

of SJS and toxic epidermal necrolysis involve Fas-mediated keratinocyte apoptosis that causes epidermal detachment, and was reported to be inhibited in vitro by monoclonal antibodies to Fas. IVIG contains natural anti-Fas antibodies and other immunomodulators that may prevent apoptosis.⁹ The incidence of hemolysis as an adverse effect of IVIG infusion is apparently rare.¹⁰ Even with the prevailing use of IVIG worldwide, only relatively few cases of hemolysis have been reported in patients requiring high IVIG doses. In some cases the anemia has been mild, and no specific intervention was done other than IVIG cessation. In a few cases, blood transfusions were required.^{2–8} Reported cases have been attributed to various IVIG preparations, and not to a particular brand. We have not encountered any reports about subcutaneous preparations or in patients receiving IVIG replacement for immunodeficiency conditions.

In a series of 16 cases, hemolysis was observed 12 hours to 10 days after the first dose of IVIG and peaked at 1 day to 2 weeks after the last dose.⁴ Patients who developed IVIG-related hemolysis had non-type O blood group and cumulative doses of at least 2 g/kg¹⁰ and can be attributed to pre-existing isoantibodies to the recipient's RBC A or B antigens.¹⁰ In 1 case, only anti-D antibodies were present against the patient's blood group O.³ Because IVIG is pooled from the plasma of thousands of donors, the antibody titers vary from 1 lot to another. Recently, Padmore et al postulated a two-hit prerequisite of an underlying severe inflammatory state and/or high HLA sensitization in conjunction with high-dose IVIG.¹¹

In summary, we have described a patient with acute hemolysis after infusion of IVIG (1 g/kg/day) for SJS. Such an adverse reaction is probably under-recognized. With the increasing indications for immunomodulating high-dose IVIG, this adverse effect may become more frequent. Hence, we recommend checking the hemoglobin level before infusion of high doses of IVIG and repeatedly thereafter. If the hemoglobin level drops, IVIG infusion may be discontinued and appropriate hemolysis workup, including a direct antiglobulin test, should be performed. Although mild cases usually recover spontaneously, severe cases may require blood transfusion.

Follow-up should continue until hemoglobin is stabilized at a normal level.

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References

- [1] Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol*. 2006;117:S525–S53.
- [2] Thomas MJ, Misbah SA, Chapel HM, Jones M, Elrington G, Newsom-Davis J. Hemolysis after high-dose intravenous Ig. *Blood*. 1993;82:3789.
- [3] Coghill J, Comeau T, Shea T, Braddy L, Bandarenko N, Afeniyi-Annan A, Harvey D. Acute hemolysis in a patient with cytomegalovirus pneumonitis treated with intravenous immunoglobulin (IVIG). *Biol Blood Marrow Transplant*. 2006;12:786–788.
- [4] Daw Z, Padmore R, Neurath D, Cober N, Tokessy M, Desjardins D, Olberg B, Timmouth A, Giulivi A. Hemolytic transfusion reactions after administration of intravenous immune (gamma) globulin: a case series analysis. *Transfusion*. 2008;48:1598–1601.
- [5] Yin F, Nesbitt JA, Tobian AA, Holt PA, Mikdashi J. Hemolytic anemia following intravenous immunoglobulin administration. *Am J Hematol*. 2008;83:825.
- [6] Kahwaji J, Barker E, Pepkowitz S, Klapper E, Villicana R, Peng A, Chang R, Jordan SC, Vo AA. Acute hemolysis after high-dose intravenous immunoglobulin therapy in highly HLA sensitized patients. *Clin J Am Soc Nephrol*. 2009;4:1993–1997.
- [7] Gordon DJ, Sloan SR, de Jong JL. A pediatric case series of acute hemolysis after administration of intravenous immunoglobulin. *Am J Hematol*. 2009;84:771–772.
- [8] Morgan S, Sorensen P, Vercellotti G, Zantek ND. Haemolysis after treatment with intravenous immunoglobulin due to anti-A. *Transfus Med*. 2011;21:267–270.
- [9] Khalili B, Bahna SL. Pathogenesis and recent therapeutic trends in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Ann Allergy Asthma Immunol*. 2006;97:272–280.
- [10] Baxley A, Akhtari M. Hematologic toxicities associated with intravenous immunoglobulin therapy. *Int Immunopharmacol*. 2011;11:1663–1667.
- [11] Padmore RF. Hemolysis upon intravenous immunoglobulin transfusion. *Transfus Apher Sci*. 2012;46:93–96.

