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REVIEW ARTICLE

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Immune modulation of i.v. immunoglobulin in women with reproductive failure

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Abstract

Background: The mechanism of maternal immune tolerance of the semi-allogenic fetus has been explored extensively. The immune reaction to defend from invasion by pathogenic microorganisms should be maintained during pregnancy. An imbalance between the immune tolerance to the fetus and immune activation to the pathogenic organisms is associated with poor pregnancy outcomes. This emphasizes that the immune mechanism of successful reproduction is not just immune suppression, but adequate immune modulation.

Methods: In this review, the action of i.v. immunoglobulin G (IVIg) on the immune system and its efficacy in reproductive failure (RF) was summarized. Also suggested is the indication of IVIg therapy for women with RF.

Main findings (Results): Based on the mechanism of the immune regulation of IVIg and following confirmation of the immune modulation effects of it in various aberrant immune parameters in patients with RF, it is obvious that IVIg is effective in recurrent pregnancy losses and repeated implantation failures with immunologic disturbances.

Conclusion: The authors recommend IVIg therapy in patients with RF with aberrant cellular immunologic parameters, including a high natural killer cell proportion and its cytotoxicity or elevated T helper 1 to T helper 2 ratio, based on each clinic's cut-off values. Further clinical studies about the safety of IVIg in the fetus and its efficacy in other immunologic abnormalities of RF are needed.

KEYWORDS

immune regulation, immunoglobulin, implantation failure, recurrent pregnancy loss, reproductive failure

1 | INTRODUCTION

Human reproduction is a relatively inefficient process. Maximal fecundity is 25%-30% and only 50%-60% of all conceptions advance beyond 20 weeks of gestation.[1] Although the fetus survives through the third trimester, there were 2.6 million stillbirths globally in 2015 and 5%-18% of live births are preterm births that are accompanied by the possibility of neonatal death across the world.[2] In spite of the remarkable development of medicine, a significant portion of pathogenesis of these reproductive failures (RFs) is still unknown. There is growing evidence that both maternal immune tolerance toward the fetus and adequate immune activation against pathogenic microorganisms are essential for a successful pregnancy.[3]

The preparation of i.v. immunoglobulin (IVIg) comes from the pooled plasma of several thousands of healthy donors and contains broad range of antibodies against foreign antigens, including pathogens

and self-antigens.[4] It consists of >95% of immunoglobulin G (IgG) and a few of immunoglobulin M, immunoglobulin A (IgA), several proteins, and albumin. After the first demonstration of the effectiveness of IVIg in immune thrombocytopenia purpura (ITP) in 1981,[5] it has been used widely in autoimmune and inflammatory diseases, such as ITP, Guillain-Barré syndrome, myasthenia gravis, corticosteroid-resistant dermatomyositis, Kawasaki's disease, graft-versus-host disease, and autoimmune uveitis.[6] Although the exact mechanisms of IVIg action have not been understood completely, intriguingly, IVIg not only has an anti-inflammatory effect, but also a pro-inflammatory effect. Sometimes, it acts like an adaptor to innate immunity; IgGs bound to their specific antigens and promoting the humoral and cellular immune response of the innate immune system via activation of the complements and binding to Fcγ receptors (FcγRs) on various immune cells. On the contrary, IVIg regulates pathogenic autoimmunity in animal models, such as K/BxN arthritis, nephrotoxic nephritis, and skin-blister diseases.[7] Thus, IVIg has drawn attention as an immune modulator for various immune disturbances and this review focuses on the immune regulatory effect of IVIg in RF.

2 | IMMUNE MODULATION OF I.V. IMMUNOGLOBULIN G

The exact mechanisms of IVIg action are not completely understood, but the immune modulation of IVIg is likely to be mediated via F(ab')2-dependent, fragment crystallizable (Fc)-dependent, and unknown portion-dependent pathways. Through these pathways, IVIg modulates the function of antigen-presenting cells (APCs) and phagocytic cells, expands regulatory T (T_{reg}) cells, suppresses effector lymphocytes, inhibits the differentiation of B cells, induces cell apoptosis, and neutralizes complements, cytokines, and autoantibodies (Figure 1).[4]

