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Review article

The effectiveness of IVIG therapy in pregnancy and live birth rate of women with recurrent implantation failure (RIF): A systematic review and meta-analysis

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ABSTRACT

Recurrent implantation failure (RIF), as a challenging problem in human reproduction, is widely improved by intravenous immunoglobulin (IVIG), especially in patients with immunologic abnormalities. In this meta-analysis, we evaluated the results of the studies in which RIF women were treated with IVIG, and pregnancy, live birth, miscarriage and implantation rate were assessed as the result of treatment. A systematic search was conducted in MEDLINE (PubMed), Embase, Cochrane Library, Google Scholar, ProQuest and clinicaltrail.gov. Two cohorts, two cross-sectional and one quasi experimental studies were included in this study. Four out of five studies were included in meta-analysis and remained one study was narratively discussed. Data analysis was conducted by RevMan 5.2 software. Our meta-analysis results demonstrated that there was a significant difference in the pregnancy rate of cohorts (OR = 1.82, 95% CI = 1.14–2.89, P = 0.01) and cross-sectional studies (OR = 11.12, 95% CI = 6.43–19.23, P < 0.00001), live birth rate of cohorts (OR = 2.17, 95% CI = 1.30–3.61, P = 0.003) and cross-sectional studies (OR = 7.57, 95% CI = 4.53–12.64, P < 0.00001) in the IVIG group when compared to the control group, but there was no significant difference in the miscarriage rate. In conclusion, IVIG may be a beneficial therapeutic strategy in RIF patients selected according to relevant immunological disturbances. However, final conclusions on the efficiency of the treatment must await prospective, randomized controlled trials of sufficient size.

1. Introduction

1.1. Background

During human gestation, the maternal immune system is required to be regulated in order to tolerate the early embryo or fetus. This is because of the paternal antigens, which are unknown for the maternal immune system and, therefore, lack of regulatory mechanisms may lead to implantation failure or pregnancy loss (Achache and Revel, 2006). Repeated or recurrent implantation failure (RIF) is a physically and emotionally challenging problem for young couples who seek for neonates. It is defined as a failure in implantation after transferring one or more good quality embryos to the uterus (Simon and Laufer, 2012). Beside anatomic, genetic, infectious, and hormonal abnormalities, immunologic factors play a key role in implantation process and pregnancy maintenance (Hill et al., 1995). Failure in the modulation of the immune responses may cause embryo or fetus rejection. The common immunologic difficulties among RIF women are increased frequency and function of natural killer (NK) cells (Aoki et al., 1995), unbalanced ratio of T helper (Th) 1/Th2 cells toward Th1 cells proportion and

Abbreviations: RIF, recurrent implantation failure; IVIG, intravenous immunoglobulin; NK cells, natural killer cells; Th1, T helper 1; Th2, T helper 2; Th17, T helper 17; Treg, T regulatory; IgG, immunoglobulin G; IgA, immunoglobulin A; ET, embryo transfer; RCT, Randomized Controlled Trials; IVF, in vitro fertilization; JBI, the Joanna Briggs Institute; PRISMA, preferred reporting items for systematic reviews and meta-analyses; OR, odds ratio; CD, cluster of differentiation; ICSI, Intracytoplasmic sperm injection; TNF, tumor necrosis factor

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related cytokines (Hill et al., 1995), increased Th17 cells number and cytokine secretion, and decreased frequency and cytokines of regulatory T (Treg) cells (Kim et al., 2014). These difficulties are susceptible to be regulated by modulatory therapeutic approaches to avoid further problems.

Intravenous immunoglobulin (IVIG) is among the most studied immunomodulatory agents, which had been used for 60 years for the treatment of different diseases, such as in immunodeficiency or autoimmunity. However, it was first used in the study of Carreras et al. in 1988 for the treatment of reproductive failure (Carreras et al., 1988). Indeed, IVIG is a pooled serum immunoglobulin, especially IgG isotype and in a lower rate IgA, of approximately 3000–60000 blood donors (Schwab and Nimmerjahn, 2013). According to the literature, it is reported that IVIG is an appropriate therapeutic agent in improving the pregnancy outcomes and live birth in RIF women, especially those with immunological abnormalities(Van Den Heuvel et al., 2007; Winger et al., 2011; Ramos-Medina et al., 2014). The exact mechanism of IVIG is still unknown, but it is somehow due to a modulatory arm of anti-inflammatory and pro-inflammatory situations of the immune system that may improve the quality of implantation and pregnancy. According to the different literature, it is suggested that IVIG is able to decrease the number and function of NK cells (Kwak et al., 1996; MORIKAWA et al., 2001), in contrast, the frequency and suppressive activity of Treg cells are increased by IVIG (Ramos-Medina et al., 2014). Autoantibodies production is inhibited by IVIG, and it is also able to neutralize the circulating maternal autoantibodies (Brand et al., 1988). Another theory suggests that activating receptors of Fc γ RI and Fc γ RIII are up-regulated and the inhibitory receptor on B cells, Fc γ RIIB, is down-regulated by IVIG on leukocytes (Omwandho et al., 2004; Virro et al., 2012).

