Iran J Public Health, Vol. 54, No.6, Jun 2025, pp.1193-1203

Review Article

Efficacy of Intravenous Immunoglobulin for Patients with Recurrent Miscarriage: A Meta-Analysis

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(Received 15 Dec 2024; accepted 23 Feb 2025)

Abstract

Background: This study aimed to evaluate the efficacy and safety of intravenous immunoglobulin (IVIG) therapy for recurrent miscarriage (RMC) using meta-analysis.

Methods: Literature from Jan 1990 to Feb 2024 was searched in PubMed, etc., using keywords such as "IVIG", "repetitive miscarriage", and "RMC". Two authors independently assessed the literature quality and risk of via Cochrane handbook, and extracted basic information and outcome indicator data. Meta-analysis was performed employing Review Manager 5.3.

Results: Eleven studies were involved, comprising 842 patients, of which 391 received IVIG therapy and 451 received placebo treatment. Relative to placebo group, IVIG group had a notably higher overall live birth rate (OR=2.24, 95% CI=1.68~2.98, Z=5.51, *P*<0.00001) and a greatly lower miscarriage rate (OR=0.46, 95% CI=0.22~0.95, Z=2.09, *P*=0.04). Subgroup analysis revealed that both primary and secondary RMC patients in IVIG group had markedly higher live birth rates versus placebo group (OR=2.13, 95% CI=1.18~3.83, Z=2.51, *P*=0.01; OR=1.50, 95% CI=0.98~2.30, Z=1.96, *P*=0.04). Nevertheless, the adverse reaction (AR) rate in IVIG group was superior to that in placebo group (OR=4.47, 95% CI=1.01~19.81, Z=1.97, *P*=0.05).

Conclusion: IVIG can markedly increase the live birth rate, reduce the miscarriage rate, and enhance pregnancy outcomes in patients with RMC. Nevertheless, the rate of ARs with IVIG therapy is relatively high, thus large-scale, multicenter, randomized controlled trials are needed for validation.

Keywords: Intravenous immunoglobulin; Recurrent miscarriage; Pregnancy outcome; Adverse reactions; Meta-analysis

Introduction

Recurrent miscarriage (RMC) is defined as experiencing two or more consecutive spontaneous abortions during pregnancy, often accompanied by symptoms such as abdominal pain and vaginal bleeding. Currently, the incidence of RMC is approximately 1-5%. This condition not only affects the normal reproductive function of patients but also causes repeated damage to the endometrium, increasing the risk of vaginal infections (1). The etiology of RMC is complex, with known causes including genetic factors, endocrine dysfunction, autoimmune diseases, and

DOI: https://doi.org/10.18502/ijph.v54i6.18897

immune imbalance at the maternal-fetal interface (2-4). However, the cause of miscarriage remains unexplained in over 50% of patients (5), with immune factors accounting for 50%-60% of RMC cases, and more than 80% of patients lacking protective blocking antibodies (6). As a result, immunotherapy for RMC is gradually being developed and utilized.

Intravenous immunoglobulin (IVIG) is a passive immunization method that has shown certain efficacy in the treatment of RMC or unexplained RMC (7). After IVIG is infused into the patient's body, it rapidly increases the levels of immunoglobulin G (IgG) in the blood, thereby enhancing the body's ability to prevent miscarriages caused by infectious factors (8,9). Moreover, IVIG can regulate the Th1/Th2 cell ratio and their associated cytokine levels, reduce the inflammatory response, and improve the pregnancy environment (10). IVIG also has the advantages of fewer side effects and high safety, with only a small number of patients experiencing mild symptoms such as nausea, palpitations, or headaches during infusion, which may be related to rapid infusion rates or individual differences (11,12). Overall, IVIG offers high efficacy and low safety risks for miscarriage treatment. However, there is no standardized treatment protocol for RMC in clinical practice, making it difficult to provide clear guidance for clinical management. Therefore, the clinical efficacy of IVIG in treating RMC requires further research and validation.

Hence, this study employed a meta-analysis approach for clinical efficacy and safety assessment of IVIG systematically and objectively in the therapy of RMC. This study aimed to provide reference data for clinical practice of IVIG therapy for RMC.

