

Marissa Caldwell

Mentors: Brie Stotler, MD MPH, Columbia University

Steven Spitalnik, MD Columbia University

## BACKGROUND

Rh Disease is a type of hemolytic disease of the fetus and newborn (HFDN) that occurs when an Rh-negative mother becomes alloimmunized to the Rh antigen, often through pregnancy with an Rh-positive fetus. In a subsequent pregnancy, anti-Rh(D) IgG antibodies cross the placenta and clear fetal blood cells, resulting in anemia, hyperbilirubinemia, hydrops fetalis and kernicterus<sup>1</sup>. Following the development of prophylactic anti-Rh(D) immunoglobulin (popularly known as RhoGAM in the United States) in the 1960s, Rh disease became virtually eradicated in many developed countries. However, it is estimated that worldwide, 50% of women who need treatment to prevent alloimmunization do not receive it, signaling that the fight against Rh disease is far from over<sup>2</sup>.

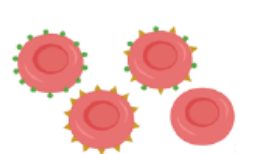
## WIRhE: Worldwide Initiative for Rh Disease Eradication

Founded in 2018, the goal of WIRhE is simple: ensure that every woman who needs anti-Rh(D) immunoglobulin during and after pregnancy receives it. In practice, this is challenging: access to prenatal care, blood typing, treatment, and even knowledge of Rh disease itself varies significantly across the world and depends on social, economic, and political factors. To that end, WIRhE is building an international community of healthcare providers, patients, advocates, and researchers to raise awareness, continue scientific investigation, and equip Rh-negative women and those caring for them with the tools they need to prevent Rh disease. WIRhE maintains a website for education, communication, and collaboration, and is in the process of developing several educational tools for the international community.

## SAMPLE PROVIDER - PATIENT HANDOUT

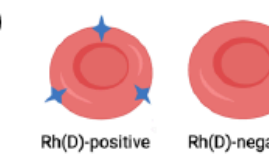
### How Rh Disease Develops

①




Not everyone has the same type of blood cells. There are many different proteins and sugars that can be found on the surface of blood cells. We use those to classify a person's blood "type" such as A, B, AB, and O. Blood types are determined genetically, and they are all normal.

②



The Rh(D) factor is a protein that can be part of your blood type. Your blood type is either Rh(D)-positive or Rh(D)-negative, and both are normal. If Rh(D) protein is on your blood cells, your blood type will be labeled "Rh(D)-positive." If Rh(D) protein is not on your blood cells, your blood type will be labeled "Rh(D)-negative."


③



Pregnancies of women who are Rh(D)-positive are not at risk of Rh disease. However, when an Rh(D)-negative mother is exposed to Rh(D)-positive blood, most often through pregnancy with an Rh(D)-positive child, her immune system sees the blood as foreign. This can cause the fetus's blood cells to be destroyed.

The following example will show you one way that this results in Rh disease.

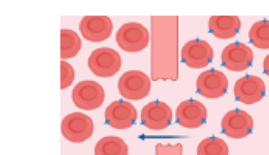
④



A woman with Rh(D)-negative blood is pregnant. This is her first pregnancy. She doesn't know it, but her baby is Rh(D)-positive.

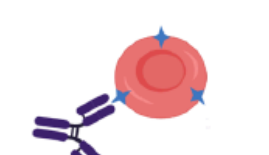
She has an uncomplicated pregnancy and delivers a healthy baby.

⑤




However, during pregnancy or at birth, the mother was exposed to the fetus's Rh(D)-positive blood cells through a small fetomaternal hemorrhage, or bleed. The mother's body saw these Rh(D)-positive cells as foreign. This triggered an immune response with antibody production against the Rh(D)-positive blood cells.

⑥



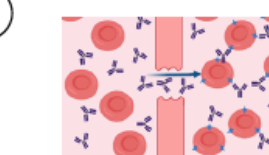
Antibodies are specialized proteins designed to get rid of things that attack the body. They also "remember" previous pathogens so that if the body is exposed to it again, the antibodies are activated to destroy it.

⑦




Now that the woman has made Rh(D) antibodies, they are present in her bloodstream. If she becomes pregnant again, those Rh(D)-positive antibodies will cross the placenta.

⑧

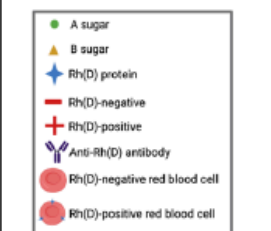



If the anti-Rh(D) antibodies encounter Rh(D)-positive red blood cells in the fetus, they will remove the red blood cells from the fetus's bloodstream. This causes Rh Disease, also known as Hemolytic Disease of the Fetus and Newborn.

⑨



Rh Disease can be life-threatening for a fetus or newborn. If a mother is known to be at risk for Rh disease, a health care provider can use a prescription drug called anti-Rh(D) immunoglobulin. This injection is given during and after pregnancy to prevent the mother's immune system from creating the harmful anti-Rh(D) antibodies. The medication is very well tolerated, but only works if the mother has not already been exposed to the Rh(D) factor.





Images created with BioRender

## NEW RESOURCES

Handouts with accompanying graphics were developed on the following topics:

- The Rh Protein
- Anti-Rh(D) Immunoglobulin
- How Rh Disease Develops
- Hemolytic Disease of the Fetus and Newborn
- 4 Steps to prevent Rh disease

These handouts will be translated into other languages. Links to recent literature relating to Rh disease, along with brief summaries, were prepared for quick access by website visitors. A list of the current commercial manufacturers of anti-Rh(D) immunoglobulin was also compiled.

## DISCUSSION

Rh incompatibility remains a major cause of fetal and newborn hemolytic disease worldwide, despite the existence of a well-tolerated and efficacious prophylactic treatment for over fifty years. Rh disease persists because of lack of information and access to appropriate medical care, and WIRhE aims to change that. The newly developed, printable handouts will make it easier for healthcare providers to educate their patients and raise awareness about Rh disease. Other new online resources, including recent findings and anti-Rh(D) immunoglobulin manufacturers allows WIRhE to address a diverse audience at any stage of the fight against Rh disease.

## REFERENCES

1. Bowman JM. RhD Hemolytic Disease of the Newborn. <http://dx.doi.org/10.1056/NEJM199812103392410>. doi: [10.1056/NEJM199812103392410](https://doi.org/10.1056/NEJM199812103392410)
2. Pegoraro V, Urbinati D, Visser GHA, et al. Hemolytic disease of the fetus and newborn due to Rh(D) incompatibility: A preventable disease that still produces significant morbidity and mortality in children. Oei JL, ed. *PLoS ONE*. 2020;15(7):e0235807. doi: [10.1371/journal.pone.0235807](https://doi.org/10.1371/journal.pone.0235807)