The continuing burden of Rh disease 50 years after the introduction of anti-Rh(D) immunoglobin prophylaxis: call to action

Gerard H. A. Visser, MD, PhD; Gian Carlo Di Renzo, MD, PhD; Steven L. Spitalnik, MD; FIGO Committee Safe Motherhood and Newborn Health

THE PROBLEM: Severe morbidity and mortality due to Rh disease have only been reduced by 50% globally during the last 50 years, despite the advent of anti-Rh(D) immunoglobin prophylaxis.

A SOLUTION: Raising public awareness of the risk and impact of this completely preventable disease, routine ABO and Rh(D) blood group typing of all pregnant women, and, most importantly, providing free and unfettered access to prophylaxis with anti-Rh(D) immunoglobulin, when clinically appropriate.

A disease that consisted of icterus neonatorum and edema was first described in 1892 by Ballantyne.[1] In 1940 and 1941, Landsteiner and Wiener[2] described the appearance of a hetero-agglutinin (serum antibody capable of agglutinating erythrocytes) in the sera of rabbits that had been injected with red cells that had been obtained from Rhesus monkeys. This antibody, called anti-D (or, equivalently, anti-Rh[D]), reacted with the red cells of approximately 85% of human subjects. In 1941, Levine et al[3] showed that most cases of hemolytic disease of the fetus and newborn infant were due to immunization to the Rh antigen (ie, Rh[D]). In 1967, Freda et al[4] in the United States and Clarke[5] in England published almost simultaneously that alloimmunization to Rh(D) because of pregnancy could be prevented by the postnatal maternal administration of immunoglobulin preparations that contained high titers of anti-Rh(D) antibodies. After this, the first clinical applications of Rh disease prevention were introduced quickly in some countries. For example, in The Netherlands, nationwide screening and postnatal anti-Rh(D) administration to all Rh(D)-negative primiparous women who had delivered a Rh(D)-positive newborn infant were started in 1969; this approach was later expanded to all multiparous women.

Prevention of Rh disease is relatively easy.[6] It involves Rh(D) typing of the mother and the cord blood of newborn infants of Rh(D)-negative women. Then, 1500 IU of anti-Rh(D) immunoglobulin should be given to Rh(D)-negative women within 3 days of delivery, if her child is Rh(D)-positive. This measure alone prevents maternal Rh(D) sensitization in approximately 90% of cases; in contrast, in the absence of such prophylaxis, 12−16% of these Rh(D)-negative mothers become alloimmunized during each such pregnancy. Over the years, the use of anti-Rh(D) immunoglobulin was extended to other indications that may involve fetal-maternal hemorrhage, which could result in Rh(D) sensitization of the mother; these include, abortion, ectopic pregnancy, bleeding during pregnancy, external version in the case of breech position, abdominal trauma, and amniocentesis. A further reduction in the occurrence of Rh disease was achieved by the routine administration of 1500 IU of anti-Rh(D) immunoglobulin to all Rh(D)-negative women at 28−32 weeks of gestation. This latter policy, which involved antenatal therapy, reduced the frequency of Rh(D) sensitization to as low as 0.1%. Based on recent advances, the Rh(D) status of the fetus can now be determined in a maternal blood sample during the first trimester of pregnancy by cell-free DNA testing, thereby preventing unnecessary antenatal anti-Rh(D) immunoglobulin administration and eliminating the need for Rh(D) testing of cord blood samples.[7]

The prevalence of Rh(D)-negative women varies widely around the globe. In white and European women, it is approximately15%; whereas in China, Japan, and Indonesia, it is only approximately 0.5%. In countries with multiethnic populations, the prevalence varies widely. For example, in South America, it ranges from 1.5% in Chile to 19% in Brazil. In Africa, it ranges from 3−15% (eg, Nigeria vs South Africa). In