Materials and Methods

Search strategy

Relevant literature from Jan 1990 to Feb 2024 was retrieved using computerized searches in databases such as PubMed, Medline, Embase, and Web of Science. The searches were conducted using a combination of free-text terms and keyword terms. Search terms included "miscarriage," "habitual miscarriage," "repetitive miscarriage", "RMC," "recurrent early pregnancy loss," and others, along with "immunoglobulin," "intravenous antibody," "IVIG," "intravenous," "Gammagard," "Gamimune," "Venogloblin," "Privigen," "Alphablobin," "Endobulin," and "Gamimone N". There were no language restrictions.

Criteria

Inclusion criteria: the study type included randomized controlled trials; the study participants were patients with RMC, defined as experiencing two or more consecutive miscarriages, with both spouses having no chromosomal karyotype abnormalities or abnormalities in reproductive organ anatomy; therapy methods included IVIG infusion, with placebo as the control.

Exclusion criteria: case reports, reviews, treatment experiences, conference abstracts; *in vitro* or basic research; incomplete clinical data; unclear outcome indicators; nonspecific medication regimens; duplicated publications.

Data extraction

Independently, two authors implemented literature search, screening, and full-text review according to the PRISMA process. Relevant data from the eligible studies were independently extracted into Excel. The extracted data included country, publication year, first author, study design, study population and inclusion criteria, treatment modality and duration, basic characteristics of study population, and outcome indicators. Outcome indicators included live birth rate (primary and secondary), miscarriage rate, newborn weight, and adverse reactions (ARs). Continuous variables were denoted as mean ± standard deviation, while categorical variables were denoted as frequencies. In case of discrepancies between the two authors, resolution was achieved through consensus or discussion with a third one.

Quality evaluation

Cochrane risk of bias assessment tool (13) was employed for quality and risk of bias assessment. The assessment criteria included random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases. Each bias assessment was categorized as low, unclear, or high risk.

Statistical analysis

All outcome indicators were analyzed independently. Meta-analysis was conducted using *Review Manager 5.3*. Firstly, heterogeneity analysis of included studies was performed using I^2. I^2<50% meant small heterogeneity among studies, and fixed-effects model (FEM) was chosen. When $I^2 \geq 50\%$, large heterogeneity was considered, and random-effects model (REM) was selected for combined analysis. Analysis of heterogeneity sources was conducted, and correction was made through subgroup analysis or sensitivity analysis. The results of the meta-analysis were presented as mean differences (MD), standardized mean differences (SMD), or weighted mean differences (WMD) with 95% confidence intervals (CIs) for continuous variables, and as odds ratios (ORs), risk ratios (RRs), or risk differences (RDs) with 95% CIs for categorical variables. A significance level of $\alpha = 0.05$ was utilized, with $P<0.05$ indicating statistical significance. The risk of publication bias was assessed by drawing a funnel plot.

Results

Retrieval outcome

Overall, 585 relevant articles were retrieved. After preliminary review of the articles and abstracts, 534 articles were excluded, including case reports, reviews, duplicate reports, irrelevant studies, and other articles that did not meet the criteria. Fifty-one articles were selected for further screening. Full-text articles were downloaded, and after reading, 40 articles were excluded, including basic research, conference abstracts, articles with unclear outcome indicators, articles with unclear medication regimens, articles involving single treatment regimens or combination therapies. Finally, 11 articles (14-24) were included (Fig. 1).