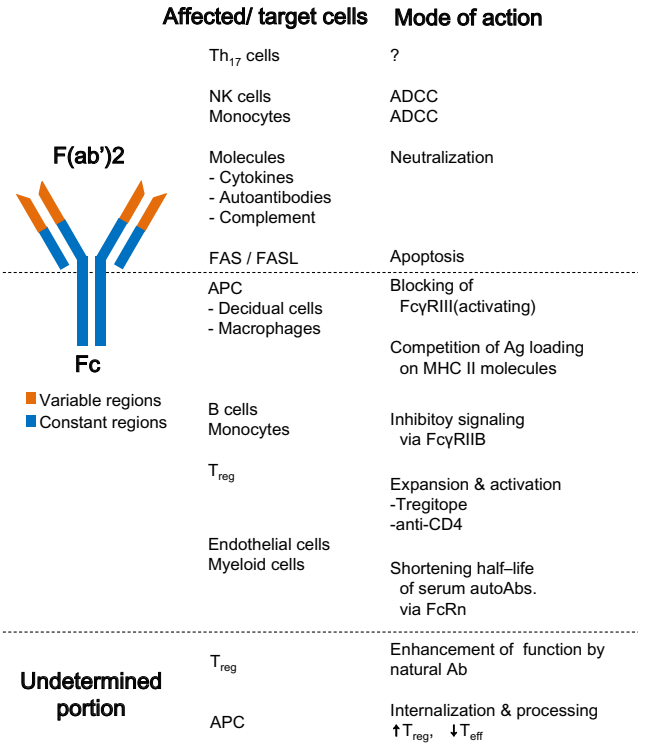

FIGURE 1 Intravenous immunoglobulin G (IVIg)-mediated immune modulation, which is likely to be mediated via F(ab')2-dependent, Fc-dependent, and unknown portion-dependent pathways. Through these pathways, IVIg modulates the function of antigen-presenting cells (APCs) and phagocytic cells, expands regulatory T cells, suppresses effector lymphocytes, inhibits the differentiation of B cells, induces cell apoptosis, and neutralizes complements, cytokines, and autoantibodies. Ab, antibody; ADCC, antibody-dependent cell-mediated cytotoxicity; Ag, antigen; $CD4^+$, cluster of differentiation 4; FASL, FAS ligand; FcRN, neonatal fragment crystallizable receptor; MHC, major histocompatibility complex; NK, natural killer; T_{eff}, effector T cell; Th, T-helper; T_{reg}, regulatory T cell

2.1 | Structure of immunoglobulin G and its receptors on immune cells

Immunoglobulin G comprises two identical light chains and two identical heavy chains. Both the light and the heavy chains consist of amino-terminal variable regions that participate in antigen recognition and carboxyl-terminal constant regions. Immunoglobulin G is divided into a F(ab')2 fragment that contains two antigen-binding sites and one Fc fragment.[8] The F(ab')2 fragment is the antigen-binding sites of IgG binding to foreign and self-antigens. Intravenous immunoglobulin G has demonstrated immune modulatory effects via the F(ab')2 fragment in both antigen-specific and antigen-non-specific ways.[7] The Fc fragment binds to its receptors on the immune cells and complements. The immune cells express various Fc receptors (FcR), which could activate or inhibit the immune response, depending on their subtype. In humans, FcγRIA, FcγRIIA, FcγRIIC, FcγRIIIA, and FcγRIIIB activate the immune system, while FcγRIIB suppresses immune reactions (Table 1). Neonatal FcR (FcRn) plays a role in extending the half-life of IgG.[7]

2.2 | Effect of i.v. immunoglobulin G on dendritic cells

Intravenous immunoglobulin G at a physiologic concentration, 12-14 mg/mL of human plasma, suppresses the differentiation and maturation of dendritic cells (DCs) from monocytes.[9] As a result, the expression of major histocompatibility complex (MHC) class II and co-stimulatory molecules, such as CD80 and CD86, decrease on the DC. Intravenous immunoglobulin G down-regulates the lipopolysaccharide (LPS)-induced interleukin (IL)-12 production of DC and up-regulates the production of anti-inflammatory IL-10 and expression of inhibitory FcγRIIB.[10] Both the Fc and F(ab')2 portions of IgG bind to the monocyte-derived DC (mo-DC) surface.[10] Even though the role of the Fc portion in the DC has not been investigated, the F(ab')2 portion has been reported to have anti-inflammatory effects on DCs by the inhibition of LPS-induced phosphorylation of extracellular signal-regulated kinase 1/2 and downstream signaling induced by Toll-like receptor ligation.[11]