From the Departments of Obstetrics, University Medical Center, Utrecht, The Netherlands (Dr Visser); Department of Obstetrics and Gynecology, Center of Perinatal and Reproductive Medicine, University of Perugia, Italy & Department of Obstetrics and Gynecology I.M. Sechenov First State University, Moscow, Russia (Dr Di Renzo); Department of Pathology and Cell Biology, Columbia University, New York, NY (Dr Spitalnik); Committee Safe Motherhood and Newborn Health, International Federation of Gynecology and Obstetrics (FIGO), London, UK. (Committee members: Gerard H.A.Visser [Chair], Gian Carlo Di Renzo, Diogo Ayres-de-Campos, Maria Fernanda Escobar, Eytan Barnea, PK Shah, Anwar Nasser, Luc de Bernis, Luming Sun, Wanda Kay Nicholson, Isabel Lloyd, Salimah Walani, Gerhard Theron, William Stones).

The authors report no conflict of interest.

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the Association of American Medical Colleges.

Corresponding author: Gerard H. A. Visser, MD, PhD. g.h.a.visser@umcutrecht.nl

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2019.05.019

addition, the rates in India and Pakistan are 4% and 11%, respectively.[8] Thus, the burden of Rh disease seems likely to be highest in regions with the highest rates of Rh-negative women; however, it should be taken into account that the most babies are born in countries with a rather low prevalence of Rh-negative women (eg, China), which, nonetheless, may still result in a very high total number of Rh disease—affected pregnancies.

The problem: failure to prevent Rh disease

In 2013, Bhutani et al[9] performed a systematic review and metaanalysis to determine the global prevalence of Rh disease—induced death and kernicterus because of severe hyperbilirubinemia. Failure to prevent Rh(D) sensitization and manage neonatal hyperbilirubinemia annually results in at least 50,000 fetal deaths, 114,000 avoidable neonatal deaths, and many children who would grow up with disabilities. Three-quarters of this death occurs in sub-Saharan Africa and South Asia. Kernicterus that accompanies Rh disease is currently highest in Eastern Europe and Central Asia. Indeed, Rh disease has only been eradicated in so-called high-income countries.

The reasons for the continuing burden of Rh disease vary widely and are difficult to assess precisely. However, from discussions with representatives from many countries around the world, we identified some important factors in some parts of the world.

Africa. In many regions, ABO and Rh blood group typing are not determined during pregnancy. In addition, anti-Rh(D) immunoglobulin is distributed frequently through private pharmacies, which may charge 4-8 times the price as in high-income countries. Moreover, anti-Rh(D) prophylaxis is performed mainly through local initiatives and not endorsed by most governments.

China. Anti-Rh(D) immunoglobulin is not available because of import restrictions. Although the prevalence of Rh(D)-negative women is low, maternal Rh(D) alloimmunization occurs often overall, given the high total number of births and the very high likelihood that the father will be Rh(D)-positive. In addition, the introduction of a "more than 1 child" policy is expected to increase the occurrence of Rh disease in that the illness becomes more and more severe in subsequent pregnancies.

Eastern Europe and Russia. Although access to anti-Rh(D) immunoglobulin is generally adequate, the supply sometimes does not fulfill the needs. The most important reason for the high rate of Rh disease—related kernicterus seems to be that quite often the need to administer anti-Rh(D) immunoglobulin is simply forgotten; the same is true for its administration after events such as abortion and bleeding in pregnancy. In addition, this situation may have deteriorated after the dissolution of the Soviet Union.

India. In rural areas, anti-Rh(D) immunoglobulin frequently is not available or its need is forgotten. In addition, the locally produced monoclonal anti-Rh(D) product has not yet been tested adequately for clinical effectiveness.

South America. The supply of anti-Rh(D) immunoglobulin is often not adequate.

Other countries. In some Western countries, such as the United States, there is no overall system in place to monitor compliance regarding the administration anti-Rh(D) immunoglobulin prophylaxis in all clinical settings.