In different studies, there are different protocols for IVIG therapy in reproduction failure, in which a 400–2000 mg/kg of IVIG is usually injected 3 days before embryo transfer (ET), but it is sometimes started before or during the ovarian stimulation. In some studies, post-transfer IVIG administration has been conducted every 3–4 weeks until week 32th of the pregnancy (Stephenson and Fluker, 2000).

IVIG therapy would be more helpful if it is prescribed for the right patient. Indeed, an etiology-based selection of participants undergoing IVIG therapy showed higher efficacy in comparison to investigations, in which patients were selected regardless of their etiology. RIF patients with abnormalities in their immune system may benefit IVIG more, because of its modulatory effects on the immune system (Winger et al., 2011). In the case of thrombophilic disorders, some patients are advised to receive anticoagulatory and anti-inflammatory medications, such as heparin and aspirin, which are able to decrease the risk of implantation failure due to coagulation and inflammation.

In this systematic review and meta-analysis, we aimed to assess available evidence, in which the IVIG effects were evaluated in the therapy of RIF patients with systemic immunological abnormalities, on the pregnancy, live birth rate, and miscarriage or implantation failure. Moreover, we updated the previous systematic review with the same topic.

1.2. Objectives

The meta-analysis and systematic review try to answer the question that how much IVIG therapy is effective on the pregnancy rate and live birth of women with recurrent implantation failure, especialy when chosen according to immunological abnormalities.

2. Methodology

2.1. Criteria for considering studies for this review

2.1.1. Types of studies

Experimental studies (Randomized Controlled Trials (RCTs) and quasi-experimental studies (non-randomized)), observational studies including (prospective and retrospective) Cohort studies, cross-sectional studies were evaluated. The inclusion criteria were studies (i) in which RIF women undergoing 3 or more IVF therapy were included, (ii) abnormal immunologic parameters were detected in participants, (iii) the results of IVIG group was compared with the control group who did not receive IVIG, (iv) pregnancy and live birth rates were assessed as the main outcomes, and implantation and miscarriage rate in some studies. Abstracts and studies without a control group were excluded.

2.1.2. Types of participants

This study included studies about IVIG therapy in women with RIF who had at least 3 or more in vitro fertilization/embryo transfer (IVF/ET) failure history and immunological abnormalities.

2.1.3. Types of interventions

The studies, which use IVIG for treatment of RIF women are included in this study.

2.1.4. Types of outcome measures

We evaluated the pregnancy, live birth, miscarriage and implantation rate of RIF women with IVIG treatment in the included studies.

2.2. Search strategy

A preliminary search of MEDLINE (PubMed) was conducted according to our search strategy and main keywords including “intravenous immunoglobulin; IVIG; recurrent, repeated and multiple implantation failure; recurrent, repeated and multiple IVF failure; recurrent, repeated and multiple IVF/ICSI failure”. The secondary search of MEDLINE (PubMed), Cochrane Library, Embase, scopus databases for published articles and search of Google Scholar, clinicaltrials.gov (registered trials) and ProQuest (thesis and dissertation) was conducted for gray literature and unpublished studies.

2.3. Study selection

The retrieved citations were entered in Endnote X7 software and duplicated articles were deleted, then a screening based on the information of title and abstract of remained studies was done by two independent expert, and studies with irrelevant topic were excluded. In case of disagreement between the reviewers, the problem was solved by a third reviewer or more discussion. A full-text assessment was done in remained studies. We tried to contact the authors of articles in which we could not get enough information needed, however, there was no reply. Studies that met our inclusion criteria were included in the analysis. The full search strategy for Embase database is illustrated in Appendix 1.

2.4. Methodology quality assessment

For assessment of the methodological quality, two independent reviewers appraised the eligibility of the studies using appraisal instruments from the Joanna Briggs Institute (JBI) for cohort, cross-sectional and quasi-experimental and studies. This review has been registered in PROSPERO with the registration number: CRD42019119469.