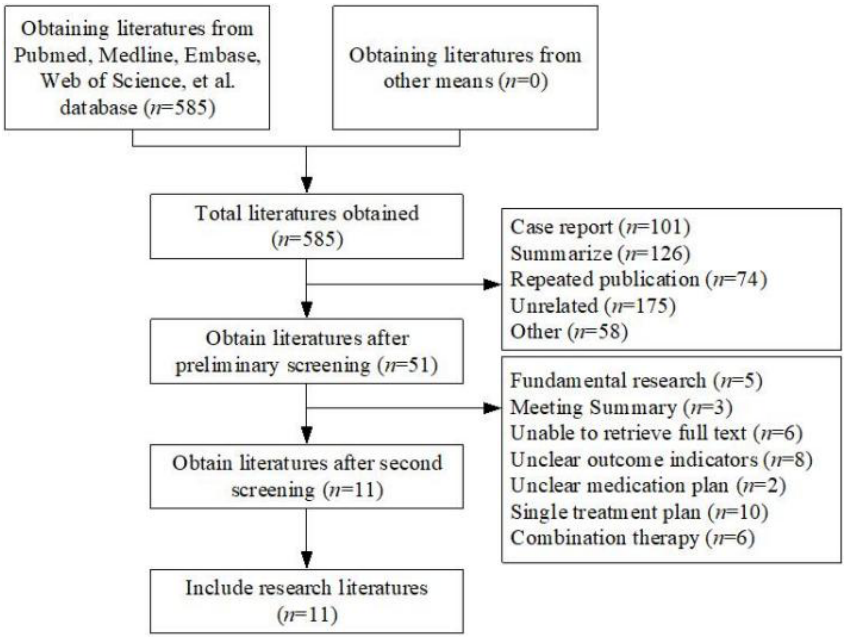

Fig. 1: Flowchart of selection process.

Basic characteristics

Eleven relevant articles were included, comprising a total of 842 patients, of whom 391 patients received IVIG therapy and 451 patients received placebo treatment. All subjects in these 11 studies were patients with unexplained RMC (Table 1).

Table 1: Basic information

Literature/Year	n	Research object	IVIG therapy plan
Carp 2001	151	RMC ≥5 times, unexplained etiology	During the follicular phase, the dosage was 400 mg/kg/day; one additional dose was administered after confirmation of pregnancy
Christiansen 1995	34	RMC ≥3 times, unexplained etiology	After confirmation of pregnancy, administer 35 g during wk 5-6, 25 g during wk 7-26, and 30 g at wk 28, 30, 32, and 34. For pregnant women with a pre-pregnancy weight of less than 60 kg, reduce each dose by 5 g. For pregnant women with a pre-pregnancy weight of more than 80 kg, increase each dose by 5 g.
Christiansen 2002	58	RMC, unexplained etiology, occurring at 26 wk of pregnancy	After confirmation of pregnancy, administer 0.8 g/kg per dose during weeks 5-20, and 1.0 g/kg per dose during weeks 20-26. Administer once per week during weeks 5-10, and then once every two weeks thereafter.
Christiansen 2015	82	RMC, unexplained etiology	After confirming pregnancy, administer 25 g per dose for pregnant women with a pre-pregnancy weight of less than 75 kg, and 35 g per dose for pregnant women with a pre-pregnancy weight of 75 kg or more.
Coulam 1995	61	RMC ≥2 times, unexplained etiology	After confirming pregnancy, administer 500 mg/kg per month until the 4th week of gestation.
Jablonowska 1999	39	RMC, unexplained etiology, occurring at 20 wk of pregnancy	After confirming pregnancy, administer 400 mg/kg per month for a total of 4 doses.
Jafarzadeh 2018	94	RMC ≥3 times, unexplained etiology	After confirming pregnancy, administer 400 mg/kg per month until the 32nd week of gestation.
Jørgensen 2020	39	RMC, unexplained etiology	After confirming pregnancy, administer 1 dose during weeks 5-10, followed by a dose every two weeks until the 26th week of gestation or miscarriage.
Peero 2024	143	RMC, unexplained etiology	Before and during pregnancy, administer 0.6-0.8 g/kg until the 20th week of gestation.
Stephenson 2010	47	RMC ≥2 times, unexplained etiology, occurring at 3 wk or more or at 20 wk or more of pregnancy	Before pregnancy, administer 500 mg/kg/day, then administer 500 mg/kg per month after confirming pregnancy until the 18th-20th week of gestation.
Yamada 2022	99	RMC ≥2 times, unexplained etiology	After confirming pregnancy, administer 400 mg/kg for 5 consecutive days during weeks 4-6.

Quality evaluation

One article had high risk of bias in random sequence generation (selection bias), while two articles had unclear risk. One article had high risk in allocation concealment (selection bias). Additionally, one article had high risk in blinding of participants and personnel (performance bias), while four articles had an unclear risk. Furthermore, one article had high risk in selective reporting (reporting bias), and two had an unclear risk. Overall, the bias risk of the eleven included articles in this study was not high, and it would not significantly affect the stability of the meta-analysis results. The bias analysis results of the included literature are presented in Fig. 2.

