

Hemolytic Disease of the Fetus/Newborn

(Erythroblastosis Fetalis)

Introduction

Hemolytic disease of the fetus or newborn is a disease that often confuses many expectant parents. By better understanding the disease, many of the treatments required may be less stressful. With proper and timely treatment, the effects of the disease can often be minimized. The purpose of this booklet is to briefly discuss the disease and its management as well as hopefully to answer any questions you may have. Below are the answers to frequently asked questions concerning **Hemolytic Disease of the Fetus/Newborn**.

1. What is red cell alloimmunization and how does one get it?

To understand red cell alloimmunization, one must first understand about the different blood group factors. These factors appear on the surface of the red blood cell in the form of **antigens**. The main blood group factor system is the commonly known ABO system. These are four basic blood types in this system: A, B, AB, and O. Rh(D) is another blood group antigen that is either present or absent on human red blood cells. When a patient is called **Rh negative**, she does not have the Rh(D) antigen present on her red blood cells, whereas if an individual is called **Rh positive**, the antigen is present. There are a variety of other red blood cells antigen systems found in humans. These include Kell, Duffy, Kidd, and MNS. In general, much like the Rh system, these antigens are either present, and the individual is called positive for the antigen, or absent, and the individual is called negative for the antigen. When a woman becomes pregnant, genes (inherited traits) from her egg are combined with genes from her partner's sperm. Together a unique embryo (future baby) is formed. This embryo carries with it genes from both the mother and the father. These genes include traits such as hair color, body build, ABO blood type, and Rh factor. **Red cell alloimmunization**, also known as **Rh disease** if the Rh factor is involved, occurs in response to an **antibody** (a protein substance that reacts to unrecognized proteins in the body) that is formed by the mother (see Diagram 1).

Diagram 1

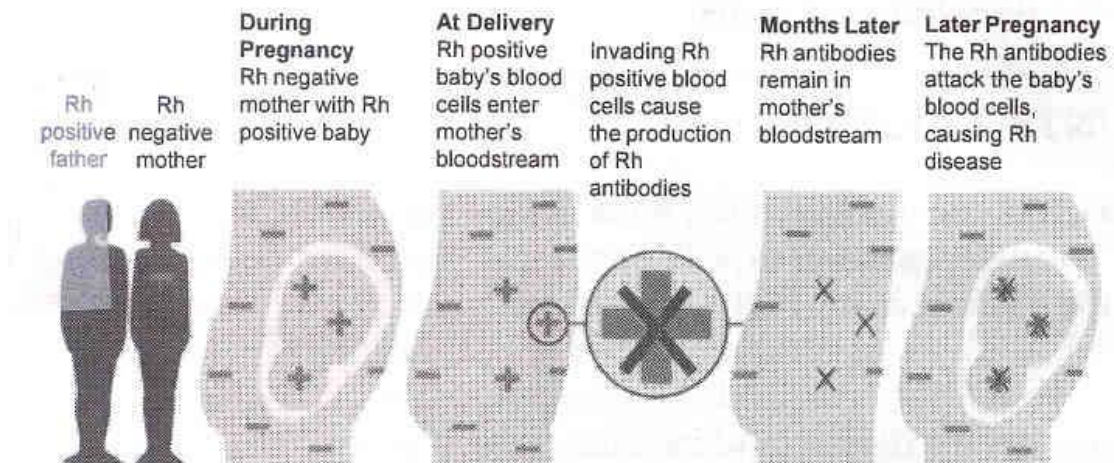


Diagram courtesy of Ortho Diagnostics

These antibodies can form in response to receiving blood during a blood transfusion that was different from your own. More commonly they form after a miscarriage, abortion, or the delivery of a child, when the baby's blood mixes with your own. If your blood is negative for a particular antigen and the baby's blood cells carry the antigen, you may form antibodies against your baby's red blood cells. During subsequent pregnancies, these antibodies cross the afterbirth (placenta), and attach to the red blood cells of the baby. These antibodies can be measured in your bloodstream through a test called a **titer**. If enough of these antibodies are present in your bloodstream (titer of 32 or more in most cases; titer of 8 for **Kell disease**), they may cause the baby's red blood cells to break open, which may cause the baby to become **anemic** (have a low blood count) or become **jaundiced** (yellow). The disease process that occurs in the fetus or baby is known as **hemolytic disease of the fetus/newborn**. It is a direct result of the red cell alloimmunization in the mother. In severe cases the baby develops generalized edema (swelling all over his/her body), also known as **hydrops fetalis**. In the most severe cases, heart failure or even death in the womb may occur.

