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Advances of intravenous immunoglobulin G in modulation of anti-fetal immunity in selected at-risk populations: science and therapeutics

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Recurrent miscarriage (RM) is the occurrence of three or more consecutive miscarriages before gestational week 20 and is a condition that affects 1–3% of women [1]. RM can be classified into two categories: primary RM (no prior live birth) or secondary RM (three or more consecutive miscarriages following a live birth). In addition to genetic and anatomical factors causing RM, many studies have suggested that signs of autoimmunity and dysregulation of natural killer (NK) cell immunity characterize women with RM.

Approximately 25 years ago, the first pilot studies on the use of intravenous immunoglobulin (IVIg) for the treatment of RM were conducted and reported a live birth rate of 80–82% [2,3], which provided support to warrant further investigation in placebo-controlled trials. In 2006, a Cochrane review of IVIg treatment for RM in eight placebo-controlled trials with 303 RM patients was conducted, concluding that IVIg did not increase live birth rates when compared to placebo [odds ratio (OR) = 0·98; 95% confidence interval (CI) = 0·61–1·58] [4]. However, this review did not differentiate between primary and secondary RM patients. Separate analysis of these two subsets of RM patients may be necessary, as several studies have observed that secondary RM is a condition dominated by immunological risk factors when compared to primary RM, suggesting large heterogeneity between these two subgroups.

Tumour necrosis factor (TNF)-α is a cytokine involved in the immune system's inflammatory response. Piosik *et al.* analysed peripheral blood samples of RM patients taken at gestational week 5, and found that TNF-α levels were increased significantly in secondary RM patients compared to primary RM patients ($P = 0·042$) [1]. This indicates that secondary RM is a condition with an increased proinflammatory response in early pregnancy.

More evidence of the role of immunological factors in secondary RM has been reported in studies that have shown associations between secondary RM patients with specific maternal human leucocyte antigen (HLA) polymorphisms. Kruse *et al.* found that there was a significantly higher prevalence of the HLA-DRB1*03 allele in secondary RM patients compared with controls (OR = 1·8; 95% CI = 1·3–2·5) [5], whereas the allele was not increased in patients with primary RM. A previous pregnancy with a boy can be a risk factor for secondary RM. In general, maternal immune recognition of male-specific minor histocompatibility (HY) antigens expressed in male fetal and trophoblast cells is well tolerated, resulting in a live birth. However, pregnancy with a boy may prime the mother's HY immunity. Nielsen *et al.* found that maternal carriage of HLA class II alleles that restrict anti-HY antigen responses reduces the chances of a live birth in secondary RM patients with a firstborn boy compared with a firstborn girl (OR = 0·17; 95% CI = 0·1–0·4; $P = 0·0001$) [6]. In another study, the prevalence of a 14 base pair insertion in exon 8 of the HLA-G gene was found to be increased significantly in secondary RM patients, compared with controls. These studies provide evidence that particular HLA polymorphisms characterize secondary RM [5–7].

Huge heterogeneity between eight randomized placebo-controlled trials of IVIg to patients with RM has been observed, with live birth rates in placebo groups ranging from 29 to 79% [8–15]. The differences in live birth rates observed between these studies raises questions as to whether the patient categories are the same.

Differences in IVIg treatment response in patients further supports the notion that primary and secondary RM patients should be investigated separately. Hutton *et al.*, in a meta-analysis of placebo-controlled trials of IVIg in RM, found that the OR of achieving a live birth in primary and secondary RM was 0·66 and 2·71, respectively, suggesting that IVIg may be effective in secondary RM patients, but not primary RM patients [16]. A recent meta-analysis of five placebo-controlled studies (Christiansen *et al.*, unpublished data) found that the OR for an unsuccessful pregnancy in secondary RM patients was 0·74

(95% CI = 0·53–1·03, $P = 0·07$), suggesting that IVIg may be beneficial for this patient subset.

Currently, the efficacy of IVIg treatment in RM has not been determined conclusively. However, evaluation of randomized control trials indicates that IVIg may be a promising treatment for secondary RM. Previously conducted studies have been small and heterogeneous. Furthermore, the borderline significance observed in our meta-analysis indicates that further studies should be conducted to determine the efficacy of IVIg treatment in secondary RM.

In addition to the heterogeneity observed in the patient population studied, IVIg treatment doses and intervals also varied in different studies, from 20 g every 3 weeks to 55 g every week [10–12,15]. Furthermore, treatment initiation varied between studies, with several trials beginning after gestational week 6/7, when most of the 'risk time' had elapsed. The trials were also very heterogeneous with regard to the intensity of treatment; in some trials only two infusions of 20 g were given in the first trimester, whereas in other trials seven infusions of 55 g IVIg were administered, which may partly explain the very different results [10,12]. Larger randomized controlled trials are needed to provide more definitive conclusions on the efficacy of IVIg treatment.

The largest double-blind, randomized, placebo-controlled trial of IVIg (Privigen®) in 82 women with secondary RM conducted over a period of 5 years will be published in 2014. Results of this trial and a forthcoming meta-analysis of all relevant trials will provide more information on whether or not IVIg is efficacious in RM. The meta-analysis may identify clinical subgroups that benefit the most from IVIg treatment.

The inclusion criteria for this study were as follows: ≥ 4 confirmed early miscarriages, at least three consecutive after a birth and ≥ 3 miscarriages with present partner. Following a positive pregnancy test, serum human chorionic gonadotrophin (s-HCG) was measured twice in 2 days. Treatment with either IVIg or placebo was initiated if s-HCG increased by at least 30%. IVIg treatment doses were simplified to either a high or low dose according to pre-pregnancy weight. Similar doses of 5% human albumin were used in the placebo group.

Studies have shown that pregnant and non-pregnant RM patients may have elevated levels of NK cells [17,18]. Furthermore, there have been a number of studies showing that NK cells, such as $CD56^+$, decline in RM patients treated with IVIg [17–22]. Heilmann *et al.* conducted a study that showed a correlation between the decline in NK cells and pregnancy outcomes. The results of this study found that the number of NK cells ($CD3^-$, $CD56^+$ and $CD16^+$) declined in women who gave birth after IVIg treatment [23]. In the future, identifying immune biomarkers that characterize RM patients who may benefit from IVIg therapy is worth investigating.

There is evidence from placebo-controlled trials to suggest that IVIg improves pregnancy outcomes in secondary RM. However, large heterogeneity in patient populations and dosing regimens has been observed in previously conducted trials in RM. Therefore, our study will hopefully provide decisive data on the efficacy of IVIg treatment in secondary RM.

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Disclosures

O. B. C. has no conflicts of interest to disclose.

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