Common variable immune deficiency and treatment with intravenous immunoglobulin during pregnancy

Common variable immune deficiency (CVID) is a disorder characterized by hypogammaglobulinemia and recurrent infections of the respiratory and gastrointestinal systems.¹ Women frequently experience symptom onset in their late 20s and are diagnosed with CVID in their early 30s.² Therefore, women of child-bearing age may require careful monitoring because of potential health risks to themselves or their fetuses. Several case reports of pregnant women with CVID have indicated a need to increase the dosage of IgG throughout pregnancy to maintain adequate levels,^{3,4} and some have documented that women with CVID may have an increased incidence in miscarriage.⁵ During pregnancy these women, as well as their neonates, may be at a higher risk of infection.^{3,4,6}

The purposes of our study were to identify complications related to intravenous immunoglobulin (IVIG) treatment in pregnant women and to determine effects on the neonates. We describe 5 patients diagnosed with CVID who received IVIG therapy during 7 pregnancies. Interview data are presented for 4 additional pregnancies that occurred during treatment at other practices.

No interview data are available for one of the pregnancies in which the mother received IVIG treatment under our care.

A survey of Atlanta Allergy and Asthma Clinic physicians was completed, and medical record reviews of potential candidates were performed. Five of 9 eligible participants met the inclusion criteria, which consisted of women within the practice who had been diagnosed with CVID and received IVIG treatment during pregnancy and for whom data were available. The study was granted exemption from institutional review board (IRB) determination by the Sterling IRB, and written informed consent was obtained before the study.

Data collected from a retrospective medical record review included age of symptom onset and CVID diagnosis; concomitant diagnoses (Table 1); changes in frequency of infections throughout pregnancy; dates and dosages of IVIG therapy; immunoglobulin levels drawn before, during, and after pregnancy; and cord blood IgG levels when available. Four of 5 patients were interviewed for history of CVID, frequency of infections during the antepartum period, pregnancy complications, and infant health outcomes.

To maintain therapeutic levels greater than 600 mg/dL, a 32% increase in IVIG dose was required in 1 pregnancy, whereas no change in dosage was necessary in 4 pregnancies. One patient's levels decreased below 600 mg/dL during the third trimester while

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Table 1
Clinical history and pregnancies of the study participants

Mother No.	Symptom onset	Age of CVID diagnosis, y	Age IgG replacement therapy initiated	Concomitant diagnoses	Total No. of pregnancies	No. of pregnancies during care at AAAC	Mother's age during pregnancies at AAAC, y
1	Infancy	3	IM injections at 3 years of age; IVIG at 8 years of age	Bronchiectasis, after partial lobectomy secondary to pseudomonas lung abscess, chronic bronchitis, chronic sinusitis, recurrent otitis media, asthma	2	2	21 and 30
2	Childhood	19	IVIG at 27 years of age	Recurrent bronchitis, chronic sinusitis, asthma, hypothyroidism	1	1	33
3	4 years old	17	IVIG at 17 years of age	Chronic bronchitis, chronic sinusitis, asthma, allergic rhinitis	2	2	16 and 24
4	Unknown	26	Unknown	Recurrent bronchitis, recurrent pneumonia, chronic sinusitis, recurrent ovarian cysts, arthralgia	3	1	29
5	1 year old	10	Blood donations at 10 years of age; IVIG at 17 years of age	Chronic bronchitis, chronic sinusitis, asthma, allergic rhinitis	3	1	31