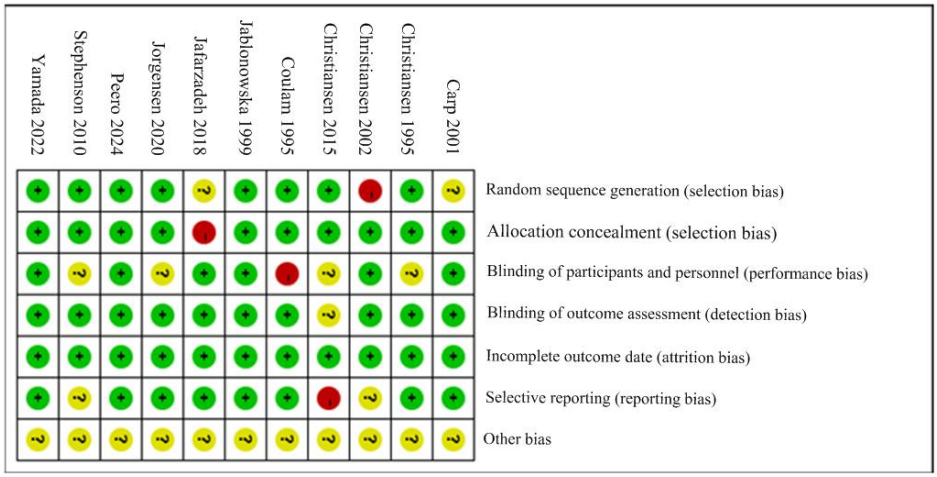

Fig. 2: Summary assessment of bias risk

Meta-analysis results

Evaluation of total live birth rate

Eleven studies analyzing the impact of IVIG on the overall live birth rate in patients with RMC were included in the literature review, comprising 842 patients (n=391 for IVIG therapy and n=451 for placebo). The overall heterogeneity test revealed an I^2 value of 43%, indicating that the 11 included studies did not exhibit significant heterogeneity. Hence, a FEM was chosen. The overall live birth rate in IVIG group was markedly superior to that in placebo group (OR=2.24, 95% CI=1.68~2.98, Z=5.51, *P*<0.00001). The forest plot (FP) of the overall live birth rate is presented in Fig. 3.

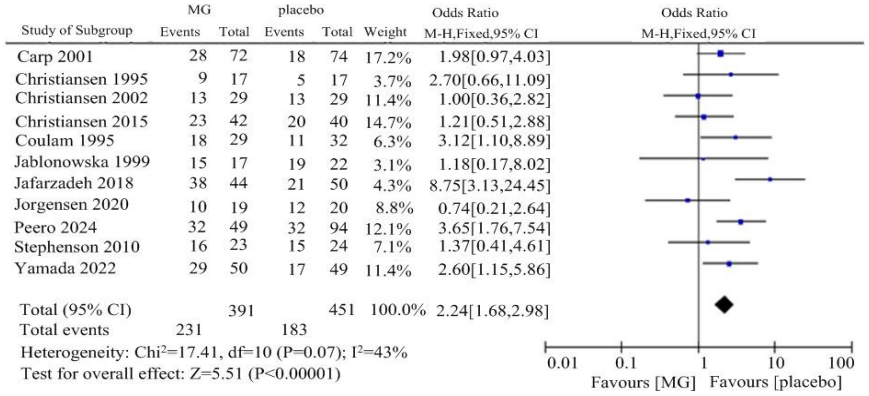

Fig. 3: FP of meta-analysis for total live birth rate after IVIG therapy of RMC

Subgroup evaluation of live birth rates in patients with primary and secondary RMC

Among the 11 included studies, four explicitly analyzed the live birth rate in primary RMC, comprising 204 patients, with 97 patients having IVIG therapy and 107 patients having a placebo. Eight studies explicitly analyzed the live birth rate in secondary RMC, comprising 361 patients (n=167 for IVIG therapy and n=194 for placebo). Hence, this study further conducted subgroup analyses for IVIG therapy in primary and secondary RMC. In the analysis of IVIG therapy for primary RMC, the overall heterogeneity test revealed an I^2 value of 42%, indicating that the inclusion of four studies did not exhibit considerable heterogeneity. Hence, a FEM was chosen. The live birth rate of primary RMC patients in IVIG group was markedly superior to that in placebo group (OR=2.13, 95% CI=1.18~3.83, Z=2.51, *P*=0.01). In the analysis of treatment for secondary RMC, the overall heterogeneity test indicated an I^2 value of 0%, indicating neglectable heterogeneity among the eight included studies. Hence, a FEM was employed. The live birth rate of secondary RMC patients in IVIG group was drastically superior to that in placebo group (OR=1.50, 95% CI=0.98~2.30, Z=1.96, *P*=0.04).