2.5. Data extraction

Using the Modified-Standardized JBI data extraction tool, the review team, including two independent reviewers, extracted the required data of the included studies. The extracted data comprised of author, publication year, number of IVIG and control group participants, type of immunological abnormalities among patients, intervention protocol and the treatment outcome that was the exact event/rate of pregnancy, live birth, implantation, and miscarriage. In case of

disagreement between the reviewers, the problem was solved by a third reviewer or more discussion.

2.6. Data synthesis

Data was, where possible, pooled with statistical meta-analysis using Revman 5.2 software. Effect sizes, expressed as odds ratio (dichotomous), and weighted mean differences (for continuous data) and their 95% confidence intervals were calculated for analysis. Heterogeneity was assessed statistically using Chi-square and I^2 tests. Statistical analyses were performed using fixed effects (Tufanaru et al., 2015). Where statistical pooling was not possible the findings were presented in narrative form including tables to aid in data presentation where appropriate.

3. Results

3.1. The procedure of the study selection

The total number of studies found at the end of electronic search was 208 studies. The first step was removing the duplicated articles, and then 168 studies were screened through their title and abstract in order to differentiate the relevant studies. Afterward, 29 out of 168 articles were selected for more evaluation. Full-text evaluation according to our inclusion and exclusion criteria resulted in five articles, for which the methodological quality assessment was conducted by the reviewers. Finally, four articles included for meta-analysis and 1 study was narratively discussed. The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the related diagram is presented in Appendix 2 (Moher et al., 2009).

3.2. Characteristics of the included studies

In most of the included studies, IVIG was administered during the IVF cycle, at 400 mg/kg body weight (200–500 mg/kg body weight) (Moraru et al., 2012a; Ramos-Medina et al., 2014, Ahmadi et al. 2017b) or dosage of 0.2 g/kg at least once(Heilmann et al., 2010a). The first dose was given 7 day-24 h before ET and it was continued for a variable length of time (as soon as fetal pulse detection, day 15, every 3 weeks during pregnancy, etc.).

A group of RIF women with the same history as the IVIG group, who did not receive any IVIG, was considered as the control group in each study. In some researches, there was also heparin and aspirin therapy for the IVIG group, and the control group also received heparin and aspirin without IVIG. Characteristics of the included studies are illustrated in Appendix 3.

All of the selected studies included the evaluation of immunological parameters in the participants. Various parameters were assessed in each study, which is summarized in Appendix 4.

3.3. Methodological quality

Articles which met our inclusion criteria were evaluated with JBI checklists critical appraisal tools. Critical appraisal of the results of eligible cohort, cross-sectional and quasi-experimental studies are illustrated in Appendix 5, 6 and 7, respectively.

4. Main results

4.1. Pregnancy rate

Analysis of the two cohort studies included in our meta-analysis showed that there was a significant difference in the pregnancy rate between the IVIG group and the control group (OR = 1.82, 95% CI = 1.14–2.89, $P = 0.01$) (Fig. 1). Analysis of two cross-sectional studies also showed the same results in which pregnancy was increased significantly in the IVIG group (OR = 11.12, 95% CI = 6.43–19.23, $P < 0.00001$) (Fig. 2). The heterogeneity of studies also was assessed by RevMan 5.2 software, which indicated $I^2 = 93\%$ and 90% of heterogeneity among the studies in the cohort and cross-sectional articles, respectively (Figs. 2 and 3).

The quasi-experimental study of Ahmadi et al., which were not included in our meta-analysis, was about RIF women with immunological abnormalities, including abnormal preconception Th1/Th2 ratio, and NK cells frequency and activity, which were treated with IVIG. At the end of the study, the results indicated that the pregnancy rate was improved in the IVIG group (60%) comparing to the control group (31.2%) (Ahmadi et al., 2017a).

4.2. Live birth rate

Analysis of cohort studies indicated that the IVIG group, when compared to the control group, showed a significantly higher rate of live birth rate (OR = 2.17, 95% CI = 1.30–3.61, $P = 0.003$), and there was 90% of heterogeneity between the two studies ($I^2 = 90\%$), (Fig. 3). In the other side, analysis of cross-sectional studies also confirmed the same results, the live birth was significantly increased in IVIG group (OR = 7.57 95% CI = 4.53–12.64, $P < 0.00001$) with the heterogeneity of 87% (Fig. 4). In case of the study, which did not enter into the meta-analysis, the study of Ahmadi et al. showed 47.5% live birth rate among RIF women who received IVIG, while the live birth rate of the control group was 21.8% (Ahmadi et al., 2017a).