TABLE 1 Fc receptors (FcRs) on the immune cells

FcR	IgG binding	Immune response	Main cellular expression
Activating			
FcγRIA (CD64)	High affinity	Activation	DCs, Mϕ, neutrophils, eosinophils
FcγRIIA (CD32a)	Low affinity, immune complex	Activation	Mϕ, neutrophils, eosinophils, B cells, platelets
FcγRIIC (CD32c)			Mϕ, neutrophils, NK cells
FcγRIIIA (CD16a)			$CD8^+$ T and γδ T cells, DCs, Mϕ, NK cells, neutrophils
FcγRIIIB (CD16b)			Neutrophils
Inhibitory			
FcγRIIB (CD32b)	Low affinity, immune complex	Inhibition	T and B cells, DCs, Mϕ, neutrophils, mast cells, platelets, endothelial cells
FcRn	Low pH, intracellular	Extends IgG half-life	Epithelial cells
DC-SIGN	Sialic acid-rich IgG	Anti-inflammatory	DCs, Mϕ, endothelial cells

DC, dendritic cell; DC-SIGN, dendritic cell-specific intracellular adhesion molecule 3-grabbing non-integrin; FcRn, neonatal fragment crystallizable receptor; IgG, immunoglobulin G; Mϕ, macrophage; NK, natural killer.

Several years ago, a new mechanism of immune regulation by IVIg was proposed: the internalization of IVIg into APCs impairs antigen presentation via competition with antigenic molecules and decreases the T cell response.[12] As a result, the total amount of presented antigen on the surface of APCs decreases, but the total amount of MHC class II molecules on the APCs does not.

Dendritic cell-specific intracellular adhesion molecule 3-grabbing non-integrin (DC-SIGN), is a C-type lectin that is expressed on human mo-DCs and macrophages. The DC-SIGN produces pro-inflammatory cytokines by binding to mannose-expressing pathogens, but the anti-inflammatory cytokine, IL-10, binds to fucose-expressing pathogens.[13] Sialylated Fc fragment-binding to the DC-SIGN seems to lead to an anti-inflammatory response via type 2 cytokine production in the humanized DC-SIGN arthritis mice model.[14] Galactosylation and sialylation of the Fc portion seem to be important to the improvement of rheumatoid arthritis.[15]

Immunoglobulin G–antigen immune complexes induce anti-inflammatory effects via activating FcγRIIIB on DCs in autoimmune disease models.[16] In mice models of ITP, the DCs that were primed with IVIg ex vivo could ameliorate ITP as much as IVIg administration to mice. This priming effect of IVIg was not observed in the FcγRIII-deficient DCs.[17] Although how the FcγRIIIB-stimulated DCs can control inflammation is still unclear, a couple of suggestions have been presented. One of them is that regulatory DCs sense IVIg or immune complexes, which could inhibit effector macrophages.[9] The other explanation is that non-specific antibodies (NAbs) in IVIg block FcγRIIIB and prevent the binding of immune complexes, which inhibits DCs' uptake of immune complexes and prevents antigen-presentation of DCs to T cells.[18]

Specific antibodies in IVIg bond to FcγRIIB and result in the inhibition of maturation and function of human DCs. These antibodies seem to act indirectly via soluble mediators that are secreted from regulatory macrophages in vivo because human DCs do not increase FcγRIIB expression following IVIg addition in vitro.[19]

Although IVIg showed inhibitory effects on the differentiation and actions of DCs in most studies, one clinical study in patients with a gammaglobulinemia demonstrated that IVIg administration up to physiologic levels restored the impaired differentiation of monocytes to DCs.[20]

2.3 | Effect of i.v. immunoglobulin G on natural killer cells

Natural killer (NK) cells express FcγRIIIA (CD16a), an activating FcγR, on their surface. Antibody-coated cells activate FcγRIIIA signaling, which induces NK cell cytotoxicity that is called "antibody-dependent cell-mediated cytotoxicity" (ADCC).[8] The expression of this activating FcγRIIIA on NK cells and myeloid cells was down-regulated following IVIg administration in mice and humans.[21,22]

On the contrary, IgG dimers and multimers, but not monomers, in IVIg can make a bridge between FcγRII on NK cells and DCs, which lyses DCs.[23]