Evaluation of abortion rate in patients with RMC

The analysis included 6 studies investigating the effect of IVIG on the miscarriage rate of RMC patients, comprising 491 patients, with 221 patients accepting IVIG therapy and 270 patients accepting placebo treatment. The overall heterogeneity test revealed an I^2 value of 61%, indicating marked heterogeneity among the 6 included studies. Hence, a REM was employed. The miscarriage rate in IVIG group was dramatically inferior to placebo group (OR=0.46, 95% CI=0.22~0.95, Z=2.09, *P*=0.04).

Evaluation of newborn birth weight in patients with RMC

The analysis included 6 studies investigating the effect of IVIG on the birth weight of newborns in patients with RMC, comprising 371 patients (n=180 for IVIG therapy and n=191 for placebo treatment). The overall heterogeneity test revealed an I^2 value of 81%, indicating notable heterogeneity among the 6 included studies. Hence, a REM was employed. The results revealed considerable difference in birth weight of newborns between IVIG and placebo groups (MD=-220.74, 95% CI=-549.37~107.88, Z=1.32, *P*=0.19).

Evaluation of ARs in patients with RMC

Three studies were included in effect analysis of IVIG on ARs in patients with RMC, comprising 264 patients, with 108 patients accepting IVIG therapy and 156 patients accepting placebo treatment. The overall heterogeneity test revealed an I^2 value of 54%, indicating observable heterogeneity among the 4 included studies. Hence, a REM was employed. The incidence of ARs in IVIG group was superior to that in placebo group (OR=4.47, 95% CI=1.01~19.81, Z=1.97, *P*=0.05). The FP for the meta-analysis of ARs is presented in Fig. 4.

Publication bias

The publication bias of the included literature was analyzed by plotting a standard funnel plot. The funnel plot exhibited good symmetry, and the included literature was evenly distributed, indicating minimal publication bias in the study designs of the included literature.

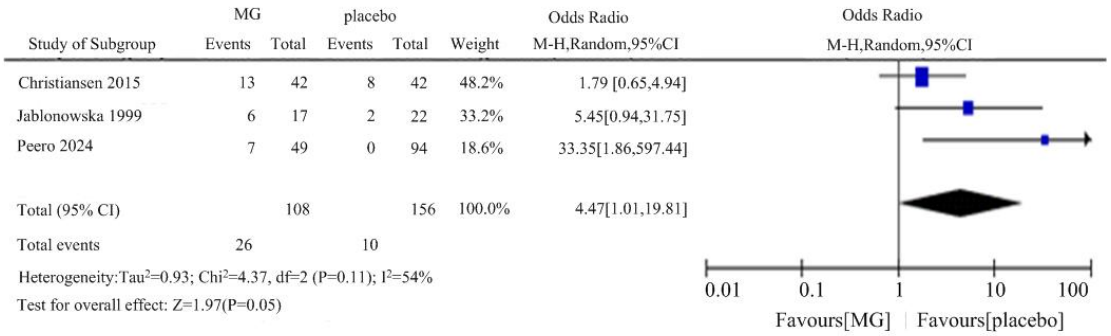

Fig. 4: FP of meta-analysis for ARs after IVIG therapy of RMC.

Discussion

The etiology of RMC includes reproductive system anatomical abnormalities, infections, genetic factors, and immune dysregulation (25). Among these, immune factors are considered the primary cause of RMC (26). In clinical practice, immunotherapy protocols such as IVIG are commonly used for treating RMC. IVIG is a biological agent with both immune-enhancing and immune-regulating properties. It is primarily derived from the plasma of healthy individuals and is composed of IgG antibodies, exerting various functions such as supplementing immune deficiencies, modulating immune functions, and preventing infectious diseases. Currently, IVIG is used to treat autoimmune diseases, secondary immunodeficiencies, and severe infections (27-30). IVIG has a high safety profile with no serious side effects, and its use in pregnant patients does not increase the risk of preterm birth (31). However, the efficacy of IVIG in RMC remains controversial. Therefore, this study includes 11 relevant studies and systematically and objectively demonstrates the effectiveness of IVIG in treating RMC. Our findings indicated that IVIG significantly improved the live birth rate in RMC patients. This is consistent with the results of through meta-analysis that IVIG can significantly improve the live birth rate in patients with recurrent spontaneous miscarriage (32). To further investigate the efficacy of IVIG in treating RMC, this study conducted a subgroup analysis to evaluate the effect of IVIG on live birth rates in patients with primary and secondary miscarriage. IVIG significantly improved the live birth rate in these patients. This suggests that IVIG exerts its therapeutic effect on RMC and increases the live birth rate primarily by modulating the immune function of patients, regulating cytokine secretion, blocking the formation of complement complexes, inhibiting maternal immune responses, and reducing cytotoxicity (33).