4.3. Miscarriage rate

Among the studies which reported miscarriage rate, the cohort studies were included in the meta-analysis and the results showed that there was no statistically significant difference in the miscarriage rate of IVIG and control group (Appendix 8).

The study of Heilmann and colleagues also investigated the miscarriage rate and the results indicated that the miscarriage rate of the IVIG group was 16.8% while it was higher (38.5%) in the control group. (Heilmann et al., 2010b).

4.4. Implantation rate

Implantation was evaluated only in the study of Heilmann et al, which demonstrated that implantation rate was higher in RIF patients who received IVIG (21%), comparing to control group (9.3%) (Heilmann et al., 2010a).

5. Discussion

In this systematic review, we evaluated the studies in which IVIG was prescribed for RIF women in order to improve the pregnancy and live birth, especially in patients with various immunological abnormalities, mostly NK cells expansion, whose immune system is not able to tolerate the embryo or fetus as a semi-allograft. According to the literature, abnormalities of various immune parameters may be risk factors or in few cases be causally related to RIF, including expansion of NK cells proportion and function (Thum et al., 2004), increased balance of Th1/Th2 ratio by a shift toward Th1 cells (Kwak-Kim et al., 2003), down-regulation of regulatory T cells proportion, function and cytokine secretion (Kwak-Kim et al., 2014; Ali et al., 2018). These findings highlight the importance of immunologic parameters evaluation before IVIG prescribing, in order to increase the positive effect of the treatment. In a recent study by Han and Lee, it is indicated that evaluation of NK cells proportion in RIF patients is in evidence level B (no RCT and based on case-controlled studies) for receiving IVIG therapy. This study recommended IVIG therapy for reproductive failure cases with abnormal cellular immunologic parameters, including elevated frequency

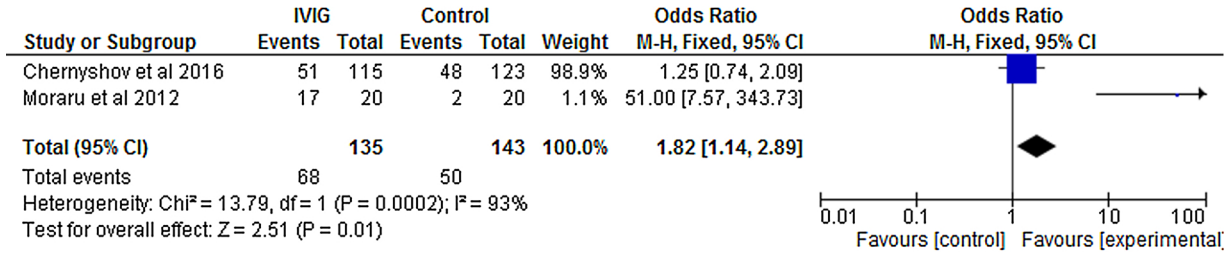

Fig. 1. Forrest plot of pregnancy outcome in cohort studies.
Abbreviation: IVIG: intravenous immunoglobulin; CI: confidence interval.

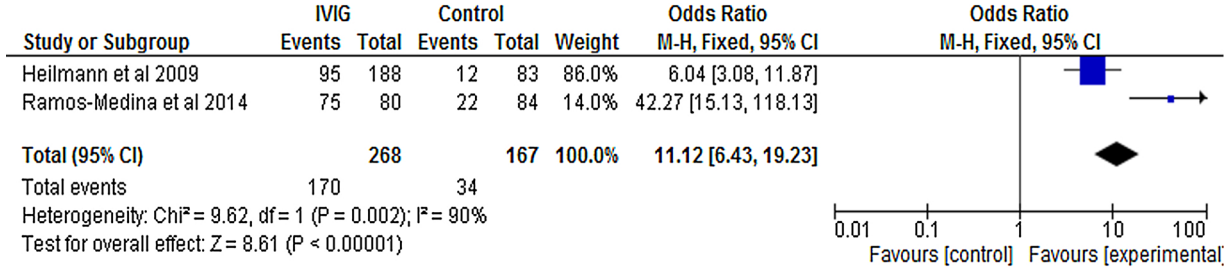

Fig. 2. Forrest plot of pregnancy outcome in cross-sectional studies.
Abbreviation: IVIG: intravenous immunoglobulin; CI: confidence interval.