2.4 | Effect of i.v. immunoglobulin G on monocytes, macrophages, and B cells

CD95 (Fas)-mediated apoptosis in human T and B cells and monocytes is involved in the therapeutic effects of IVIg,[24] which is likely to block the binding of immune complexes to the activating receptors of mononuclear phagocytic cells. Intravenous immunoglobulin G treatment up-regulated the expression of the inhibitory Fc receptor, FcγRIIB, on macrophages, circulating B cells, and monocytes in many autoimmune animal models.[17,25,26] However, the expression of the interferon-gamma receptor on the $FcγRIIIB^+$ macrophage was suppressed by IVIg.[18]

2.5 | Effect of i.v. immunoglobulin G on T cells

In a study with ITP in children, IVIg brought stable remission by skewing type 1 cytokine-producing T helper cells (Th1)-mediated immunity to type 2 cytokine-producing T helper cells (Th2)-mediated immunity.[27] Intravenous immunoglobulin G inhibits cytokine production and the proliferation of human T cells as effectively as cyclosporine or tacrolimus.[28] However, the action of IVIg on conventional T cells is still unknown.

The fact that i.v. immunoglobulin G binds not only to cluster of differentiation (CD)8$^+$ T cells that express activating FcγRIIIA (CD16a), but also to CD4$^+$ T cells without FcRs suggests that IVIg could function in CD4$^+$ T cells via FcR-independent mechanisms: (i) the modulation of APC function by IVIg contributes to T cell inactivation as discussed above; and (ii) highly purified human T cells without APCs have been controlled by NAbs.[29] The NAbs include autoantibodies against T cell surface signaling molecules, such as CD4$^+$ and T cell receptor (TCR)-β chain,[30,31] and IVIg directly interacted with conventional CD4$^+$ and CD4$^-$ T cells in mice.[32] Intravenous immunoglobulin G induced the apoptosis of human leukocytes, including T and B cells and monocytes, via a Fas-dependent way.[24] Interleukin-2 secretion and the proliferation of T cells were diminished by IVIg via the blockage of CD3 and CD28.[33] The induction of T_{reg} cells by IVIg is likely to be involved in the immune regulation of effector T (T_{eff}) cell function.

2.6 | Effect of i.v. immunoglobulin G on regulatory T cells

There is obvious evidence that IVIg expands T_{reg} cells and strengthens their suppressive function.[32,34] A study demonstrated that the addition of IVIg to a T_{reg} cell culture system significantly increased the expression of forkhead box (Fox)p3, IL-10, and transforming growth factor (TGF)-β and stimulated the suppressive function of the T_{reg} cells in order to inhibit TGF-α.[34] However, the exact mechanism of IVIg on T_{reg} cells is still under investigation. The binding affinity of T_{reg} cells to IVIg is higher than that of conventional T cells,[32] which indicates that the T_{reg} cells might be modulated easily by IVIg. Anti-CD4$^+$ Ab enhances the suppressive function of human CD4$^+$CD25$^+$Foxp3$^+$ T_{reg} cells in a dose-dependent manner.[35] A new hypothesis has been proposed that the NAbs in IVIg might bind to and activate T_{reg} cells via one or more surface molecules not related to FcγR.[36] Two small peptides of the Fc portion, known as "Tregitope," are internalized into the APCs and presented to the T_{reg} cells. Tregitope on MHC class II molecules of the APCs, such as DCs, binds to the TCR of T_{reg} cells and activates them to suppress the T_{eff} cells (Figure 2). In the same study, Th2 immunity in allergic patients turned into Th0 and Th1 immunities following IVIg treatment.[36]

2.7 | Effect of i.v. immunoglobulin G on interleukin-17-producing T-helper 17 cells

The addition of IVIg to a human CD4$^+$ T cell culture system inhibited the differentiation and expansion of Th17 cells.[37] As IVIg does not contain anti-IL-17 antibodies, IVIg's effects on Th17 cells are not related to the neutralization of IL-17. Although the mechanism to control Th17 cells by IVIg is not clear yet, IVIg seems to play a role, both directly and indirectly. The addition of IVIg to CD4$^+$ T cells without APCs directly down-regulated Th17 cell function, including the secretion of inflammatory cytokines, such as IL-17A, IL-17F, IL-22, and CCL20, as well as the phosphorylation of signal transducer and activator of transcription-3 and Rorgamma expression.[38] The F(ab')2 fragment could inhibit the production of IL-17, IL-21, and CCL20 from the Th17 cells, as well as intact IVIg.[38] Some IVIg effects on the Th17 cells might mediate the APCs or T_{reg} cells as IVIg induces tolerogenic DCs and T_{reg} cells.[37]

