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Review article

Intrauterine administration of peripheral blood mononuclear cells activated by human chorionic gonadotropin in patients with repeated implantation failure: A meta-analysis

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ABSTRACT

The purpose of this study was to assess whether intrauterine administration of peripheral blood mononuclear cells (PBMCs) activated by human chorionic gonadotropin (hCG) could improve the pregnancy and live birth rates in women with repeated implantation failure (RIF), and whether the parameters of co-culture of hCG and PBMCs would affect the clinical outcomes. Six databases (PubMed, Ovid, Medline, NCBI, Cqvip and Wanfang) were searched up to October 2020 by two independent reviewers. Seven studies were included according to specific inclusion and exclusion criteria. A meta-analysis showed that the pregnancy and live birth rates were significantly increased in the case group compared with the control group (odds ratio [OR]: 3.43, 95 % confidence interval [CI]: 1.78–6.61; $P = 0.0002$ and OR: 2.79, 95 % CI: 1.09–7.15; $P = 0.03$), especially when hCG was cultured with PBMCs for 48 h or PBMCs administration was performed two or three days before embryo transfer (ET). Neither the dosage of the hCG co-cultured with PBMCs nor the mean concentration of the administered PBMCs appeared to influence the therapeutic efficiency. In conclusion, intrauterine administration of PBMCs co-cultured with hCG for 48 h, conducted two or three days before ET, could be an effective therapy for women experiencing RIF. Due to the limitations of sample size and quality of the included studies, further high-quality studies with large sample sizes are warranted to optimize the parameters of hCG and PBMC co-culture to help more RIF patients benefit from this therapy.

1. Introduction

Repeated implantation failure (RIF) is defined as a failure of successful clinical pregnancy after repeated transfer of a morphologically high-quality fresh or frozen embryo to a normal uterus in in vitro fertilization (IVF) (Zohni et al., 2016). According to various studies, implantation failure in patients with RIF can be caused by a lack of initial inflammation (Nakayama et al., 2002; Yoshioka et al., 2006; Madkour et al., 2015). In successful implantation, T lymphocytes and macrophages are recruited at the maternal–fetal interface (Mor et al., 2011). These immune cells are essential to the initial inflammation at the implantation site (Song et al., 2016; Marziyeh et al., 2017). Intrauterine administration of peripheral blood mononuclear cells (PBMCs), mainly consisting of B and T lymphocytes, monocytes and macrophages, has been used to treat patients with RIF (Okitsu et al., 2011). In animal experiments, embryo implantation was facilitated by intrauterine

Abbreviations: PBMCs, peripheral blood mononuclear cells; hCG, human chorionic gonadotropin; RIF, repeated implantation failure; ART, assisted reproductive technology; ET, embryo transfer; IVF, in vitro fertilization; uNK cell, uterine natural killer cell; Th, T helper; Treg, regulatory T cell; ICSI, intracytoplasmic sperm injection; CNKI, China National Knowledge Infrastructure; MeSH, Medical Subject Headings; PRISMA, preferred reporting items for systematic reviews and meta-analyses; PROSPERO, International Prospective Review of Systematic Reviews; RCTs, randomized controlled trials; OR, odds ratio; CI, confidence interval; PBS, phosphate-buffered saline; TNF, tumor necrosis factor; LIF, leukemia inhibitory factor.

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administration of PBMCs, and embryo spreading and invasion were promoted by human chorionic gonadotropin (hCG) (Nakayama et al., 2002; Fujiwara, 2006). Although the onset of implantation requires initial inflammation, persistent pregnancy requires an immune balance between embryonic trophoblasts and endometrial tissue (Yong-Hong et al., 2017). Therefore, to minimize the detrimental influence on endometrium of this therapy, it is necessary to determine the proper duration and dosage of hCG co-culture with PBMCs (Shurin et al., 1999) and the mean concentration and timing of PBMCs administration.

According to our systematic search of scientific databases, accumulating evidence suggests that the hormone hCG enhances the effects of PBMCs therapy by controlling the recruitment of macrophages and dendritic cells (DCs), the proliferation of uterine natural killer (uNK) cells, the balance of T helper 1 (Th1)/Th2, or the secretion of cytokines and the ratio of Th17 to regulatory T cells (Treg) to improve reproductive outcomes in women with RIF (Norris et al., 2011; Pourmoghadam et al., 2020). However, there is a lack of conclusive results and a comprehensive review regarding the effects of the parameters of hCG co-culture with PBMCs on the outcome of IVF/intracytoplasmic sperm injection (ICSI) cycles. Therefore, in this systematic review and meta-analysis, our objective was to assess the effects of intrauterine insemination of hCG-activated PBMCs on IVF outcomes in patients with a history of RIF, and provide practical guidance on the parameters of hCG and PBMCs co-culture to improve the treatment effectiveness for future trials.

2. Material and methods

2.1. Search strategy

A comprehensive search was performed in the English-language databases PubMed, Ovid and Medline, and Chinese-language databases CNKI, Cqvip and Wanfang. The searches were restricted to studies published up to October 2020. The Medical Subject Headings (MeSH) terms used included “repeated implantation failure” and “peripheral blood mononuclear cell.” The following string was developed: (“repeated implantation failure” [MeSH Terms] OR “repeated, implantation, failure” [Text Word] OR “recurrent implantation failure” [Text Word] OR “recurrent, implantation, failure” [Text Word] OR “multiple implantation failure” [Text Word] OR “RIF” [Text Word] OR “MIF” [Text Word]) AND (“peripheral blood mononuclear cell” [Text Word] OR “peripheral, blood, mononuclear, cell” [Text Word] OR “PBMCs” [Text Word] “lymphocyte transfusion” [Text Word] OR “lymphocyte, transfusion” [Text Word] OR “lymphocyte therapy” [Text Word] OR “lymphocyte insemination” [Text Word] OR “lymphocyte injection” [Text Word] AND “intrauterine perfusion” [Text Word] OR “intrauterine insemination” [Text Word] OR “intrauterine injection” [Text Word]). The protocol for this study was developed according to the PRISMA guidelines. This predetermined protocol was registered at PROSPERO with the registration number CRD42020218774.

