WEB OF SCIENTIST: INTERNATIONAL SCIENTIFIC RESEARCH JOURNAL
ISSN: 2776-0979, Volume 3, Issue 7, July, 2022

INTRAVENOUS IMMUNE GLOBULIN USES IN THE FETUS AND NEONATE: A REVIEW

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Abstract
Intravenous immune globulin (IVIG) is made after processing plasma from healthy donors. It is composed mainly of pooled immunoglobulin and has clinical evidence-based applications in adult and pediatric populations. Recently, several clinical applications have been proposed for managing conditions in the neonatal population, treatment, and prophylaxis for sepsis in high-risk neonates, enterovirus parvovirus and fetal and neonatal immune-induced thrombocytopenia, neonatal hemochromatosis, neonatal Kawasaki disease, and some types of immunodeficiency. The dosing, mechanism of action, effectiveness, side effects, and adverse reactions of IVIG have been relatively well studied in adults but are not well described in the neonatal population. This review aims to provide the most recent evidence and consensus guidelines about the use of IVIG in the fetus and neonate.

Keywords: immunoglobulins; fetus; neonates; sepsis; hemolysis; hyperbilirubinemia; necrotizing enterocolitis; coronavirus.

Introduction

Immunoglobulin therapy is defined as the use of a combination of antibodies obtained from healthy human donors to treat different conditions. The principal components of intravenous immunoglobulin (IVIG) are IgG antibodies, which compromise about 90% of the IVIG. Antibodies are glycoproteins synthesized and secreted by plasma cells (activated B cells) to respond to antigenic stimulation with the primary purpose of a specific immune response to result in different physiological and/or pathological processes. The basic structural unit is primarily formed by two heavy and two light chains. The difference between the heavy chains results in different kinds of antibodies: IgG, IgA, IgM, IgE, and IgD. After synthesis, formed antibodies functions by binding with a specific antigen epitope. This binding subsequently results in

specific actions that ultimately help neutralize and inactivate the pathogenic organisms or trigger a specific immune response (Figure 1).

IVIG clinical applications and indications have expanded rapidly in recent years. Several of these clinical applications have extended to include children, neonates, and fetuses. Although the Food and Drug Administration (FDA) has not yet approved IVIG therapy for use in the neonate, it has been used off-label in the management of challenging and progressing conditions in many fetuses and neonates. The roles that IVIG may play in immunomodulation (inhibition or activation of the immune response, modulation of FcgR expression on B cells, inducing phagocytosis or direct cytotoxicity, regulating apoptosis, modulation of antigen-presenting cells) were the driving factors to study the use of IVIG in this population subset.