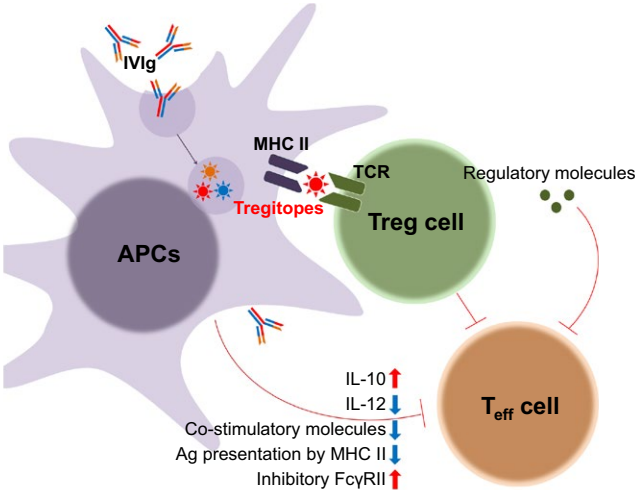

FIGURE 2 Action of i.v. immunoglobulin G (IVIg) through Tregitopes. Two small peptides of the Fc portion, known as the 'Tregitope', are internalized into antigen-presenting cells (APCs) and are presented to regulatory T (T_{reg}) cells. The Tregitope on the major histocompatibility complex (MHC) class II molecules of the APCs, such as dendritic cells (DCs), binds to the T cell receptor (TCR) of the T_{reg} cells and activates the T_{reg} cells to suppress the effector T (T_{eff}) cells. Ag, antigen; IL, interleukin

2.8 | Effect of i.v. immunoglobulin G on the rest of the immune system

Intravenous immunoglobulin G contains IgGs that are reactive to self-antigens, such as cytokines, other antibodies, Fas, CD95 ligand (FasL), T cell-expressed antigens, blood group antigens, gangliosides, B cell-activating factor, a proliferation-inducing ligand, and adhesion molecules.[7] Furthermore, IgG binds to sialic acid-binding immunoglobulin-like lectin (SIGLEC)9, expressed on neutrophils, and SIGLEC8, expressed on eosinophils, which deplete neutrophils and eosinophils, thus contributing to the down-regulation of tissue inflammation.[7] The F(ab')2 fragments in IVIGs also can react to the activated complements, C3a and C5a, and neutralize them so as to not activate immune cells.[7]

Neonatal Fc receptors contribute to extending the half-life of IgG.[39] Neonatal Fc receptors on the cell surface of endothelial or myeloid cells bind to IgG, which is endocytosed into the cells at low pH conditions.[7] Intravenous immunoglobulin G can compete with

pathogenic autoantibodies for binding to FcRn. As a result, this decreased endocytosis of autoantibodies leads to a decreased half-life of autoantibodies and blocks tissue inflammation.[40]

3 | EFFECT OF I.V. IMMUNOGLOBULIN G USE IN REPRODUCTIVE FAILURE

Dysfunctional immune alterations are involved in reproductive failure. The proper differentiation and development of each component of feto–maternal interface is essential for the successful implantation and maintenance of pregnancy. Furthermore, a valid peripheral immune modification in order to accept a semi-allogeneic fetus is critical during pregnancy.[41] Although the precise mechanism of maternal immune modulation during pregnancy is not fully elucidated, the balance of T_{eff} cells, such as Th1, Th2, and Th17 cells, and regulators, including T_{reg} cells and Tr1 cells, is likely to be a key of immune tolerance of pregnancy. Pregnancy-related vascular remodeling and trophoblast invasion are regulated by dNK cells.[42] The dysregulation of these cells and aberrant cytokine production cause unbalanced immune modulation and are responsible for placental dysfunction through the induction of excessive trophoblast apoptosis, shallow trophoblast invasion, and impaired spiral artery remodeling.[43-45] This phenomenon is known to be associated with not only late adverse pregnancy outcomes, such as preeclampsia, but also recurrent pregnancy losses (RPLs) and unexplained infertility. Indeed, some studies have suggested that these series of adverse pregnancy outcomes share a common pathophysiology[46,47] and can be treated together through immunomodulatory agents, such as IVIg.[41,48-50] The clinical safety and effectiveness of IVIg treatment are demonstrated in various immune disorders, such as idiopathic thrombocytopenia, Rh sensitization, and hypogammaglobulinemia.[5,51,52]