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) The target studies involved patients undergoing assisted reproductive technology (ART) who had experienced RIF; (2) the case group consisted of patients receiving intrauterine administration of PBMCs co-cultured with hCG before embryo transfer (ET); (3) the control group received placebo or no treatment; (4) all studies were randomized controlled trials (RCTs), case-controlled or cohort studies in which confirmed pregnancy outcomes were reported; (5) the original available data were provided in the articles.

Exclusion criteria: (1) reviews and case reports; (2) duplicate publications; (3) studies without a control group or full text available; (4) animal experiments.

2.3. Data extraction and quality assessment

Two researchers independently and carefully extracted the following information from each eligible study: (1) authors’ last name(s) and year of publication; (2) country; (3) population (number of cases and controls); (4) the definition of RIF; (5) specific details about the interventions; (6) pregnancy outcome measures (implantation rate, pregnancy rate, live birth rate and miscarriage rate). Cochrane’s tool was used to assess the risk of bias for RCTs. The Newcastle-Ottawa Scale was used to evaluate the quality score of cohort studies (Wells et al., 2011; Wells, 2014). The quality scores of studies ranged from 0 to 9 points and included three aspects: selections, comparability and exposure (Wells et al., 2011; Wells, 2014). Any inconsistent opinions were resolved by discussion or with the help of a third reviewer.

2.4. Statistical analysis

The extracted data were analyzed with Review Manager 5.3 software (Cochrane Collaboration, Oxford, U.K.). The effect sizes were expressed as odds ratios (OR) and calculated using their 95 % confidence intervals (CI). Heterogeneity was assessed graphically with forest plots and quantified by the I^2 value. To reduce the influence of inter-study heterogeneity, a random effects model was used to obtain the pooled estimates. To examine the potential heterogeneity sources, subgroup meta-analyses were performed according to the duration and dosage of hCG co-culture, the mean concentration of PBMCs and the time of PBMCs administration. Publication bias, which can be evaluated using a funnel plot, was not considered in this meta-analysis as the number of included studies was less than 10. A P-value <0.05 was considered statistically significant.

3. Results

The PRISMA flow diagram of the study process is presented in Fig. 1. The search strategy yielded 62 publications (17 from NCBI, 9 from Cqvip, 15 from Wanfang, 17 from PubMed, 1 from Ovid, 1 from Medline and 2 from other sources), of which 21 were removed as duplicates. Five studies were excluded for not fulfilling the experiment criteria after screening. The full manuscripts of 36 articles were evaluated, of which 10 were excluded due to being meta-analyses or systematic reviews. Seven publications the full text was not accessible, but for two of those we successfully extracted the data from other meta-analyses, two additional studies were included. A total of 14 articles were removed for not meeting the inclusion criteria. Thus, a total of seven publications with available full texts remained. Finally, we included seven studies that met the eligibility criteria for quantitative data synthesis.

3.1. Study characteristics

The main characteristics of the included studies are shown in Table 1. The publication dates of the eligible studies ranged between 2006 and 2020. The numbers of patients ranged from 35 to 633. Three studies were RCTs (Sudoma et al., 2011; Yu et al., 2016; Pourmoghadam et al., 2020), and four were nonrandomized cohort studies (Yoshioka et al., 2006; Kremenska et al., 2010; Li et al., 2017; Zhang et al., 2019). The randomization method was reported in one of the three RCTs (Pourmoghadam et al., 2020). The risk of bias assessments for the RCTs and cohort studies are summarized in Supplementary Tables S1 and S2. The studies were conducted in China (three studies), Ukraine (two studies), Japan (one study) and Iran (one study). The patients in the case group underwent ET with intrauterine PBMCs in all seven studies. The patients in the control group underwent ET without intrauterine administration in six studies and with intrauterine phosphate-buffered saline (PBS) in one study. PBMCs were co-cultured with hCG for 24 h (three studies) or 48 h (four studies). The dosage of hCG ranged from 3 to 10 IU/mL in six studies and was 40 mg/mL in one study. The mean