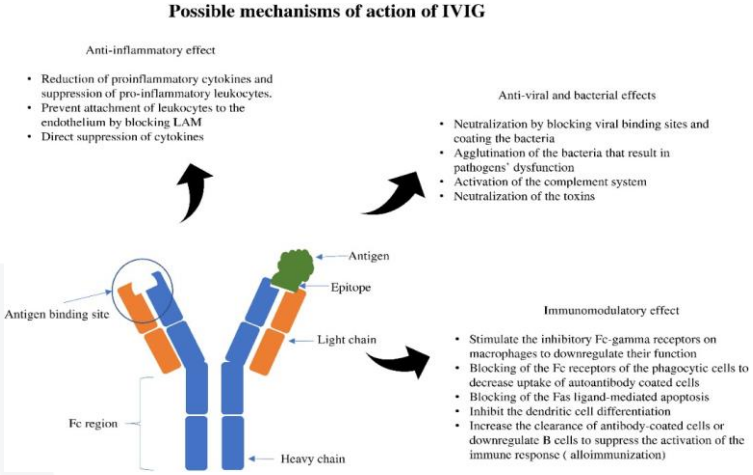


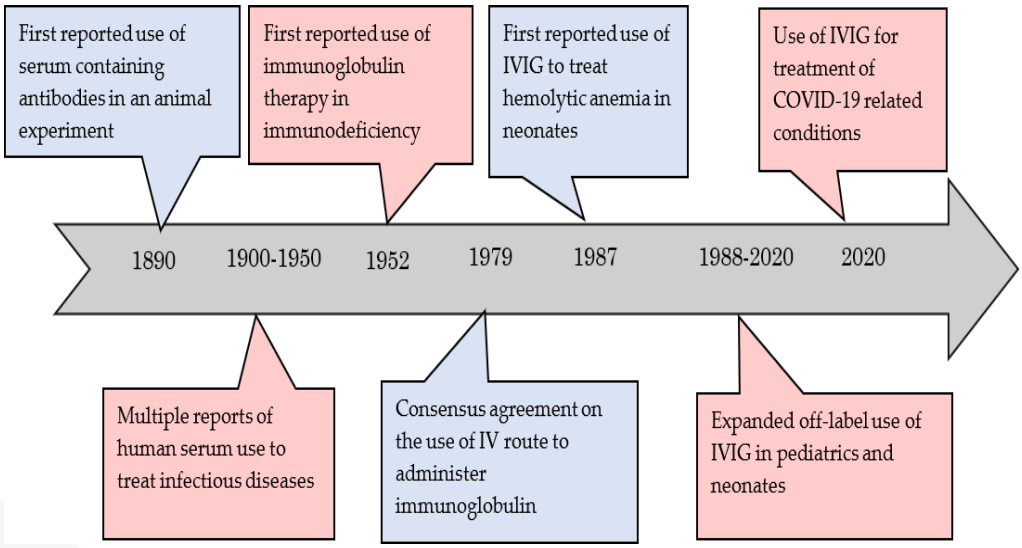
Figure 1. Antigen-antibody binding and specific effects. LAM; leukocyte adhesion molecule.

The use of human serum in the scientific field has been reported as early as the 19th century. Before the mid-20th century, most IVIG uses revolved around the management of infectious diseases. The use of immunoglobulin isolated from the human serum in non-infectious conditions was first reported in 1952. International collaborations were organized to investigate the use of immunoglobulins further. These collaborations' main goals were to standardize the treatment dose, efficacy, indications, and route of administration.

Expanded efforts suggested using the intravenous formulation in the management of specific conditions in the non-adult population. The first use of IVIG in neonates was reported in 1987 by Hara et al., who used IVIG to treat an infant with hemolytic anemia due to Rh incompatibility. Since that time, clinical use and application in neonates and fetuses have increased significantly, and investigators have attempted to search for the best evidence for use, safety, and adverse effects. Recently, tremendous effort has been placed on the role of IVIG therapy to treat complications

related to Coronavirus-19 viral infection in adults as well as the pediatric and neonatal population. A snapshot of important events in immunoglobulin therapy history is shown in Figure 2.

Figure 2. Timeline showing the important historical events in the process of



immunoglobulin discovery, synthesis, and clinical applications. IVIG: Intravenous immunoglobulin.

Despite the strong evidence and the clear indications for using IVIG in adults and its clinical applications in the pediatric population, the evidence is less clear regarding neonates. A summarized list of suggested clinical indications for IVIG use in the neonatal population is shown in Table 1. As this research area has been active for the past 40 years, this review highlights the practical aspects and the most recent evidence about IVIG use in the fetal and neonatal population.

Table 1. Suggested Clinical Indications of IVIG Use in Fetuses and Neonates.
Alloimmune hemolytic disease of the newborn
Fetal and Neonatal immune-mediated thrombocytopenia (FNAIT and ITP) Neonatal infections:
Sepsis treatment and prophylaxis Enterovirus infection
Parvovirus infection
COVID-19 related neonatal disease Congenital CMV
Neonatal hemochromatosis (GALD) Primary immunodeficiency
Neonatal Kawasaki disease
Neonatal lupus
Clinical Use in Fetuses and Neonates
Clinical Indication Suggested IVIG Dose Strength of Evidence
Postnatal management 1 gm/kg Limited evidence

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ISSN: 2776-0979, Volume 3, Issue 7, July, 2022

Neonatal thrombocytopenia due to maternal ITP (postnatal management) 1 gm/kg/dose [72] The best approach is to give IVIG after the first platelet transfusion if the platelet count is

Neonatal thrombocytopenia due to maternal autoimmune disease 1 gm/kg/dose daily for 2 days or 0.5 gm/kg/dose daily for 4 days Limited evidence

Neonatal infections:

Clinical Indication	**Suggested IVIG Dose**	**Strength of Evidence**
Postnatal management	1 gm/kg	Limited evidence
Neonatal thrombocytopenia due to maternal ITP (postnatal management)	1 gm/kg/dose [72]	The best approach is to give IVIG after the first platelet transfusion if the platelet count is
Neonatal thrombocytopenia due to maternal autoimmune disease	1 gm/kg/dose daily for 2 days or 0.5 gm/kg/dose daily for 4 days	Limited evidence
Neonatal infections: Sepsis treatment	0.5 gm/kg/dose	Not recommended
Sepsis prophylaxis	0.5–1gm/kg/dose	Limited evidence
Enterovirus infection	750 mg/kg/dose	Limited evidence
Parvovirus infection	1 gm/kg q3 weeks	Limited evidence
Neonatal COVID-19	2 gm/kg	Limited evidence
Neonatal hemochromatosis Antenatal management	1 gm/kg/week starts at 14–18 weeks of gestation	Recommended
Postnatal management	1 gm/kg	Recommended. Given immediately after double volume exchange transfusion
Primary immunodeficiency	Varies between studies to achieve Ig level of 800–1000 mg/dl	Limited evidence
Neonatal Kawasaki	2 gm/kg	In addition to high-dose aspirin. Evidence derived from the pediatric population

Note: The suggested dose of intravenous immunoglobulin (IVIG) for use in different neonatal clinical indications. AAP; American Academy of Pediatrics, ACOG; American College of Obstetricians and Gynecologists.

Neonatal Infections

Neonatal Sepsis Treatment and Prophylaxis

The use of IVIG in adults with sepsis has been a debatable topic. Multiple systematic reviews, meta-analyses, and other trials have shown conflicting results. The non-standardized approach, different formulations, and dosing strategies have represented significant limitations in these studies. This ambiguity about a beneficial effect in adults with sepsis applies to the neonatal population as well. Given the high incidence of sepsis in very low birth weight infants of 1.9% and the associated high mortality, a great effort has been directed toward improving the outcomes in this highly susceptible population. One measure that has been derived from adult studies is the use of IVIG. The proposed mechanism of action of using IVIG in sepsis is based on the essential role that immunoglobulins play in opsonization and complement activation.

The International Neonatal Immunotherapy Study (INIS) collaborative group enrolled almost 3500 infants cared for by neonatologists in nine different countries in 113 hospitals. The study aimed to evaluate the use of IVIG in neonatal sepsis. The primary outcomes were death or major neurodevelopmental disabilities at two years of age. There was no difference in the mortality rate or disabilities at two years of age between the two groups. The authors concluded the study with the statement that "IVIG therapy does not affect the outcomes of suspected or proven sepsis". After the results of this well-conducted study, researchers tried to address the use of IgM-enriched IVIG to evaluate effectiveness in infants with clinical sepsis. Capasso et al. analyzed 40 infants who received IVIG enriched with IgM and a 39-infant control group who did not receive immunoglobulin therapy. The authors found that IVIG enriched with IgM resulted in a decreased short-term mortality rate compared to the control group. However, this study was limited by its retrospective nature, small sample size, and the fact that it addressed only short-term mortality.

Molina et al. randomized very low birth weight infants with sepsis into two groups; one received antibiotics, and the other group received IVIG at 0.5 g/kg/day for seven days in addition to antibiotics. The mortality rate was five times higher in the group that did not receive IVIG.

As more studies showed that IVIG might provide a beneficial response in neonates with sepsis after the INIS trial, a meta-analysis was necessary to answer this debatable question. A recent Cochrane review performed by Ohlsson et al. included nine studies with a total of 3973 subjects analyzed. Multiple outcomes were evaluated in this analysis, including mortality during hospitalization, the combined outcome of death or major disability at two years of age, and length of hospital stay. After thorough analysis, the authors found that IVIG administration, including IgM enriched formulation, did not result in any beneficial effect. The authors concluded that the

evidence is strong against the use of IVIG or IgM-enriched IVIG in proven or suspected neonatal sepsis and that no further research is recommended to address this topic.

Ohlsson and Lacy to compare the outcomes between the preterm or low birth weight infants who received IVIG prophylaxis for sepsis and those who did not receive sepsis IVIG prophylaxis performed another meta-analysis. There was no difference between the two groups regarding mortality or the incidence of necrotizing enterocolitis, bronchopulmonary dysplasia, and intraventricular bleeding. However, there was a decrease in the rate of sepsis (3%) associated with those who received prophylactic IVIG (R.R.: 0.85, 95% CI (0.74–0.98) with a number need to treat of 33).