3.1 | Effect of i.v. immunoglobulin G in unexplained recurrent pregnancy losses

Although the range of "unexplained RPLs" is not exactly the same in each study, most of the investigators defined it as a RPL without classically proved etiologies, such as genetic, anatomic, infectious, and endocrine factors, or antiphospholipid syndrome (APS). One study insisted that about half of women have unexplained RPLs and a certain part of unexplained RPLs is contributed to by non-APS thrombophilias and immunologic causes.[53] It was first proposed in 1986 that IVIg treatment in 20 patients with unexplained RPLs had promising results[54] and following pilot studies also described favorable pregnancy outcomes with IVIg in women with RPLs.[55,56] Furthermore, it was proven in an abortion-prone mouse model.[57] However, since then, a controlled double-blind study was performed by the same authors that failed to prove the clinical effect of IVIg in women with RPLs[58] and a recent meta-analysis with eight randomized controlled trials (RCTs) showed no significant benefit of IVIg in the pregnancy outcomes of unexplained RPLs.[59] These insights have stimulated attempts to find the right indications for IVIg for RPLs. One study suggested that to find modifiable immunologic abnormalities with IVIg is important for the appropriate use of IVIg for RPLs.[60-62]

3.2 | Effect of i.v. immunoglobulin G in recurrent pregnancy losses and repeated implantation failure with cellular immune abnormalities

Compared to normal fertile control, an elevated NK cell proportion and its cytotoxicity and elevated Th1 and Th17 cytokine production have been reported in women with RPLs and/or repeated implantation failures (RIFs).[63-66] Intravenous immunoglobulin G has shown significant regulatory effects on abnormal NK cell proportions and its cytotoxicity and Th1/Th2 cytokine ratio.[50,67,68] According to a recent study, an elevated Th17/T_{reg} ratio in RPLs also could be regulated with IVIg.[63,69] Based on these results, IVIg was used in patients with RPLs or RIFs with these cellular immune abnormalities and many observational studies reported favorable pregnancy outcomes.[50,67,70-72] The authors' previous study also demonstrated a significantly higher live birth rate using IVIg with women with unexplained RPLs and with cellular immune abnormalities (n = 49), as compared with that of IVIg non-using women with unexplained RPLs and with cellular immune abnormalities (n = 39) who were reported in other studies (81.6% vs 30.8%).[73,74] The authors treated 189 patients with RPLs with or without IVIg, according to their etiologies: known conventional etiologies, thrombophilia, including APS, and cellular immune abnormalities, including the peripheral NK cell proportion and its cytotoxicity, and the Th1/Th2 ratio. The live birth rate of the total 189 patients with RPLs with etiology-based treatment was significantly higher than that of the other's report (n = 1309) without a cellular immunologic test (86.8% vs 65%) (Figure 3).[73,75] In addition, the live birth rate of the women with RPLs with cellular immune abnormalities after IVIg treatment was comparable with that of the women with RPLs without cellular immune abnormalities (84.7% vs 89.7%).[73] Another study in the unexplained infertility of patients with RPLs or RIFs and cellular immune abnormalities showed significantly improved outcomes in the IVIg-using group than the non-using group.[76,77] However, most studies to date are limited, with relatively small study populations, and there is not a large amount of data available about the natural course of RPLs with cellular immune abnormalities yet.

Unexplained infertility, which remains unknown even after a systemic infertility work-up, and RIFs, even after good embryo transfers over three times, have been considered to share a common part of their etiology with RPLs.[41,78-83] Various remedies for RPLs also were tried in unexplained infertility and RIFs and most of them are immune-modulating agents. Intravenous immunoglobulin G also has shown favorable results for RIFs and unexplained infertility with cellular immunologic disturbances.[70,76,77,84]

3.3 | Effect of i.v. immunoglobulin G in recurrent pregnancy losses with antiphospholipid syndrome and other autoimmune diseases

Antiphospholipid syndrome is characterized by antiphospholipid antibodies, such as lupus anticoagulant (LAC), anticardiolipin andibodies,