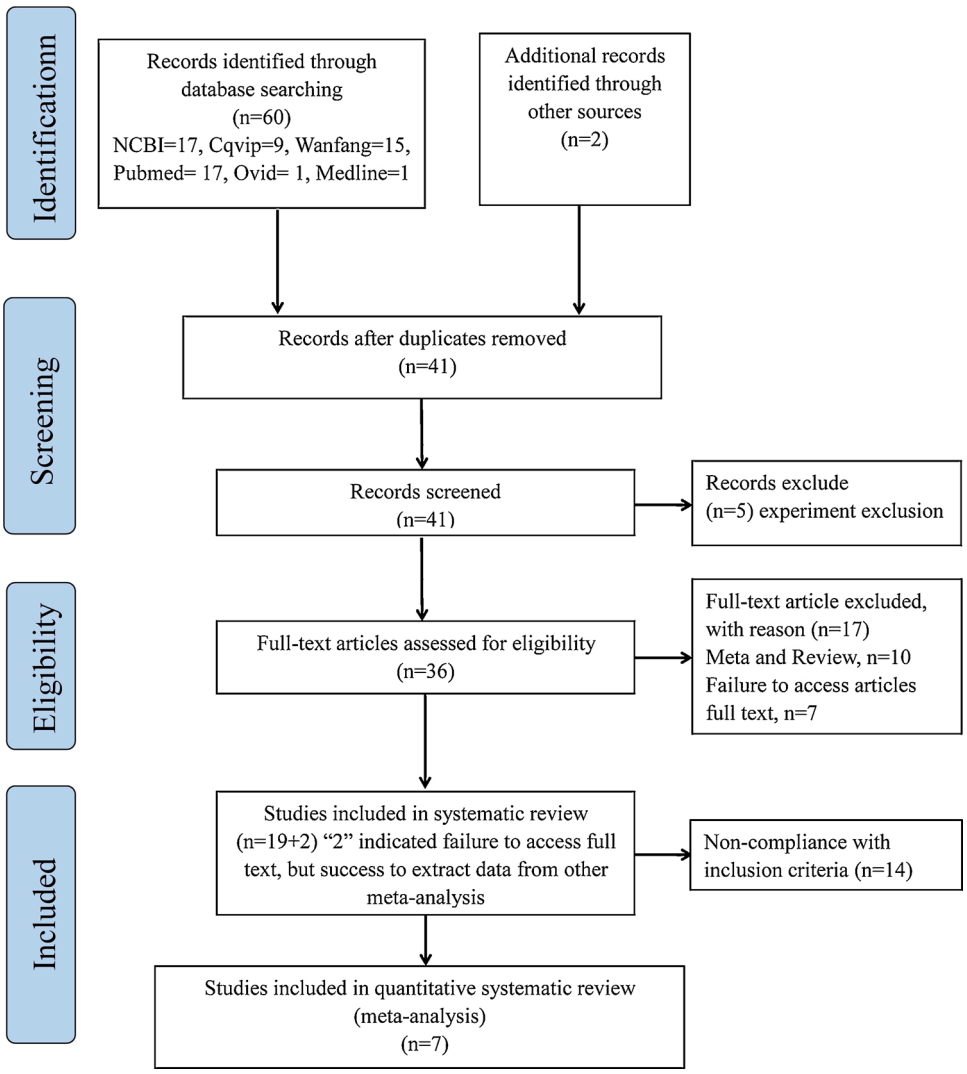

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowcharts.

PBMCs concentrations for administration were in the range 30–500 × 10^6/mL. The timing of PBMCs administration was one day before ET (two studies), two days before ET (two studies) or three days before ET (three studies: fresh Day 5 embryos were transferred two days after oocyte retrieval in two of those studies).

3.2. Pregnancy rate

The meta-analysis of pregnancy rate outcomes was based on the data derived from seven studies (564 cases and 609 controls): three RCTs (Sudoma et al., 2011; Yu et al., 2016; Pourmoghadam et al., 2020) and four cohort studies (Yoshioka et al., 2006; Kremenska et al., 2010; Li et al., 2017; Zhang et al., 2019) (Fig. 2). The pregnancy rate was significantly higher in the case group than in the control group (OR: 3.43, 95 % CI: 1.78–6.61; $P =$ 0.0002; random effects model; heterogeneity; $I^2 = 75$ %).

3.2.1. Pregnancy rate in studies with different durations of hCG and PBMCs co-culture

There was no significant difference in the pregnancy rate between the case and control groups when hCG was co-cultured with PBMCs for 24 h (OR: 2.26, 95 % CI: 1.00–5.10; $P =$ 0.05; random effects model; heterogeneity; $I^2 = 80$ %). The pregnancy rate was significantly higher in the case group than in the control group when hCG was co-cultured with PBMCs for 48 h (OR: 5.13, 95 % CI: 2.82–9.33; $P <$ 0.00001; random effects model; heterogeneity; $I^2 = 0$%) (Fig. 2).

3.2.2. Pregnancy rate in studies with different dosages of hCG co-cultured with PBMCs

The pregnancy rate was significantly higher in the case group than in the control group when the dosage of hCG co-cultured with PBMCs was less than 7.5 IU/mL (OR: 4.33, 95 % CI: 1.65–11.34; $P =$ 0.003; random effects model; heterogeneity; $I^2 = 0$%) or equal to or more than 7.5 IU/mL (OR: 2.77, 95 % CI: 1.04–7.39; $P =$ 0.04; random effects model; heterogeneity; $I^2 = 88$ %) (Fig. 3).

3.2.3. Pregnancy rate in studies with different mean PBMCs concentrations for administration

The pregnancy rate was significantly higher in the case group than in the control group when the mean PBMCs concentration for administration was less than 100 × 10^6/mL (OR: 2.77, 95 % CI: 1.04–7.39; $P =$ 0.04; random effects model; heterogeneity; $I^2 = 88$ %) or equal to or more than 100 × 10^6/mL (OR: 4.33, 95 % CI: 1.65–11.34; $P =$ 0.003; random effects model; heterogeneity; $I^2 = 0$%) (Fig. 4).