Multiple explanations have been suggested for the limited effect of IVIG for prevention or treatment of neonatal sepsis, including insufficient dosing, different sepsis causative agents, the definition for sepsis, the immature immune function of the premature infants, and lower functional complement levels.

Neonatal Enterovirus Infection

Enteroviruses are RNA viruses that belong to the picornaviridae family. In contrast to the mild clinical presentation in adults, neonatal infection with enteroviruses can have severe systematic involvement.

IVIG has been suggested as a possible beneficial intervention when administered to neonates with enterovirus infection. However, the literature's evidence is not clear about this effect and is based on only a few studies. Abzug et al. evaluated the neonatal response to IVIG in 16 neonates who developed enterovirus infection. Nine infants were randomized to receive IVIG (750 mg/kg). A mild increase in serum neutralizing titers was noted in the infants who received IVIG but did not significantly reduce the viral load in blood or urine. In one case report, IVIG resulted in a good outcome in a neonate who developed disseminated infection caused by echovirus (a member of the enterovirus family). Another case series showed a promising beneficial response in two out of six infants who developed myocarditis and central nervous system (CNS) infections caused by echovirus 11 infection. The most extensive study to date is the one done by Yen et al. in which data from 65 neonates with severe enteroviral infection were retrospectively analyzed. A total of 41 (63%) received IVIG, 29 of whom received it within the first 72 h of illness. The outcomes were significantly more favorable in the group of infants who received the therapy early in the disease course. However, the dose and frequency of IVIG administration were not stated in this study.

Neonatal Parvovirus Infection

Parvovirus is a small single-stranded DNA virus. Perinatal maternal infection can result in severe consequences for the fetus, including hydrops and fetal anemia. These

effects' primary etiology are results of the viral targeting of the packed red blood cell precursors located in the bone marrow.

The evidence of using IVIG to treat neonates with parvovirus infection is minimal and only reported in the literature in two infants who were treated successfully with IVIG. One infant was treated at 15 days of life; information about dosing and frequency was not mentioned in that report. The second infant was treated with IVIG 1 g/kg administered every three weeks for eight months.

Neonatal Coronavirus Disease 2019 (COVID-19)

Coronavirus disease is an infectious disease caused by severe acute respiratory distress syndrome-related coronavirus 2 (SARS-CoV-2). At the time of this article, COVID-19 is still an ongoing pandemic that has resulted in an overwhelming number of cases worldwide. The disease mainly affects adults and tends to have severe consequences in the elderly. However, there are increasing reports of cases in the pediatric population. COVID-19 can result in a unique vasculitis-Kawasaki-like illness in the pediatric age group. This poorly understood association usually results in multisystem inflammatory effects. Neonatal cases of COVID-19 have been described recently in the literature. The exact mode of transmission, the disease's progression, and the associated morbidity and mortality remain unclear due to the low number of reported cases.

The use of IVIG has been shown by some studies to have a possible beneficial impact on adults with COVID-19 respiratory illness. This effect has not been well investigated in the neonatal population. Huaping et al. reported a case series of 10 neonates born to mothers with COVID-19–related pneumonia. One female infant born at 34 weeks and six days of gestation developed severe symptoms most likely related to maternal COVID-19 infection. The infant's manifestations were shortness of breath, fever, gastrointestinal bleeding, and disseminated intravascular coagulation. She responded successfully to IVIG 2 g/kg. Based on the results from this case series and another case report, Yuanqiang et al. suggested in their review that the use of immunoglobulins in neonates may be beneficial. However, further exploration is needed.

Neonatal Congenital cytomegalovirus (CMV)

Intrauterine infection with cytomegalovirus is one of the most common infections during pregnancy. Only about 10–15% of the infected fetus with CMV will show symptoms after birth; however, there is significant morbidity and mortality seen in these symptomatic infected infants. Due to this high morbidity, scientific basic and clinical research has been directed toward evaluating and managing congenital CMV [111]. One of the possible treatment options that have been suggested is the use of IVIG. In a relatively large, randomized placebo-controlled double-blinded trial, 124

pregnant women with primary CMV infection were randomized to either received IVIG or placebo every four weeks until 36 weeks of gestation. The authors found the use of IVIG didn't improve the newborns' outcomes. Tanimura et al. did another small clinical trial to evaluate IVIG efficacy in mothers diagnosed with primary CMV infection. IVIG with a high titer of anti-CMV antibodies failed to decrease the risk of maternal-fetal transmission.