2. *Can red cell alloimmunization and subsequent hemolytic disease of the fetus/newborn be prevented?*

Cases of Rh disease can be prevented. All Rh-negative women should receive a medication called **Rhesus immune globulin** after an abortion, miscarriage, or delivery of an Rh-positive infant. Rh-negative women should also routinely receive this medication during a pregnancy at 28 weeks' gestation (7 months). Other rare times when the medication is required include tubal pregnancy (ectopic pregnancy), amniocentesis, and after automobile accidents. This medication is given as an injection in the arm or hip. If given correctly, Rhesus immune globulin is over 99% effective in preventing Rh disease. Unfortunately, the protection from this injection is not permanent. It must be given each time there is a chance for fetal red blood cells to enter your bloodstream. In some pregnancies, this may mean two or three injections for the protection.

An equivalent medication to Rhesus immune globulin is not available to protect women from forming antibodies to other red cell antigens such as Kell, Duffy, and MNS.

3. *Does red cell alloimmunization cause repeated miscarriages?*

No. Your anti-red cell antibodies do not even begin to cross to the unborn child until approximately 10 weeks' gestation (two and a half months of pregnancy).

4. *How is hemolytic disease of the fetus/newborn diagnosed?*

One of the first steps in determining if your unborn baby may be affected by your antibodies is to check the blood type of the baby's father. In cases of Rhesus disease, the father of your unborn baby will be Rh negative (like your blood type) in 15 out of 100 cases. This will result in the baby not being affected at all. In other cases, the baby has a chance of being Rh positive (a different blood type from you). In these cases, the baby may develop a low blood count (**anemia**) while in the womb. If the father of the baby is Rh-positive, there is a 1 in 2 chance that his blood type is of a mixed variety (**heterozygous**). This means that half of this offspring will be Rh-negative (will have no problems) and the other half will be Rh-positive (may develop anemia). This occurs by chance, like a roll of the dice, at the time of fertilization of the egg. If the father of the baby is found to be a pure Rh-positive blood type (**homozygous**), then all of his children will be Rh-positive and have the chance to be affected by your antibodies. A simple

blood test on your partner can determine in most cases if he is heterozygous or homozygous. In cases of red cell alloimmunization due to other red cell antigens, a father can also be tested to see if he is heterozygous or homozygous.

If the father of the fetus is heterozygous, the next step in the process of evaluating the unborn baby is to take a sample of amniotic fluid from the womb to determine the baby's blood type. This will usually be performed after 15 weeks of gestation (four months and one week). Your doctor will obtain this fluid by performing a procedure known as **amniocentesis**. With the aid of ultrasound, a needle will be inserted through your abdomen (stomach) and guided into the bag of water (**amniotic sac**) around the baby (see Diagram 2). Your doctor will then withdraw some fluid and send it to the laboratory. The fluid will be analyzed by testing the genetic material (DNA) in order to tell the baby's blood type. A sample of your blood and the baby's father's blood must also be sent to the laboratory with the fluid sample to verify the results. The results are typically available in approximately one week. If the results should show that the baby is negative for the red cell antigen involved, there is no further risk to your pregnancy and you will be referred back to your primary care physician for the remainder of your prenatal care. If, however, the results show that the baby does carry the antigen for which you have antibodies, then additional testing will be required later in the pregnancy. The chance of fetal loss after amniocentesis is about 1 in 200 procedures.

Diagram 2

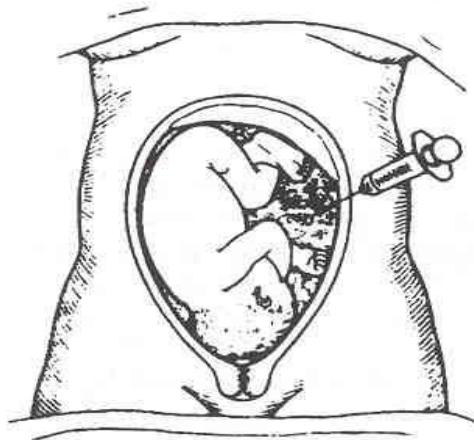


Diagram courtesy of John T. Quennan MD Fetal and Maternal Medicine, John Wiley & Sons, 1980

