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REVIEW

The effect of intravenous immunoglobulin passive immunotherapy on unexplained recurrent spontaneous abortion: a meta-analysis

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Abstract The aim of this study was to investigate the effect of passive immunotherapy using intravenous immunoglobulin (IVIG) on unexplained recurrent spontaneous abortion (RSA). Live birth rates were analysed and binary data were calculated using risk ratio and 95% confidence interval. Meta-analysis of 11 studies showed that the difference in the live birth rate between the IVIG treatment and placebo groups was on the margin of significance (RR = 1.25, 95% CI 1.00 to 1.56, $P = 0.05$). Both cumulative and trial sequential meta-analyses indicated potential beneficial effect of IVIG but the evidence was inconclusive. Subgroup analysis showed that the live birth rate in primary (RR = 0.88, 95% CI 0.71 to 1.07) and secondary (RR = 1.26, 95% CI 0.99 to 1.61) RSA patients was not significantly different between the IVIG and placebo groups. Live birth rate was significantly different when IVIG was administered before conception (RR = 1.67, 95% CI 1.30 to 2.14, $P < 0.0001$) but not after implantation (RR = 1.10, 95% CI 0.93 to 1.29). Evidence is insufficient to support the beneficial effects of IVIG on an unexplained RSA. Further high quality studies are needed to elucidate the effectiveness of IVIG.

KEYWORDS: IVIG, meta-analysis, primary RSA, randomized controlled trial, recurrent spontaneous abortion, secondary RSA

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Introduction

Recurrent spontaneous abortion (RSA) is defined as two or more spontaneous abortions (with the same partner) before 20th gestational week of pregnancy or loss of pregnancy when fetal weight is less than 500 g. It is further categorized into primary RSA and secondary RSA. Primary RSA refers to a series of spontaneous abortions without a previous live birth; and secondary RSA refers to a series of spontaneous abortions ensuing a live birth or stillbirth. Between 1 and 5% of all women are affected by RSA during childbearing years (Kuon et al., 2012). The risk of subsequent spontaneous abortion in women who have experienced RSA also increases with the number of previous spontaneous abortions. This risk can reach as high as 50% after two pregnancy losses. Clinically, it is crucial to prevent RSA by certain interventions when possible (Xiao and Zhao, 2014). Various factors contribute to the occurrence of RSA, including chromosome abnormalities, genital anatomic abnormality, endocrine disturbances, autoimmune disturbance, infectious disease and pro-thrombophilic status. Some patients, however, experience unexplained RSA, which may be related to alloimmunity (Cohen and Bischof, 2007), including elevated compatibility in human leukocyte antigen (HLA), phenotypic changes in immune cell subsets, Th1/Th2 cytokine imbalance, and deficiencies in generation of blocking (protective) antibodies (Lin, 2003).

Immunological disturbances were reported to play an important role in RSA. High levels of natural killer cell subsets, autoantibodies and inflammatory cytokines were found in the peripheral blood of patients who had experienced RSA. Activated leukocyte and certain specific natural killer cells that were beyond normal level were also found in the decidua of these patients (Hill et al., 1995; Kruse et al., 2004; Quack et al., 2001; Xu et al., 1990). Further evidence indicated that secondary RSA showed worse immune rejection than that of primary RSA, particularly in immunological disturbances of white blood cell heterogeneity. Additionally, gene expressions of *HLA-DR3* and *HLA-G* were higher in secondary RSA compared with primary RSA and control groups (Christiansen et al., 2012). A previous study also showed that the risk of RSA was higher in those with a firstborn boy compared with a firstborn girl, owing to the reaction of male-specific (H-Y) antigens to the immune system (Nielsen et al., 2010).

In the late 1980s, passive immunization with intravenous immunoglobulin (IVIG) was used to treat RSA, and was reported to have beneficial effects. The underlying mechanism might be associated with neutralization of autoantibodies in the circulatory system, inhibition of natural killer cell, attenuation of complement-mediated cytotoxicity and release of regulatory T lymphocytes (Schwab and Nimmerjahn, 2013). Today, unexplained RSA is commonly treated off-label with IVIG in a clinical setting (Hutton et al., 2007). Immunoglobulin is extracted from normal blood donors, and therefore might pose some potential risks to receivers including allergies and infectious diseases, such as HIV, hepatitis and prions. Although, IVIG is generally well tolerated, common adverse reactions (headaches, myalgia, fevers, chills, dizziness, nausea, and vomiting) occur in less than 5% of the patients. In addition, IVIG therapy does not increase the risk of premature birth (Schwab and Nimmerjahn, 2013).

The effectiveness of IVIG treatment on unexplained RSA has been controversial. Coulam et al. (1995) and Christiansen et al. (1995) both suggested that passive immunization with IVIG improved or showed trend of improving the live birth rate in women who had experienced RSA women relative to treatment with placebo. Randomized controlled trials also demonstrated otherwise (Christiansen et al., 2002; Group, 1994; Jablonowska et al., 1999; Perino et al., 1997; Stephenson et al., 1998, 2010). Recently, diverging results suggest that, although the effect of IVIG treatment observed in patients with primary RSA is not beneficial, women with secondary RSA have a higher live birth rate (Christiansen, 2014; Christiansen and Nielsen, 2005; Christiansen et al., 1995, 2002; Hutton et al., 2007; Stephenson et al., 1998). These observations, however, need to be confirmed, as each study was limited by the relatively low number of participants.

Therefore, our present study aimed to review the currently available randomized controlled trials to determine the effectiveness of IVIG in improving the chance of live birth in unexplained RSA patients, which included studies on the Chinese population, and to further identify the efficacy of IVIG in different subgroups.

Materials and methods

Inclusion criteria and participants

Primary RSA is defined as two or more spontaneous abortions occuring before the 20th gestational week of pregnancy without a history of live birth. Secondary RSA is defined as three or more spontaneous abortions occuring before the 20th gestational week of pregnancy subsequent to a live birth or stillbirth. Women at any age who have the following conditions were excluded: chromosomal abnormality in either couple, chromosomal abnormality in abortion specimen, abnormality in family genetic histories, maternal reproductive tract abnormalities, uterine malformations, maternal endocrine abnormalities, acquired or inherited thrombophilia, environmental factors and other unexplained recurrent abortions.

Intervention

The treatment group received IVIG before pregnancy or during the first trimester of pregnancy. The control group received a placebo.

Studies outcomes

The primary outcomes are the live birth rates, the number of achieved pregnancies and the number of live births.

Types of studies

Studies were selected from both Chinese and English languages. Publications with randomized, randomized-controlled,

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