Furthermore, this study found that IVIG significantly reduced the miscarriage rate in RMC patients. This finding is consistent with the results of meta-analysis that found IVIG treatment effectively reduced the number of miscarriages and improved live birth rates in antiphospholipid antibody-positive patients with high miscarriage risk (34). Immune factors are among the primary causes of RMC. Natural killer (NK) cells, which are crucial immune cells in the body, can directly kill target cells and are also involved in immune regulation (35). When NK cell numbers are reduced or their function is impaired, they may directly harm the embryo and disrupt the immune microenvironment of the decidua, ultimately leading to miscarriage (36,37). IVIG, a blood product rich in antibodies, can modulate NK cell function through several mechanisms. On one hand, antibodies in IVIG can bind to NK cell surface receptors and inhibit their activation. On the other hand, IVIG can also regulate the function of other immune cells, such as T cells, thereby indirectly influencing NK cell activity and function (38). After IVIG treatment for RMC, patients showed a significant reduction in NK cell percentage and cytotoxicity, which was associated with improved pregnancy outcomes (39).

Additionally, IVIG can modulate the Th1/Th2 balance in the body. Spontaneous miscarriage is associated with an increase in Th1 cytokines (e.g., IL-2, IL-12, TNF-α, and IFN-γ) or a decrease in Th2 cytokines (e.g., IL-4, IL-6, IL-10, and TGF-β) (40,41). IVIG treatment in in vitro fertilization-embryo transfer (IVF-ET) patients with elevated pre-pregnancy Th1/Th2 and/or NK cell levels improved implantation success and live birth rates (42). IVIG treatment led to a dramatic increase in peripheral blood Th2 lymphocytes, a decrease in the Th1/Th2 ratio, and a live birth rate of 87.5% in RMC patients (43). Therefore, IVIG may improve pregnancy outcomes in RMC patients by influencing the activity and function of immune cells such as NK cells and Th1/Th2 cells. However, further clinical trials are needed to validate this hypothesis.

This study found that IVIG treatment had no significant effect on neonatal birth weight. Simultaneous administration of tumor necrosis factor inhibitors, IVIG, and heparin improved live birth rates in RMC patients, with no impact on neonatal birth weight or Apgar scores, which is consistent with our findings (44). Neonatal birth weight is influenced by multiple factors, including genetics, maternal nutrition during pregnancy, maternal health status, and fetal growth and development. As an immunomodulatory agent, IVIG does not directly participate in the growth and development of the fetus during RMC treatment, and therefore does not exert a direct effect on neonatal birth weight. Severe adverse effects associated with the clinical use of IVIG have been rarely reported, but it may cause systemic ARs such as fever, chills, rash, nausea, and headache (45). These ARs often occur during the initial infusion or when the infusion rate is too rapid. Our study results showed that the incidence of ARs in 108 patients with RMC was 24.07% (26/108), slightly superior to the 6.41% (10/156) in placebo group. The clinical application of IVIG requires slow infusion and pre-treatment evaluation of patient IgA levels. This is crucial for reducing the occurrence of ARs to IVIG treatment.

Conclusion

IVIG was shown to significantly increase the live birth rate and reduce the miscarriage rate in patients with RMC. However, this study has certain limitations. Future research should incorporate more clinical data to further explore the changes in peripheral blood NK cells and the Th1/Th2 balance following IVIG therapy for RMC. Overall, this study provides valuable reference data for understanding the effectiveness and safety of IVIG therapy in the treatment of RMC.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Data Availability Statement

All data generated or analyzed during this study are included in this published article.

Acknowledgments

No financial source was received for this study.

Conflict of interest

The authors declare that there is no conflict of interests.

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