Abbreviations: AAAC, Atlanta Allergy and Asthma Clinic; CVID, common variable immune deficiency; IM, intramuscular; IVIG, intravenous immunoglobulin.

receiving a stable dose. Another patient was nonadherent and had sporadic IVIG infusions before and during her second pregnancy. Her IgG level was less than 50 mg/dL when IVIG was regularly resumed at 24 weeks. At delivery, her IgG level was 1,143 mg/dL, and the infant cord blood IgG level was 1,166 mg/dL.

Only 1 mother reported increased infections during pregnancy, including bronchitis, sinusitis, and asthma exacerbations, which occurred throughout the period she was nonadherent to IVIG therapy. She denied having any symptoms after resuming IVIG therapy. No interview data are available for 1 mother, so it is unknown whether she had increased infections during pregnancy.

Pregnancy complications included miscarriage (1), ectopic pregnancy (1), preterm labor (4), preterm birth (2), preeclampsia (1), HELLP (Hemolysis, Elevated Liver enzyme level, and Low Platelet count) syndrome (4), and mastitis (2).

Only 1 child reportedly experienced recurrent infections (sinusitis), but his immunoglobulin levels and pneumococcal titers were normal. Another child was IgA deficient but otherwise asymptomatic.

IgG levels and IVIG doses varied greatly among the women. These patients should be regularly monitored, and adjustments to IVIG doses may be necessary to prevent pregnancy-associated infections or potential complications and for adequate IgG transport to the newborn.

Study limitations include recall bias attributable to the retrospective nature of the study. Also, many of the cases of preterm labor and HELLP syndrome occurred in 1 mother during 3 separate pregnancies (3 cases in mother 5 and 1 case in mother 3 for each condition). Mastitis was identified in 2 of the 5 women, both of whom breastfed their infants. Therefore, infection control practices may need to be reviewed carefully with these mothers. The study also includes a small number of participants, and conclusions may not be representative of all pregnant women receiving IVIG. Nevertheless, our data suggest that preg-

nant women with CVID should be observed carefully by immunologists and obstetricians.

The results of our study are comparable to reports^{7,8} that focus on the health of neonates born to women undergoing IgG replacement therapy as all were born healthy. However, these studies did not follow up with the children after birth, so it is unclear whether the children developed any immunodeficiencies or other illnesses. To our knowledge, these studies did not find any pregnancy complications during treatment with IgG replacement therapy.

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References

- [1] Yong PF, Tarzi M, Chua I, Grimbacher B, Chee R. Common variable immunodeficiency: an update on etiology and management. *Immunol Allergy Clin North Am*. 2008;28:367–386.
- [2] Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol*. 1999;92:34–48.
- [3] Schaffer FM, Newton JA. Intravenous gamma globulin administration to common variable immunodeficient women during pregnancy: case report and review of the literature. *J Perinatol*. 1994;14:114–117.
- [4] Sacher RA, King JC. Intravenous gamma-globulin in pregnancy: a review. *Obstet Gynecol Surv*. 1989;44:25–34.
- [5] Shalev E, Ben-Ami M, Peleg D. Common variable hypogammaglobulinemia in pregnancy. *Br J Obstet Gynaecol*. 1993;100:1138–1140.
- [6] Fait G, Gull I, Kupfermanc MJ, et al. Fever in a pregnant woman with common variable immunodeficiency. *J Obstet Gynaecol*. 1998;18:188–189.
- [7] Kurecová B, Janků P, Litzman J. Common variable immunodeficiency in pregnancy (set of case reports). *Ceska Gynekol*. 2009;74:197–201.
- [8] Gardulf A, Andersson E, Lindqvist M, Hansen S, Gustafson R. Rapid subcutaneous IgG replacement therapy at home for pregnant immunodeficient women. *J Clin Immunol*. 2001;21:150–154.