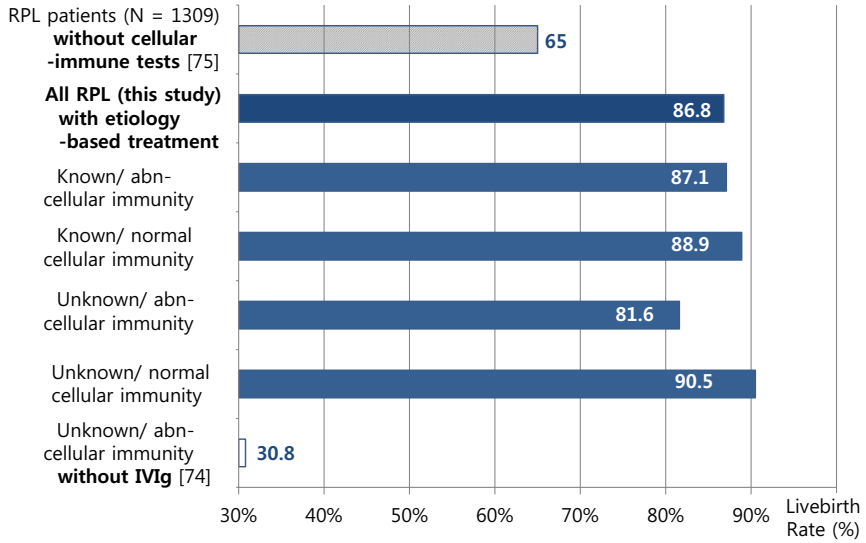

FIGURE 3 Etiology-based treatment outcome with i.v. immunoglobulin G (IVIg) in women with recurrent pregnancy losses (RPLs). In the authors' previous report, 189 patients with RPLs were treated with or without IVIg, according to their etiology: known conventional etiology; thrombophilia, including antiphospholipid syndrome (APS); cellular immune abnormalities, including the peripheral natural killer (NK) cell proportion and its cytotoxicity; and the T-helper 1/T-helper 2 (Th1/Th2) ratio. The live birth rate of the total 189 patients with RPL etiology-based treatment was significantly higher than that of another's report (n = 1309) without a cellular immunologic test (86.8% vs 65%)[75] and another's report (n = 39) without IVIg.[74] abn, abnormal

and/or anti-β2-glycoprotein I antibodies, and causes pregnancy losses or thrombo-embolic events.[85] At first, prednisone was applied to women with pregnancy losses from APS. However, maternal and fetal complications from the corticosteroid lead researchers to find alternative regimens and low-dose aspirin combined with prophylactic-dose heparin has been regarded as the reasonable treatment for RPLs with APS to date.

One study first described the neutralization of LAC through idiotype/antiidiotype interaction and successful pregnancy outcomes after IVIg infusion in a patient with RPL with LAC.[86] Based on this mechanism (neutralization of the autoantibodies), IVIg was tried and resulted in live births, especially in those whom had never gotten a live birth with any other remedy without IVIg.[87-89] Another study described that IVIg can be a possible additional or alternative therapy in patients with refractory APS with other medications, such as heparin and low-dose aspirin, or in women who have side-effects or contraindications to heparin and/or aspirin.[90-92] However, IVIg cannot be a first-line therapy for RPLs with APS.[93,94]

Although numerous efforts have been made, there is no supportive RCT about IVIg that was used in RPLs with autoantibody-mediated autoimmune diseases yet.[70] Recently, one article described a healthy live birth and complete regrowth of the patient's hair by using IVIg in a woman with RPLs with Hashimoto's thyroiditis, which is known as an antithyroid antibody that is mediated by destructive thyroid disease, accompanied by alopecia totalis.[95]

3.4 | Determination of indications for recurrent pregnancy losses in reproductive failure

Natural killer cells and T_{reg} cells play an important role in placental development and maternal immune tolerance. Several aberrant cellular immune alterations, such as a high NK cell proportion in the peripheral blood and its cytotoxicity, and an elevated Th1/Th2 cytokine ratio or Th17/T_{reg} ratio are considered as predictable markers for various RFs. In addition, those parameters can be used to evaluate the efficacy of the immunomodulatory agents.[41] However, the cut-off values for those immunologic parameters for each RF have not been standardized. In terms of the NK cell proportion, several researchers have regarded that the NK cells have to be >12% of the peripheral blood mononuclear cells (PBMCs) as the cut-off for a high NK cell level, which is associated with poor reproductive outcomes, one study defined that >16.4% was necessary, and another one that was done in Australia considered that the abnormal NK cell proportion was >18%.[96-98] Indeed, the measured NK cell proportion is different, depending on the method of measurement, even with the same individual's blood sample. This leads to confusion in the interpretation of the results. Therefore, each clinic needs to set up its own standard for the measurement method and the cut-off value of each immune parameter.