3.2.4. Pregnancy rate in studies with different timings of PBMCs administration

There was no significant difference in the pregnancy rate between

Table 1
main characteristics of the included studies.

author	year	country	Study design	Defination of RIF (number of IVF-ET failures)	Sample size		Intervention (s)	control	Fertilization	PBMCs Type	hCG culture (hours)	hCG dosage	PBMCs administration	Mean PBMCs concentration ($\times 10^6$/mL)	Timing of PBMCs administration	Transfer type	Stage of embryo	Outcome meastures
					Case	Control												
Kremenska	2010	Ukraine	Clinical trial	Four or more	40	40	Underwent ET with Intrauterine PBMCs	Underwent ET without intrauterine administration		Co-cultured with HCG	48	–	–	–	2 days after oocytes retrieval	Fresh embryos	Blastocyst Stage (Day 5)	Implantation rate Pregnancy rate
Li	2016	China	Clinical trial	One or more	294	339	Underwent ET with Intrauterine PBMCs	Underwent ET without intrauterine administration	ICSI	Co-cultured with HCG	24	10 IU/mL	1-2 $\times$ 10^7 cells in 200 μl	50−100	1 day before ET	FET	Cleavage Stage (Day 3) or Blastocyst Stage (Day 5 or Day 6)	Implantation rate Pregnancy rate Live Birth rate
Pourmoghadam	2020	Iran	Double-blind, Randomized control Clinical trial	Three or more	50	50	Underwent ET with Intrauterine PBMCs	Underwent ET with intrauterine PBS	IVF	Co-cultured with HCG and suspended in the PBS	48	10 IU/mL	15-20 $\times$ 10^6 cells in 500 μl PBS	30−40	2 days before ET	FET	Early Cleavage stage (Day 3) or Blastocyst (Day 5)	The Th17/Treg Ratio Implantation rate Pregnancy rate Live Birth rate
Sudoma	2011	Ukraine	Randomized Clinical trial	Three or more	42	20	Underwent ET with Intrauterine PBMCs	Underwent ET without intrauterine administration		Co-cultured with HCG	48	40 mg/mL	–	–	2 days after oocytes retrieval	Fresh embryos	Blastocyst Stage (Day 5)	Pregnancy rate
Yoshioka	2006	Japan	Clinical trial	Four or more	17	18	Underwent ET with Intrauterine PBMCs	Underwent ET without intrauterine administration	ICSI	Co-cultured with HCG	48	5 IU/mL	2 $\times$ 10^7 cells in 200 μl PBS	100	2 days before ET	Fresh embryos	Blastocyst Stage (Day 5)	Implantation rate Pregnancy rate Live Birth rate
Yu	2016	China	Randomized Clinical trial	Three or more	93	105	Underwent ET with Intrauterine PBMCs	Underwent ET without intrauterine administration	IVF/ICSI	Co-cultured with hCG	24	10 IU/mL	1-2 $\times$ 10^7 cells in 200 μl	50-100	1 day before ET	FET	Cleavage Stage (Day 3)	Implantation rate Pregnancy rate Live Birth rate Miscarriage rate
Zhang	2019	China	Clinical trial	Two or more	28	37	Underwent ET with Intrauterine PBMCs	Underwent ET without intrauterine administration	IVF	Co-cultured with HCG	24	5-10 IU/mL	5-40 $\times$ 10^7 cells in 500-800 μl 0.9% saline solution	100-500	3 days before ET	FET	Cleavage Stage	Implantation rate Biochemical Pregnancy rate Clinical Pregnancy rate Miscarriage rate

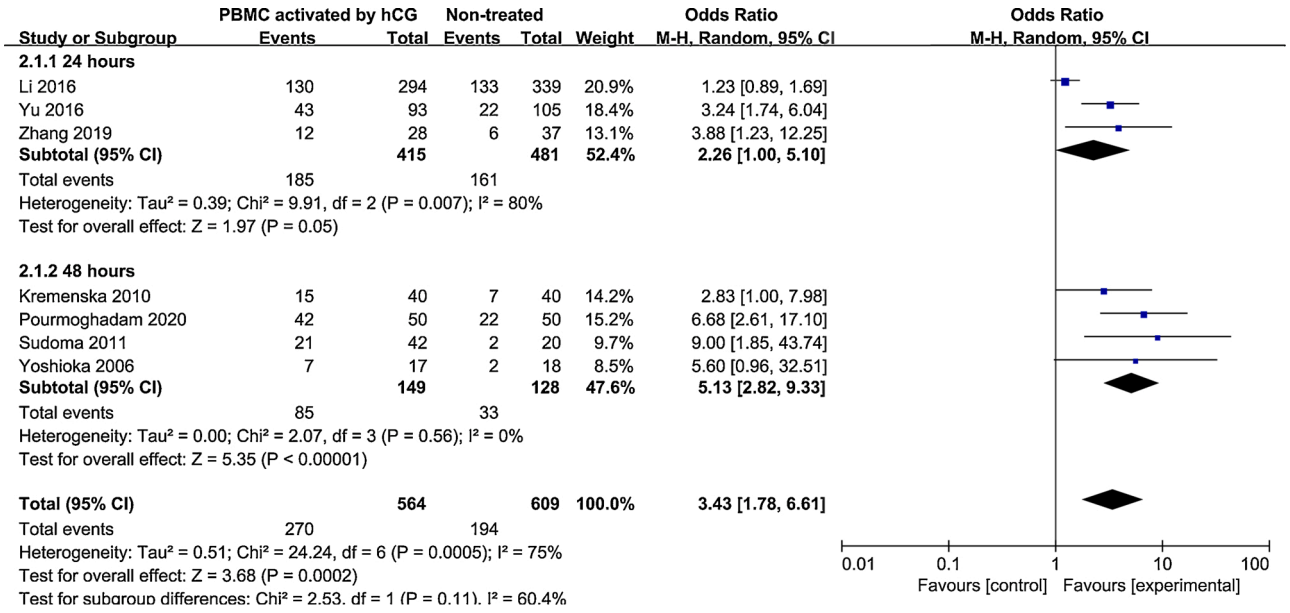

Fig. 2. Forrest plot for the effect of PBMC activated by hCG-therapy on pregnancy rate in studies with different durations of hCG and PBMCs co-culture.