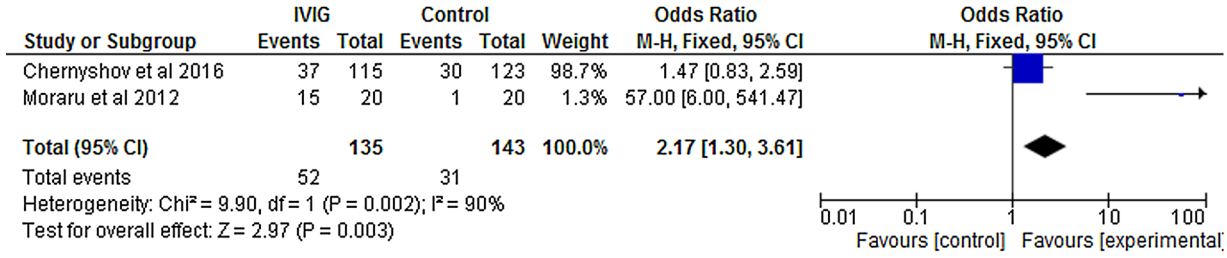

Fig. 3. Forrest plot of Live birth outcome in cohort studies.
Abbreviation: IVIG: intravenous immunoglobulin; CI: confidence interval.

and cytotoxicity of NK or increased Th1/Th2 ratio (Han and Lee, 2018).

A search of PROSPERO and the Cochrane Database of Systematic Reviews was conducted, and no current or underway systematic reviews on the topic were identified. Almost all of the included studies reported a positive effect of the IVIG therapy in RIF patients, including higher pregnancy and live birth rate, and lower implantation failure or miscarriage. In the current study, we also updated the previous systematic review and meta-analysis.

Two cohorts, two cross-sectional and one quasi-experimental studies were included in our assessment; the limitation of this study is that in the included studies in the meta-analysis, patients received placebo or no IVIG in the control groups for economic reasons, concerns of safety or obscure reasons.

Chernyshov ; et al. cohort study evaluated the RIF patient's responsiveness to IVIG in the subgroups of none, one, two, three or more immunologic abnormalities, in which the results indicated that patients with higher immunologic abnormalities would benefit more from IVIG therapy, in comparison to the patients with one or two immune deviations. Immune deviation was described as elevated number and cytotoxicity of NK cells alongside the increased or decreased expression of CD158a and CD8 in these cells, increased expression of CD56, CD158a in T lymphocytes and decreased levels of CD4 T lymphocytes, upregulated expression of HLA DR in CD8 + T cells and NK cells in this study. (Chernyshov et al., 2016). The same result was observed in the studies of Moraru et al, Ahmadi et al, Heilmann et al and Ramos Medina et al., in which IVIG was administrated in RIF women who had elevated NK cell numbers.

The modulatory effect of the IVIG is promising in improving the various immunological abnormalities through different mechanisms. Participant selection for the IVIG therapy, according to the

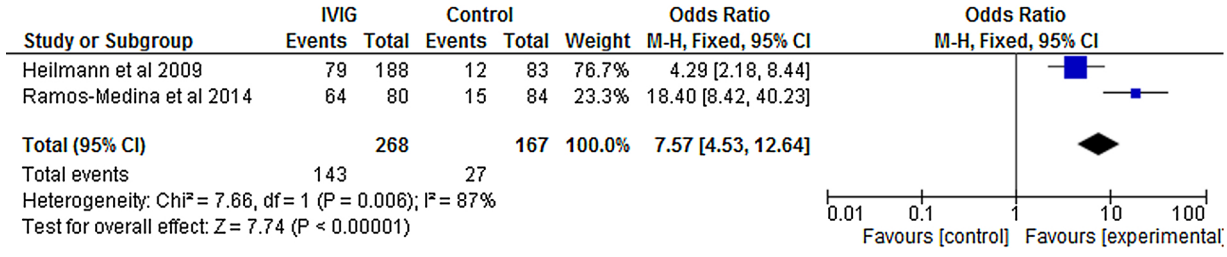

Fig. 4. Forrest plot of Live birth outcome in cross-sectional studies.
Abbreviation: IVIG: intravenous immunoglobulin; CI: confidence interval.

immunological disturbance, resulted in better pregnancy outcome. Another abnormalities, including increased Th1, Th17 cells number and cytokine secretion, and decreased number of Th2 and Treg cell, have also been mentioned in various articles as the problematic issues in the process of implantation or pregnancy, which have been settled by the IVIG therapy (Han and Lee, 2018).