Neonatal Hemochromatosis

Neonatal hemochromatosis (N.H.), also known as gestational alloimmune liver disease (GALD), is a rare condition that affects neonates. The pathophysiology is best explained as an immune process caused by the maternal transfer of IgG antibodies directed toward antigens located on the fetal hepatocytes. The prognosis was poor for this condition, as most infants affected developed severe liver failure. Traditional treatment for N.H. depended mostly on the use of chelating agents to decrease iron disposition in the hepatocytes. However, this treatment showed only mild improvement. Most of the treated infants required liver transplantation to improve survival. With a greater in-depth understanding of this condition's pathophysiology, newer treatment modalities have focused on controlling the immune-mediated process.

Treatment protocols were developed to prevent the severe consequences of anticipated N.H. by intervening during pregnancy. Whittington et al. showed in a relatively large sample that IVIG administered during pregnancy to mothers who had previous infants who developed N.H. resulted in significantly better outcomes. A total of 188 pregnant women who received treatment were compared to other women with high-risk pregnancies who did not receive treatment. The final analysis showed a significant difference in outcomes, as only 30% of the untreated pregnancies resulted in healthy infants compared to 94% in the treated group.

Another recent report, by Okada, et al., noted a significantly favorable outcome for infants with neonatal hemochromatosis by administering IVIG to high-risk N.H. pregnancies. In their small trial, they treated a total of eight pregnancies in six women with IVIG (1 g/kg) administered at the beginning of the second trimester at weekly or biweekly dosing frequency. This regimen was continued until 18 weeks of gestation, then weekly until the time of delivery. Only three out of the eight infants born in this study developed liver dysfunction. In these three infants, the abnormalities were transient and resolved without treatment [117].

Another successful approach used a double exchange transfusion followed by IVIG (1g/kg) immediate administration to clear the attacking maternal antibodies. Rand et al. reported promising outcomes and significantly improved prognosis defined as

survival without the need for a liver transplant. In total, 12 out of 16 (75%) infants with N.H. survived without the need for liver transplantation compared to only 23 (17%) out of 131 infants in the historical control group. Further reports confirmed favorable outcomes with a similar postnatal management approach.

Primary Immunodeficiency

Making the diagnosis of primary immunodeficiency in neonates may be challenging in the first few months of life due to the presence of maternal antibodies in the fetal circulation. However, certain conditions may manifest early in life, mainly those associated with a severe deficiency in the humoral immune response (X-linked hyper-IgM syndrome, severe combined immunodeficiency (SCID), X-linked agammaglobulinemia, and others). Treatment with IVIG in this age group remains controversial. IVIG replacement therapy is primarily indicated for those with recurrent severe or unusual infections associated with different types of immune deficiencies like hypogammaglobulinemia, common variable immune deficiency, and others.

Agammaglobulinemia, due to the complete absence of B cells, requires IVIG replacement therapy to protect against different pathogens in this critical period of life. The dosing regimen and administration schedule can vary, but generally, achieving an IgG level goal of 500 mg/dl to 800 mg/dl is recommended to prevent serious complications. Usually, these levels are achieved with lifelong administration of IVIG of 400–500 mg/kg at monthly intervals.

Conclusions

Despite lacking FDA approval, intravenous immunoglobulin (IVIG) has been used more recently to manage different clinical conditions in fetuses and neonates. The rationale behind its use is based on the immunomodulatory, anti-inflammatory, and immune-protective effects. Continuous monitoring during and after the infusion is recommended to observe for rare adverse effects associated with IVIG use in this population subset. Different clinical practice guidelines supported the use of IVIG in neonatal autoimmune hemolytic anemia, neonatal hemochromatosis, and antenatal management of neonatal alloimmune thrombocytopenia, neonatal hemochromatosis, and neonatal Kawasaki. The evidence is limited for other conditions (postnatal management of neonatal alloimmune thrombocytopenia, neonatal thrombocytopenia due to maternal autoimmune disease, neonatal infections, primary immunodeficiency, and others. Because of the unclear risk-benefit ratio of using IVIG to treat infectious and immune-mediated diseases, further studies are needed to evaluate IVIG's efficacy and safety in fetuses and neonates.

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