 12 proteins (including six growth factors, three anti-inflammatory cytokines and three pro-inflammatory cytokines) in activated PRP are increased [45]. These cytokines and growth factors may boost the endometrium receptivity. Besides, a mouse experiment showed that autologous PRP intrauterine infusion accelerated and enhanced the regeneration of impaired endometrium and reduced endometrial fibrosis [46]. Owing to the limitation of the quantity of the studies, currently there is no meta-analysis to analyze the effect of PRP on LBR, so additional high-standard studies are required to verify the benefits of PRP on LBR.

Intrauterine infusion of PBMC is also a good choice for RIF patients. PBMC is mainly composed of T lymphocytes, B lymphocytes and monocytes [47]. It has been reported that PBMC is able to regulate a variety of cytokines production, and also promote the spread and invasion of blastocysts to the endometrium and the *in vitro* receptivity of the endometrium [36]. The results of a recent RCT indicate that PBMC is an effective treatment strategy for RIF-related infertility [22]. Besides, consistent with the results of our research, Maleki-Hajiagha et al. found that PBMC can increase the CPR and LBR of RIF patients [11]. This study uncovered that PBMC can significantly increase the CPR, LBR and IR of RIF patients in contrast to the control group. The implantation promotion effect of PBMC can be explained by a variety of mechanisms. It is reported that PBMC can regulate the production of several cytokines, such as IL-1 α , IL-1 β , TNF- α , and promote the spread and invasion of blastocysts to the endometrium and the receptivity of the endometrium *in vitro* [48]. In addition, *in vivo* studies have shown that the administration of PBMC can promote implantation and clinical pregnancy rates, and may optimize the *in vitro* fertilization results of patients with multiple failures of *in vitro* fertilization/ICSI [21, 49]. Although our research shows that its clinical effects are positive, adverse reactions should also be considered, which requires further research to evaluate.

While, limitations are existed in our study. Firstly, the number of selected studies is relatively small, and there is only one RCT on hCG. Secondly, the included studies may be biased, and undermined hypercoagulative and immunological abnormalities are not investigated and intervened appropriately. Thirdly, few studies reported the adverse events of interventions within the qualified studies, so it is lacking of the safety evaluation on different drugs in RIF treatment. Finally, there are differences in the dose of the same drug in different studies, but because of the restricted sample size, it is unfeasible to further divide the subgroups for analysis.

Conclusions

This network meta-analysis showed that PBMC, PRP, SC-GCSF and hCG administration can significantly increase CPR and IR compared to the control group. Furthermore, PBMC and PRP had a higher LBR compared with the control group. Based on our findings, among the different available immunotherapeutic medications, PBMC and PRP may provide the best therapeutic efficacy. More top-quality RCTs are necessitated in the future to verify the trustworthiness of the conclusions drawn in this research due to the restricted number of RCTs.

Declarations

Authors have no conflict of interests to declare.

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Figures

Figure 1

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Figure 2

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Figure 3

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Figure 4. Network forest plot of CPR.

Figure 4

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Figure 5. Network forest plot of LBR.

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Figure 6. Network forest plot of IR.

Figure 6

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Figure 7

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