This study's own cut-off values were determined for cellular immune markers with blood samples from 42 patients with unexplained RPLs and 29 fertile controls by using flow cytometry. A NK cell proportion that was >16.1% in PBMCs, NK cell cytotoxicity that was >34.3% at the effector/target cell (E:T) ratio of 50:1, 23.8% at an E:T ratio of 25:1, and 9.6% at an E:T ratio of 12.5:1, as well as a TNF-α and IL-10 cytokine-producing T helper cell ratio (Th1/Th2) that was >36.2 were considered as abnormal cellular immunologic values for RPLs.[99] Intravenous immunoglobulin G has been applied only to women who have abnormal cellular immunologic values according to this standard and relatively good pregnancy outcomes were able to be achieved, with ~85% of a live birth rate in a pregnancy index after IVIg therapy in women with RPLs.[73]

TABLE 2 Korean Society of Reproductive Immunology's guideline of i.v. immunoglobulin G (IVIg) treatment for women with reproductive failure

Indication for IVIg therapy	Validation	Evidence level
For recurrent pregnancy loss:		
Without immunologic work-up	No	A
With cellular immune abnormalities	Yes	A
With autoimmunity	No	C
For antiphospholipid syndrome	No	A
For repeated implantation failure (RIF):		
Without immunologic work-up	No	B
With cellular immune abnormalities	Yes	B
With autoimmunity	No	C
Recommended cellular immune tests		
Peripheral blood NK cell proportion	Yes	B
Peripheral blood NK cell cytotoxicity	Yes	C
Peripheral blood Th1/Th2 cytokine production ratio	Yes	C

NK, natural killer; RIF, Level A, based on a meta-analysis and/or randomized controlled trials (RCTs); Level B, no RCT and based on case-controlled studies; Level C, expert opinion and/or clinical experiences of respected authorities;[94] Th, helper cell.

Although IVIg has been reported as an effective therapy for various patients with RF, there is no consensus or established guideline for the indications and treatment protocol yet. Thus, Korean Society of Reproductive Immunology published a guideline for IVIg practice in patients with RF recently (Table 2).[94] According to the guideline, IVIg treatment is indicated in women with RPLs or RIFs and with cellular immune abnormalities, based on the following tests: (i) peripheral blood NK cell proportion; (ii) its cytotoxicity; and (iii) Th1/Th2 cytokine cell ratio.

3.5 | Safety of i.v. immunoglobulin G in patients with reproductive failure

Anaphylactic reaction immediately after IVIg was reported in IgA-deficient (<7 mg/dL) patients and the sugar stabilizer of IVIg is associated with renal insufficiency after high-dose IVIg treatment.[100-102] Therefore, every patient should have blood tests for their serum IgA level and blood creatinine before IVIg administration. Mild side-effects, such as fever, malaise, myalgia, and headache, have been reported in 4% of patients and most of them were tolerable.[103]

There has been no report of serious adverse effects after the use of IVIg in neonates.[104,105] Antenatal IVIg use for fetal neonatal alloimmune thrombocytopenia was not associated with premature maturation or other unusual reactions of the neonatal immune system.[106] To date, there has been no report with significant side-effects in the mother and the baby in those using IVIg prior to conception and during pregnancy for the last 20 years in this field. However, the number of published studies regarding the safety for the baby after intrapartum IVIg therapy is small.

4 | SUMMARY

Based on the mechanism of immune regulation of IVIg and following confirmation of its immunomodulatory effects in various aberrant immune parameters in patients with RF, it is obvious that IVIg is effective in RPL and RIF with immunologic disturbances. The authors recommend IVIg therapy in patients with RF with aberrant cellular immunologic parameters, including a high NK cell proportion and its cytotoxicity or elevated Th1/Th2 ratio, based on each clinic's cut-off values. Further clinical studies about its safety for the fetus and its efficacy in other immunologic abnormalities of RF are needed.

DISCLOSURES

Conflict of interest: The authors declare no conflict of interest. *Human and Animal Rights*: This article does not contain any study with human and animal participants that was performed by any of the authors.

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