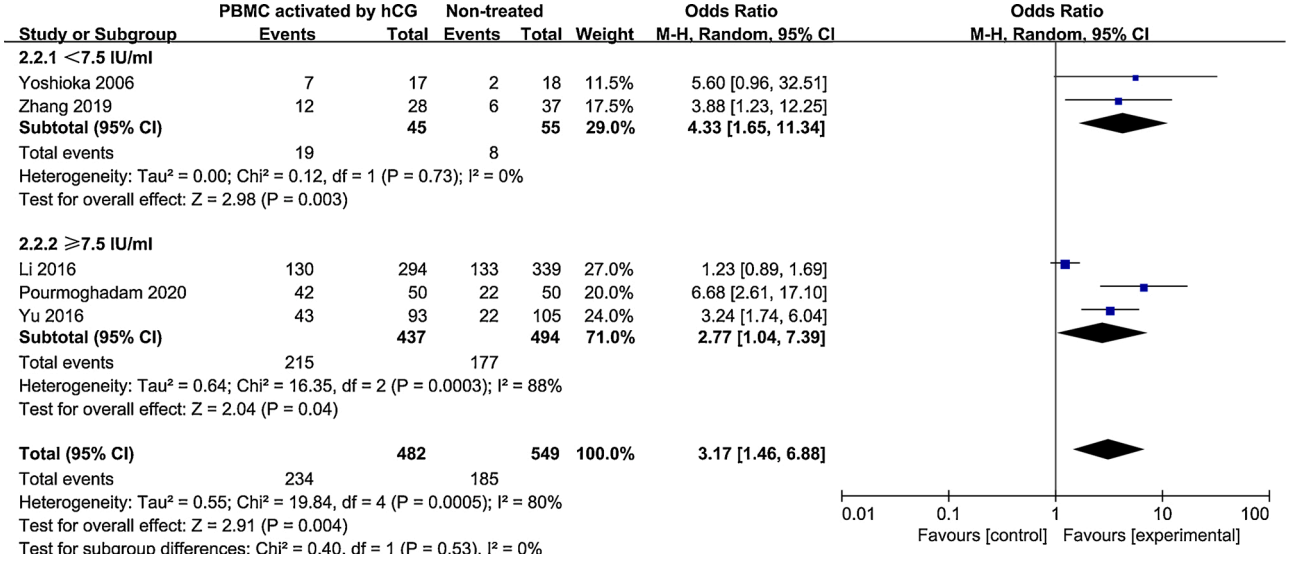

Fig. 3. Forrest plot for the effect of PBMC activated by hCG-therapy on pregnancy rate in studies with different dosages of hCG co-cultured PBMCs.

the case and control groups when PBMCs administration was performed one day before ET (OR: 1.92, 95 % CI: 0.74–4.96; $P = 0.18$; random effects model; heterogeneity; $I^2 = 87$ %) (Fig. 5). The pregnancy rate was significantly higher in the case group than in the control group when PBMCs administration was performed two days before ET (OR: 6.42, 95 % CI: 2.80–14.72; $P < 0.0001$; random effects model; heterogeneity; $I^2 = 0$%) or three days before ET (OR: 3.96, 95 % CI: 1.98–7.91; $P < 0.0001$; random effects model; heterogeneity; $I^2 = 0$%) (Fig. 5).

3.3. Live birth rate

The meta-analysis of live birth rate outcomes was based on data derived from four studies (454 cases and 512 controls): two RCTs (Yu et al., 2016; Pourmoghadam et al., 2020) and two cohort studies (Yoshioka et al., 2006; Li et al., 2017) (Fig. 6). The live birth rate was significantly higher in the case group than in the control group (OR: 2.79, 95 % CI: 1.09–7.15; $P < 0.03$; random effects model; heterogeneity; $I^2 = 83$ %).

3.3.1. Live birth rate in studies with different durations of hCG and PBMCs co-culture

A meta-analysis of the studies showed no significant difference in the live birth rate between the case and control groups when hCG was co-cultured with PBMCs for 24 h (OR: 1.75, 95 % CI: 0.61–5.04; $P = 0.30$; random effects model; heterogeneity; $I^2 = 87$ %). However, a significant benefit of the therapy was observed when hCG was co-cultured with PBMCs for 48 h (OR: 5.17, 95 % CI: 2.32–11.56; $P < 0.0001$; random effects model; heterogeneity; $I^2 = 0$%) (Fig. 6).

3.3.2. Live birth rate in studies with different timings of PBMCs administration

Our meta-analysis showed no significant difference in the live birth rate between the case and control groups when PBMCs administration was performed one day before ET (OR: 1.75, 95 % CI: 0.61–5.04; $P = 0.30$; random effects model; heterogeneity; $I^2 = 87$ %). However, a significant benefit of the therapy was demonstrated when PBMCs administration was performed two days before ET (OR: 5.17, 95 % CI:

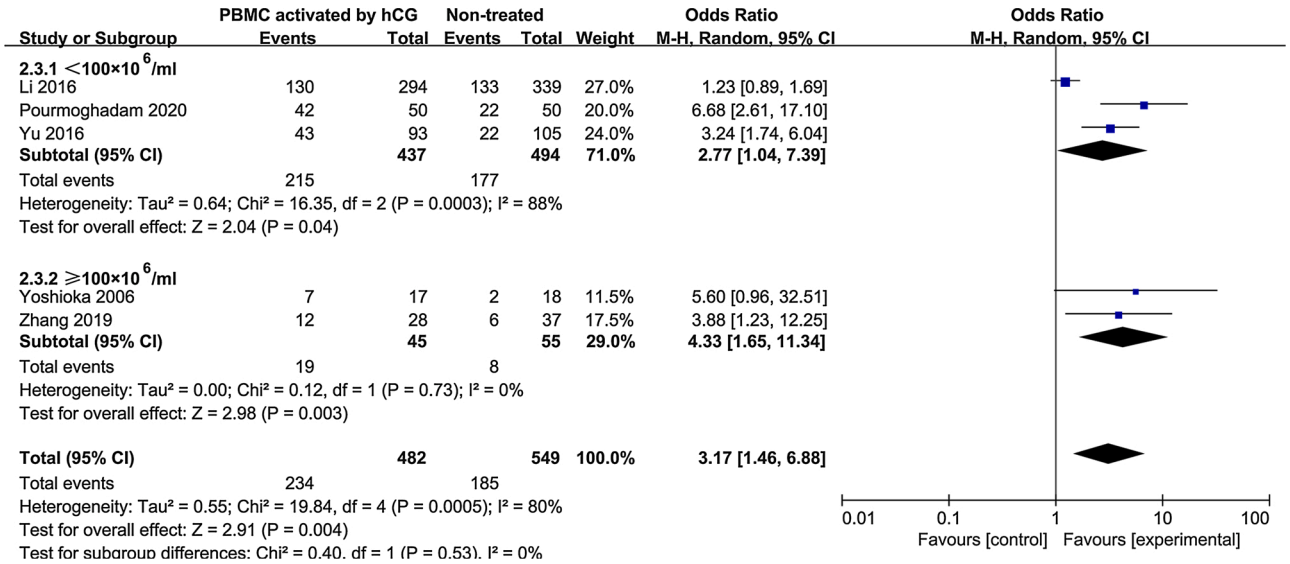

Fig. 4. Forrest plot for the effect of PBMC activated by hCG-therapy on pregnancy rate in studies with different mean PBMCs concentrations for administration.

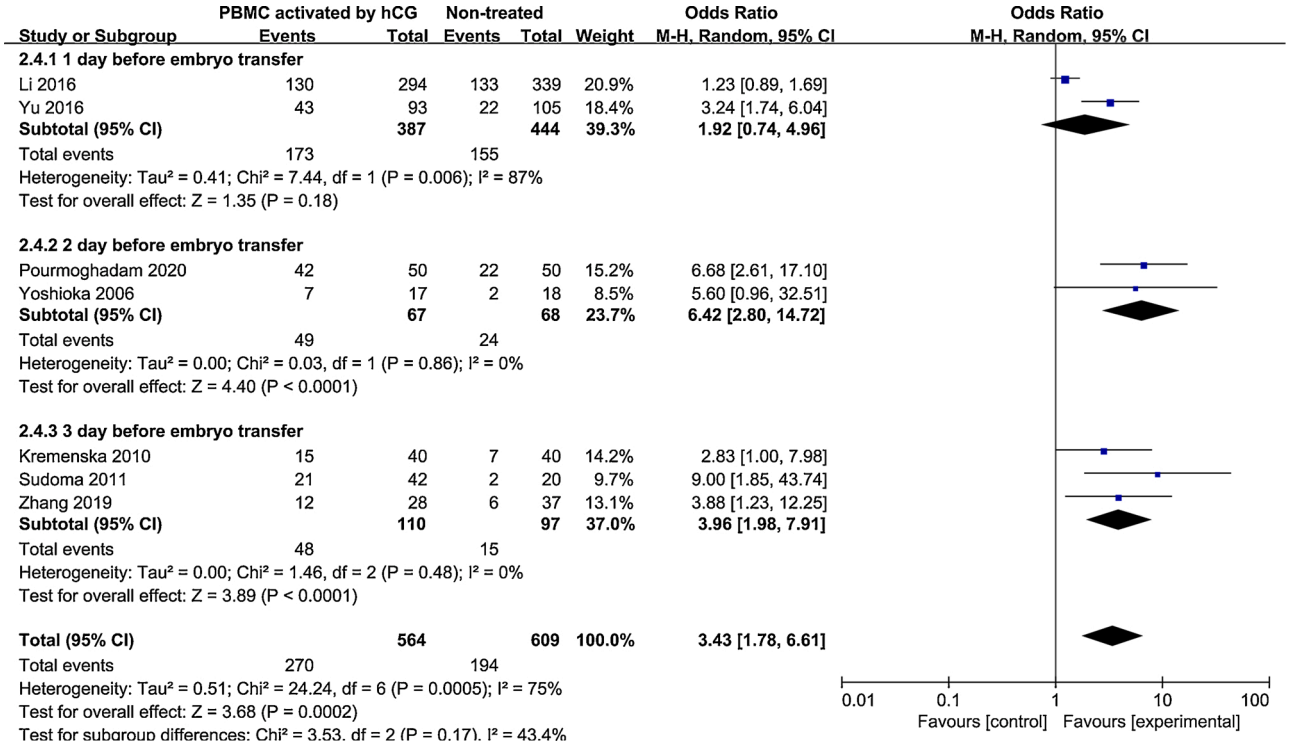

Fig. 5. Forrest plot for the effect of PBMC activated by hCG-therapy on pregnancy rate in studies with different timings of PBMC administration.

2.32–11.56; $P < 0.0001$; random effects model; heterogeneity; $I^2 = 0\%$) (Fig. 7).

