Revisiting the use of intravenous immune globulin (IVIG) for Kell alloimmunization

James R. Scott, MD

The development of anti-D (Rh) immune globulin and its antepartum and postpartum use is one of the remarkable success stories in obstetrics as it has nearly eliminated fetal deaths from Rh immunization. In contrast, Kell immunization, although rare, is still present since there is no prophylactic anti-Kell immune globulin. The critical titer for identifying affected pregnancies and optimal care of Kell-sensitized pregnancies has remained controversial.[1,2] When severe Kell alloimmunization occurs, intrauterine blood transfusion is essential to prevent fetal death. However, intravascular fetal transfusions can be technically challenging <22 weeks' gestation.

The use of intravenous immunoglobulin (IVIG) for severe red cell alloimmunization in pregnancy dates back to the late 1980s with the publication of case reports followed by a number of small series.[3–10] Most, but not all,[7] have suggested a beneficial effect on reducing the severity of fetal hemolytic disease. The most impressive results seemed to be with Kell-sensitized patients.[7,8] Possible mechanisms of action that were proposed included inhibition of maternal antibody synthesis, blockade of Fc-mediated antibody transport across the placenta, and an Fc blockade of the fetal reticuloendothelial system.[8,9] However, the doses of IVIG used and duration of treatment varied and were sometimes combined with plasmapheresis.[10] A problem with all these reports is that there are no controls for comparing the efficacy of IVIG treatment alone, or in addition to intrauterine transfusions, with that of standard treatment with multiple intrauterine transfusions alone. The nature of the studies raised the possibility of selection, observer, and publication bias, but numerous calls for randomized controlled trials have not materialized.

In this issue of the *American Journal of Obstetrics and Gynecology*, Zwiers and colleagues[11] report on the addition of IVIG to usual management in severely Kell-alloimmunized pregnancies. Specifically, their purpose was to evaluate whether IVIG <20 weeks' gestation delayed severe hemolytic disease of the fetus and could be utilized as a noninvasive alternative to early intrauterine transfusions.

This is an experienced group of investigators that deserve credit for the great deal of effort they put into this challenging multicentered study to attempt to ascertain whether IVIG is useful. In this cohort study, patients with an earlier pregnancy with severe hemolytic disease were seen beginning in the first trimester and treated either with IVIG or were managed without IVIG. The authors chose to compare the difference in gestational age at the onset of severe fetal anemia and the need for intrauterine transfusion between the 2 groups as the primary outcome, but this is a surrogate marker. It would have been preferable to select perinatal morbidity and live birth rate as the primary outcome. This is the most meaningful outcome and is what patients and physicians want to know.[12] The overall infant survival was an impressive 88% but did not differ between the IVIG-treated and untreated groups. The problem again is the retrospective observational study design with rather limited numbers (because of the rarity of the condition), heterogeneity of both patients and treatments, and a number of potential confounding variables that limit the interpretation and validity of results and conclusions. For example, although severe fetal anemia in pregnancies with IVIG developed on average 15 days later than in the mother's previous pregnancy, 11 of 28 fetuses without IVIG treatment also had a later onset of fetal anemia than in the previous pregnancy. In other words, association does not equal causation even with the sophisticated statistical methods used to correct for nonrandomization. For these reasons, the bottom line is that the value of IVIG could not be convincingly proven.

Therefore, we are still left with a dilemma since the results are not conclusive, similar to previous observational studies. IVIG seems promising, but too many times promising treatments have been prematurely introduced into clinical practice only to be abandoned after they were refuted by high-quality trials. Nevertheless, this publication could play an important role by raising awareness and bringing attention to this issue and perhaps stimulating an important, but rather difficult to accomplish, prospective, protocol-driven, multicentered randomized controlled trial that definitively answers this question. In the meantime, caution is still warranted regarding the use of IVIG for red cell alloimmunization in pregnancy and is best considered as an as yet not completely proven and very expensive therapy. ■

From the Department of Obstetrics and Gynecology, University of Iowa Carver College of Medicine, Iowa City, IA.

Received June 21, 2018; accepted June 22, 2018.

The author reports no conflict of interest.

Corresponding author: James R. Scott, MD. james.scott@hsc.utah.edu

0002-9378/free

https://doi.org/10.1016/j.ajog.2018.06.018

Related article, page 291

REFERENCES

1. American College of Obstetricians and Gynecologists. Management of alloimmunization during pregnancy. ACOG Practice bulletin no. 192. Obstet Gynecol 2018;192:e82–90.

2. McKenna DS, Nagaraja HN, O'Shaughnessy R. Management of pregnancies complicated by anti-Kell isoimmunization. Obstet Gynecol 1999;93:667–73.
3. Berlin G, Selbring A, Ryden G. Rhesus hemolytic disease treated with high-dose intravenous immunoglobulin. Lancet 1985;1:1153.
4. de la Camara C, Arrieta R, Gonzalez A, Iglesias E, Omenaca F. High-dose intravenous immunoglobulin as the sole prenatal treatment for severe Rh immunization. New Engl J Med 1988;318:519–20.
5. Scott JR, Branch DW, Kochenour NK, et al. Intravenous immunoglobulin treatment of pregnant patients with recurrent pregnancy loss caused by antiphospholipid antibodies and Rh immunization. Am J Obstet Gynecol 1988;159:1055–6.
6. Porter T, Silver R, Jackson GM, Branch D, Scott JR. Intravenous immune globulin in the management of severe Rh D hemolytic disease. Obstet Gynecol Surv 1997;52:193–7.
7. Chitkara U, Bussel J, Alvaez M, Lynch L, Meisel RL, Berkowitz RL. High-dose intravenous gamma globulin: does it have a role in the treatment of severe erythroblastosis fetalis? Obstet Gynecol 1990;76:703–8.
8. Ruma MS, Moise KJ, Kim E, et al. Combined plasmapheresis and intravenous immune globulin for treatment of severe maternal red cell alloimmunization. Am J Obstet Gynecol 2007;196:138.e1–6.
9. Fox C, Martin W, Somerset DA, Thompson PJ, Kilby MD. Early intraperitoneal transfusion and adjuvant maternal immunoglobulin therapy in the treatment of severe red cell alloimmunization prior to fetal intravascular transfusion. Fetal Diagn Ther 2008;23:159–63.
10. Connan K, Kornman L, Savoia H, Palma-Dias R. IVIG—is it the answer? Maternal administration of immunoglobulin for severe fetal red cell alloimmunization during pregnancy: a case series. Aust N Z J Obstet Gynaecol 2009;49:612–8.
11. Zwiers C, van der Bom JG, van Kamp IL, et al. Postponing early intrauterine transfusion with intravenous immunoglobulin treatment; the PETIT study on severe hemolytic disease of the fetus and newborn. Am J Obstet Gynecol 2018;219:291.e1–9.
12. Harbin Consensus Conference Workshop Group. Improving the reporting of clinical trials of infertility treatments (IMPRINT): modifying the CONSORT statement. Fertil Steril 2014;102:952–9.e15.