The cohort study of Moraru and colleagues in 2012 showed 85% successful pregnancy and 75% live birth rate in the IVIG treated group, which supported the IVIG effect as a promising therapeutic agent in improving the success rate of pregnancy in RIF women with an increased NK ($CD3^-CD56^+/CD16^+$) and NKT-like cell ($CD3^+CD56^+/CD16^+$) activity (Moraru et al., 2012b). Elevated NK cell frequency and cytotoxicity were also considered as the key factors of implantation failure in the study by Ahmadi et al., besides an elevated Th1/Th2 ratio; patients in both the IVIG and control groups also received heparin and aspirin in order to diminish the effect of coagulatory parameters and inflammatory responses on the implantation process (Ahmadi et al., 2017a). Heparin and aspirin therapies, in addition to IVIG, were also conducted in the study of Ramos-Medina et al., in RIF women with an expansion of blood NK cells ($CD3^-CD56^+CD16^+$, $CD3^-CD56^+CD16^-$ lymphocytes) as proportions above 12% of total lymphocytes and an elevated NKT-like cells ($CD3^+CD56^+$) as proportions above 10% of total lymphocytes; this is due to a placental vessel alteration following the NK cells expansion and also anti-phospholipid syndrome, which are improved by aspirin and heparin therapies, which are required in case of RIF women, who have high risk of prothrombotic or cardiovascular problems (Ramos-Medina et al., 2014). Finally, all of the five included studies, unanimously confirmed that IVIG is a beneficial and safe therapeutic strategy in cases with positive clinical outcomes, especially in RIF patients with an immunologic basis, and it may cause a shift toward a favorable immune response.

A randomized controlled trial (RCT) study by Stephenson et al. was conducted about RIF women who received IVIG without pre-treatment immunological parameters evaluation, which is why we excluded this article. The results indicated that IVIG is not able to improve the implantation, pregnancy and live birth rate in patients (Stephenson and Fluker, 2000). Considering the results of our systematic review, unfavorable results of this study may be probably due to ignoring the etiology of the IVF failure in the included patients and it highlights the importance of immunologic disturbance evaluation, in patients and treatment approaches selection in order to get better results.

In line with our study, previous meta-analysis and systematic review studies of Clarck et al. (2006) and Li ; et al.; (2013) about IVIG therapy in RIF women, also indicated the same results, supporting the positive effect of the IVIG therapy in these patients. In the Clarck et al. study, a meta-analysis of 3 published RCTs about the effect of IVIG in early pregnancy and IVF failure demonstrated that IVIG was able to significantly increase the live birth rate per woman. It was estimated that the patient's selection according to the abnormal immune results is among the variables that affect the results of the IVIG therapy (Clark et al., 2006). In the systematic review and meta-analysis of Li et al., 10 case-control studies, comparing IVIG therapy with placebo in IVF/Intracytoplasmic sperm injection (ICSI) and/or unexplained infertility women were included. The results demonstrated that IVIG was a helpful option for improving the implantation, pregnancy, and live birth in RIF patients, alongside with decreasing the miscarriage (Li et al., 2013). Similarly, our meta-analysis results showed that there was a significant difference in the pregnancy and live birth rate in the IVIG group when compared to the control group, and the success rate was higher in the IVIG group.

Lack of enough investigations about the effect of IVIG treatment in RIF women with immunologic disturbance, limits the number of included studies and conclusion, and highlights the need for more related studies with a larger treatment and control group in order to get more specific results. Also more specific future studies are needed to indicate which immunologic parameters evaluation is more helpful for right selection of patients for treatment. Also in new controlled trials, control groups receiving placebo or no IVIG must be selected by random allocation and not obscures reasons.

6. Conclusions

The findings of this study suggest that IVIG may be a helpful agent in improving the implantation and pregnancy outcome in RIF women, especially those with immunological disturbance. However, for final conclusions on the efficiency of the treatment, more studies especially RCTs are suggested to evaluate the effect of patient's selection for IVIG treatment based on all kinds of immunologic disturbance involved in implantation and pregnancy failure. Moreover, conjugated treatment protocols, including IVIG with anti-tumor necrosis factor (TNF) agents like Humira (Adalimumab) are recommended to be investigated in further studies.

Declaration of Competing Interest

The authors declare no conflict of interest.

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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.2019.07.006.

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