The way forward towards a solution

A Consortium for Universal Rh disease Elimination (CUR(h)E), which was initiated at Stanford University in March 2017, suggested that the devastating problem of Rh disease can be solved by 3 simple steps: (1) raising public awareness of the risk and impact of this completely preventable disease, (2) routine ABO and Rh(D) blood group typing of all pregnant women, and (3) most importantly, providing free and unfettered access to prophylaxis with anti-Rh(D) immunoglobulin, when clinically appropriate.

The International Federation of Obstetrics and Gynecology completely agrees with this initiative. The reasons for the continuing burden of Rh disease differ in different parts of the world. However, the enthusiastic involvement of governments and healthcare officials is essential, everywhere! The International Federation of Obstetrics and Gynecology calls for collaboration between local obstetrics & gynecology societies and official political and medical institutions and is willing to assist where needed. New preventive measures, such as antenatal vaccination against group B streptococcal infection and against respiratory syncytial virus infection, will be introduced in the near future and may fail if the barriers for successful anti-Rh(D) immunoglobin prophylaxis still prevail. These new types of vaccinations during pregnancy will need actively involved obstetric caregivers, similar to what is required for Rh disease prevention; in particular, this differs markedly from the approaches of healthcare organizations that provide vaccinations to young children. Thus, a highly effective system to prevent diseases of the newborn infant, by tackling the problem both antenatally and immediately after delivery, must be developed. In this way, Rh disease can and should be eradicated. ■

ACKNOWLEDGMENTS

We are grateful for a grant by Kedrion Biopharma, Italy, which is supporting this initiative through a specific memorandum of understanding with FIGO.

REFERENCES

1. Ballantyne JW. Studies in foetal pathology and teratology; the investigation of foetal disease. Trans Edinb Obstet Soc 1892;17:53–68.
2. Landsteiner K, Wiener AS. Studies on an agglurinogen (Rh) in human blood reacting with anti-Rhesus sera and with human isoantibodies. J Exp Med 1941;74:309–20.

3. Levine P, Vogel P, Katzin EM, Burnham L. Pathogenesis of erythroblastosis fetal: statistical evidence. Science 1941;94:371-2; Am Med Assn 1941:116–82.
4. Freda VJ, Gorman JG, Pollack W. Suppression of the primary Rh immune response with passive Rh IgG immunoglobulin. N Engl J Med 1967;277:1022–35.
5. Clarke CA. Prevention of Rh-haemolytic disease. Br Med J 1967;4:7–12.
6. Committee on Practice Bulletins-Obstetrics. Practice Bulletin No. 181: Prevention of RhD alloimmunization. Obstet Gynecol 2017;130:e57–70.
7. Vivanti A, Benachi A, Huchet FX, Ville Y, Cohen H, Costa JM. Diagnostic accuracy of fetal rhesus D genotyping using cell-free fetal DNA during the first trimester of pregnancy. Am J Obstet Gynecol 2016;215:606.e1–5.
8. Flegr J. Heterozygote advantage probably maintains rhesus factor blood group polymorphism: ecological regression study (+supplementary data). PLoS ONE 2016;11:e0147955.
9. Bhutani VK, Zipursky A, Blencowe H, et al. Neonatal hyperbilirubinemia and Rhesus disease of the newborn: incidence and impairment estimates for 2010 at regional and global levels. Pediatr Res 2013;74(suppl1):86–100.

ABSTRACT

The continuing burden of Rh disease 50 years after the introduction of anti-Rh(D) immunoglobin prophylaxis: call to action

Severe morbidity and death because of Rh disease have only been reduced by approximately 50% globally during the last 50 years, despite the advent of anti-Rh(D) immunoglobin prophylaxis, which has resulted in >160,000 perinatal deaths and 100,000 disabilities annually. This apparent failure to take appropriate preventive measures is of great concern. Thus, there is a great need to do much better. We wish to draw attention to the unnecessary continuing burden of Rh disease, to discuss some of the reasons for this failure, and to provide suggestions for a better way forward.

Key words: alloimmunization, blood groups, fetal anemia, hemolysis, hemolytic disease of the fetus and newborn, hyperbilirubinemia, isoimmunization, prevention, Rh disease