4. Discussion

In this review, meta-analyses of seven studies revealed that the intrauterine administration of PBMCs activated by hCG significantly improved the pregnancy rate for 1173 women with RIF (564 cases and 609 controls) and the live birth rate for 966 women with RIF (454 cases and 512 controls). To the best of our knowledge, this is the first systematic review and meta-analysis of the effects of the parameters of hCG and PBMCs co-culture on reproductive outcomes in patients with RIF. We used a comprehensive literature search strategy in the relevant databases according to the latest guidelines, limited it to publications written in English and Chinese. Only one double-blinded RCT of high quality was included in our study. In addition, the heterogeneity of the included studies was high, especially in the results of the pregnancy rate when the dosage of hCG was equal to or more than 7.5 IU/mL and the mean concentration of PBMCs activated by hCG was less than 100×10^6/mL (both $I^2 = 88.0$ %). The main source of heterogeneity was the study by (Li et al., 2017). Possible contributory factors to the heterogeneity include the number of IVF-ET failures, dosage of hCG, concentration of PBMCs administered, small sample size or study design.

It has been proposed that a desirable inflammatory condition of the endometrium during the implantation window is crucial to stimulate the endometrial attachment of embryo trophoblast cells. Intrauterine

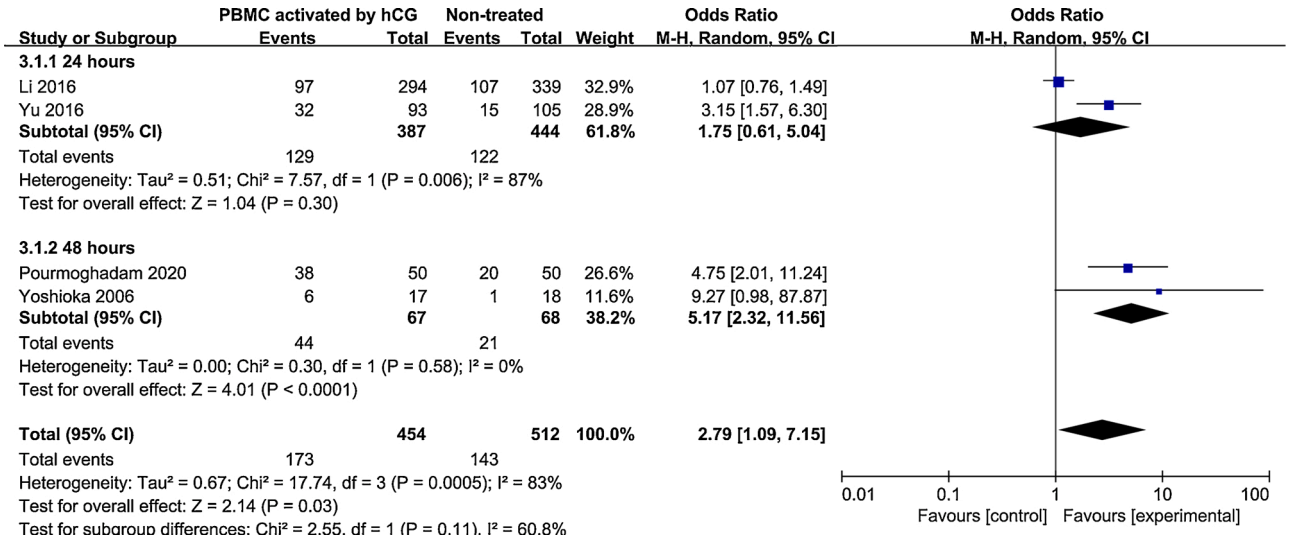

Fig. 6. Forrest plot for the effect of PBMC activated by hCG-therapy on live birth rate in studies with different durations of hCG and PBMC co-culture.

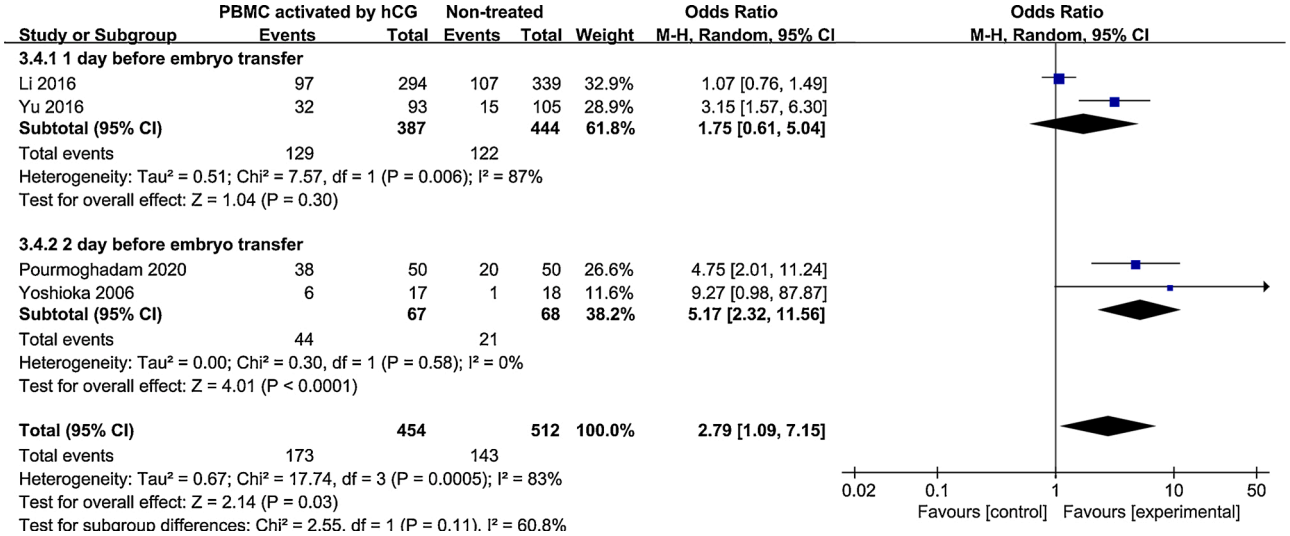

Fig. 7. Forrest plot for the effect of PBMC activated by hCG-therapy on live birth rate in studies with different timings of PBMC administration.

