

Rh Incompatibility in Pregnancy ^[1]

By: Antonios, Nathalie Keywords: [Fetus](#) ^[2] [Human development](#) ^[3]

[Rh incompatibility](#) ^[4] occurs when a pregnant woman whose blood type is Rh-negative is exposed to Rh-positive blood from her [fetus](#) ^[5], leading to the mother's development of Rh antibodies. These antibodies have the potential to cross the [placenta](#) ^[6] and attach to fetal red blood cells, resulting in hemolysis, or destruction of the fetus's red blood cells. This causes the [fetus](#) ^[5] to become anemic, which can lead to hemolytic disease of the newborn. In severe cases, an intrauterine blood transfusion for the [fetus](#) ^[5] may be required to correct the [anemia](#) ^[7].

The first case involving [Rh incompatibility](#) ^[4] was reported in 1939, although the Rh factor, a protein found on the surface of red blood cells, had not yet been discovered. This first case was reported by immunohematologist, Philip Levine and physician, Rufus Stetson, who published their case in *The Journal of the American Medical Association* ^[8]. The authors presented an anonymous, twenty-five year old woman who checked into a local hospital during her thirty-third week of [pregnancy](#) ^[9] complaining of labor pains and vaginal bleeding. The next day, she delivered an emaciated, stillborn [fetus](#) ^[5] weighing only one pound and five ounces. The physicians had to expel the woman's [placenta](#) ^[6] to stop her from bleeding to death. The patient received a blood transfusion from her husband, as the two of them were of blood-type O. Ten minutes after completing the transfusion, the patient developed a chill and began feeling pain in her head and legs. When her vaginal bleeding resumed she was given a [hysterectomy](#) ^[10], followed by another blood transfusion from a different donor. Throughout her entire visit, the patient received transfusions from 104 Type O blood donors. Remarkably, the mother showed no blood transfusion reaction to twenty-one of those donors. Further tests indicated that the patient's serum, or the plasma in the blood minus the clotting factors, specifically agglutinated her donors' cells—or rather, 80 percent of all her blood transfusions.

The two physicians tried to discover what was causing the patient's reaction. Initially, they believed that temperature was affecting agglutination in the patient's blood, but they soon realized that temperature did not affect agglutination. The physicians reported that it was difficult to recreate these agglutinations for further testing since they still had not yet solved what was causing these isoimmunizations, or the development of antibodies in response to an antigenic stimulation.

It was not until a year later, Karl Landsteiner and Alexander S. Wiener coined the term "Rh factor" as the cause of the isoimmunization. They originally believed that *Macacus rhesus*, or Rhesus monkey, contained the same red blood cell surface antigen (Rh) as the one found in human red blood cells. This was soon proven wrong, as the composition of human sera and rhesus sera are different. Nonetheless, the term "Rh factor" has continued to be used to describe these human antigens, and the term "anti-Rh" is used to describe human antibodies formed against the Rh factor.

The most common form of [Rh incompatibility](#) ^[4] occurs when an Rh-negative mother and an Rh-positive father produce an Rh-positive [fetus](#) ^[5]. The situation does not become dangerous, however, until there is leakage from the fetal circulation into the maternal circulation. Once a significant amount of Rh-positive blood is released into the mother's bloodstream, a process known as red-cell alloimmunization begins. This primary exposure of Rh-positive blood into the maternal circulation leads to sensitization, which results in the maternal production of Rh-positive antibodies called Rh immunoglobulin G (IgG). The mother's IgG antibodies may pass through the [placenta](#) ^[6] and attack the fetal red blood cells inside the [fetus](#) ^[5] since they are recognized as foreign.

The fetal effects of red-cell alloimmunization are known as hemolytic disease of the newborn, which is sometimes referred to as Rhesus disease. Once red-cell alloimmunization occurs, the IgG antibodies released into maternal circulation and the Rh-positive fetal red blood cells bind to form antigen-antibody complexes. These complexes are initiated for destruction, resulting in alloimmune-induced hemolytic [anemia](#) ^[7]. Although the Rh blood group system is comprised of several antigens (i.e., D, C, c, E, e) - the Rh D antigen accounts for the majority of all cases involving [Rh incompatibility](#) ^[4] since it is the most immunogenic. Once red blood cells are broken down, they produce bilirubin, which causes an infant to become jaundiced.

In the majority of cases, sensitization occurs during delivery, and even then, Rh-positive firstborn infants are usually not affected. The process of sensitization trains the body to have a response to future antigens; in this case the Rh factor present in the fetus's red blood cells. After sensitization, it takes time for the mother to develop Rh antibodies against the fetal blood and for her antibodies to equilibrate in the fetus's circulation. Because of the sensitization process, firstborn infants are usually not affected by the mother's sensitization, unless she has been sensitized through previous a [miscarriage](#) ^[11] or [abortion](#) ^[12]. If the mother has not been sensitized before the delivery, the mother does not produce enough IgG antibody response during delivery, leaving the firstborn unharmed.

The risk and severity of sensitization response increases with each subsequent [pregnancy](#) ^[9] involving an Rh positive [fetus](#) ^[5]. Without treatment, women who have increased effects of [Rh incompatibility](#) ^[4] may produce a mildly anemic second child.

Subsequent births, however, may result in fetal death due to severe antibody-induced hemolytic [anemia](#)^[7]. This most extreme form of [Rh incompatibility](#)^[4] is what occurred in the first reported agglutination case in 1939.

Prevention remains the best treatment for [Rh incompatibility](#)^[4]. Since the antibody Rh IgG, or RhoGAM, was first released in 1968, it has been remarkably successful in decreasing [Rh incompatibility](#)^[4]. The administration (injection) of this antibody, was originally referred to as “Big D” in blood-banking circles and was made from the plasma of other Rh-positive mothers who had given birth to an Rh-positive child. Women who had usually high concentrations of “Big D” were reported to have made up to 80,000 dollars a year for selling their plasma. Nonetheless, the commercial production of this antibody has reduced the risk of [Rh incompatibility](#)^[4] from 10 to 20 percent to less than 1 percent. The antibody is administered whenever there is a chance of Rh-positive fetal cells entering the maternal circulation of an Rh-negative mother. When indicated, it is normally administered at 28 to 32 weeks of [pregnancy](#)^[9] and again within 72 hours after delivery. Threatening or spontaneous [miscarriage](#)^[11], amniocentesis, or chorionic villus sampling results may also indicate the need for administration of RhoGAM.

The exact mechanism of how RhoGAM works is still unknown and it is only used for preventing Rh disease. Once sensitization has occurred in the mother, RhoGAM is not effective in preventing the progression of the disease. Once the affected infant is born, aggressive hydration and phototherapy using bilirubin lights can be used as treatment against [jaundice](#)^[13]. In severe cases, an intrauterine blood transfusion may be required while the [fetus](#)^[5] remains in the [uterus](#)^[14]. In order to correct the fetus' [anemia](#)^[7], this procedure involves a needle directed into the [umbilical cord](#)^[15] under [ultrasound](#)^[16] guidance. The transfusions take place every two to three weeks through the remainder of the [pregnancy](#)^[9].

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