administration of PBMCs before ET evidently promotes the initial inflammatory response (Mor et al., 2011). Some studies have also shown that PBMCs can promote initial inflammation through changing the endometrial function and molecular structure (Yu et al., 2015; Fujiwara et al., 2016). Several cytokines, including interleukin (IL)-1α, IL-1β and tumor necrosis factor (TNF)-α, can be induced by PBMCs. These highly expressed inflammatory cytokines can facilitate embryo implantation through regulating the inflammatory condition of the uterus (Fujiwara et al., 2009, 2016). Our results confirmed that pregnancy and live birth rates were significantly increased after PBMCs administration. In other cases, an over-activated uterine inflammatory condition was an impediment to embryo implantation (Chou et al., 2015), and inflammatory cytokines were not stimulated immediately upon intervention, but after four weeks (Priya et al., 2018). To improve pregnancy outcomes, it is important to determine the mean concentration and timing of PBMCs administration that are most likely to promote a suitable inflammatory condition. Our results demonstrated that there were no significant differences between the subgroups of PBMCs concentration (30–500 $\times$ 10^6/mL). Therapy with hCG-activated PBMCs had positive effects on the pregnancy and live birth rates when the administration was performed two or three days before ET.

hCG is well known as an essential glycoprotein hormone that contributes to maternal tolerance between the endometrium and the embryo through regulating immune cell activities at the maternal-fetal interface (Schumacher et al., 2009; Norris et al., 2011; Schumacher, 2017). hCG prevents the upregulation of surface markers of mature dendritic cells that originate from PBMCs. hCG also inhibits DC-induced antigen-specific T-cell proliferation, which protects against embryo immune rejection (Segerer et al., 2009). hCG can also convert the traditional T-cells into Treg cells, and boost the secretion of IL-10 (Schumacher et al., 2009; Poloski et al., 2016). In addition, hCG enhances the number of regulatory B cells and the secretion of IL-10 (Fettke et al., 2016). A recent study also demonstrated that high levels of immunoglobulin G (IgG) and low levels of IL-10-synthesizing B cells might be related to recurrent miscarriages (Danaii et al., 2020). As a key immunosuppressant cytokine, high levels of IL-10 persist throughout nearly the whole pregnancy period and are associated with immune tolerance (Hanna et al., 2000). Exogenous IL-10 can induce PBMCs to reduce IgG1 levels and increase IgG4 production (Boer et al., 1998; Satoguina et al., 2005). Enrichment of IgG4-positive cells was found in a variety of tumors, and their production was found to be involved in immune evasion, which resulted in poor cancer prognosis (Wang et al.,

2020). Whether IgG4 has the same function during pregnancy as in cancer is still uncertain, and may be worth studying. In in vitro experiments, it was reported that hCG could enhance the effectiveness of PBMCs with respect to spreading and invasion in both murine blastocysts and BeWo cells (Egawa et al., 2002; Nakayama et al., 2002). Inactivated PBMCs were stimulated by hCG in vitro, and the secretion of leukemia inhibitory factor (LIF) and IL-1β was enhanced during this procedure. However, prolonged hCG exposure proved to be detrimental to endometrial receptivity and led to low pregnancy rates (Evans and Salamonsen, 2013). Our results demonstrated that a variety of hCG dosages (5–10 IU/mL) positively influenced the pregnancy rate. A recent study found that PBMCs co-cultured with hCG for 48 h could induce greater secretion of cytokines (TNF-α, IL-1β and IFN-γ) compared with that for 24 h or 2 h and improved both the pregnancy and live birth rates (Pourmoghadam et al., 2020). Our results were consistent with those of this recent study, in that the pregnancy and live birth rates were significantly increased in the subgroup of PBMCs co-cultured with hCG for 48 h, but not 24 h.

Although the intrauterine administration of PBMCs activated by hCG significantly increased the pregnancy and live birth rates in our included studies, we noted that the control group comprised patients without intrauterine administration in six studies and patients with intrauterine PBS in one study. The operation of intrauterine administration might cause endometrial trauma, which would influence the clinical outcomes (El-Toukhy et al., 2012; Panagiotopoulou et al., 2015). Therefore, further research on patients receiving intrauterine administration of PBMCs cultured in isolation, as a control group, should be encouraged to eliminate the effects of the operation and determine the exact role of hCG in this therapy. Additionally, advanced maternal age resulted increased aneuploidy rate of oocytes and embryos (Chiang et al., 2010; Grande et al., 2012; Nagaoka et al., 2012; Yan et al., 2012). Patients with advanced maternal age usually have poor clinical outcome and high miscarriage rate (Grande et al., 2012; Yan et al., 2012). To reduce the influence of the embryos caused by maternal age, further study is necessary to explore whether the maternal age would affect the treatment efficiency. It is also worthwhile to evaluate whether patients with unexplained primary infertility or recurrent spontaneous abortion could benefit from this intervention.

5. Conclusion

The results of our systematic review and meta-analysis indicate that the intrauterine administration of PBMCs co-cultured with hCG for 48 h, conducted two or three days before ET, could significantly improve the pregnancy and live birth rates for patients with RIF. However, there are still some limitations, further research of high-quality double-blinded RCTs with large sample sizes is required to optimize the treatment with co-cultured hCG and PBMCs to maximize the number of patients with RIF who can benefit from this therapy.

Funding

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Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgments

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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.2021.103323.

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