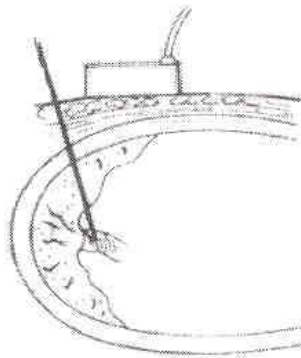
A newer way to determine your baby's blood type uses a blood sample from you. The blood is sent to a special laboratory and the baby's genetic material (DNA) is separated from your DNA to check the baby's blood type. At this time, the blood test can only be done for Rh. Your doctor may offer you this test but special arrangements are necessary to do the test.

If your baby is determined to carry the antigen that is a problem and your titer is high enough, your doctor will use a specialized type of ultrasound to detect if your baby is becoming anemic. As the baby becomes anemic, he/she compensates by increasing the speed that the blood moves through its body in order to provide more oxygen to its tissues. This is accomplished by the baby increasing the efficiency of how its heart pumps. Using specialized ultrasound (**Doppler**) for measuring the speed of the blood, the baby's head is visualized and a special computerized color image of a special blood vessel in the head is noted. This vessel is known as the **middle cerebral artery**. Once the speed of the blood is determined, it is plotted on a standardized graph. Depending on the actual value, the test may be repeated every one to two weeks. If the

Doppler study reveals a very high velocity indicating that the baby may be anemic, your doctor will typically consider cordocentesis to assess the baby's blood count directly.

Cordocentesis is a method of determining how well your baby is doing is by drawing some blood from your baby while the baby is still inside your womb. This procedure is known as **Percutaneous Umbilical Blood Sampling** but is also known as **PUBS** for short or **Cordocentesis**. The procedure is very much like amniocentesis with the exception that instead of inserting the needle into the bag of water around the baby, your doctor will insert the needle into the umbilical cord to get a sample of blood (see Diagram 3). This method enables your doctor to perform a variety of tests to predict the severity of disease in your baby. These include confirmation of blood type, blood count (**hematocrit**), bilirubin level, number of new blood cells being made by the baby (**reticulocyte count**), and the amount of antibody attached to the baby's red blood cells (**direct Coombs**). This procedure is usually reserved until amniocentesis confirms that the baby is positive for the involved red cell antigen, as it is associated with a fetal loss rate of approximately 1%.

Diagram 3



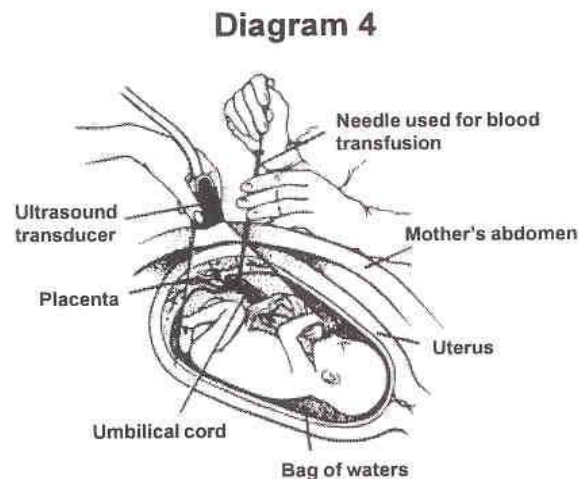
*Diagram courtesy of Contemporary OB/GYN, June Special Issue, 1987 and
Beth Willert Studios, Roselle, New Jersey*

5. How is hemolytic disease of the fetus/newborn treated?

If your unborn baby's blood count is very low, your doctor will probably suggest a blood transfusion for your baby (**intrauterine blood transfusion**). This procedure is typically done at the time of the first cordocentesis in an effort to minimize the risk of puncture of the umbilical vein. At the time of the initial cordocentesis, a small sample of blood is taken from the baby's umbilical cord and a rapid assessment of the hematocrit (baby's blood count) will be performed in the same room. Since most babies are generally very active inside the womb, your doctor will probably want to administer a medication to keep your baby from moving during the procedure. This is usually accomplished by administering a drug called vecuronium, which will *temporarily* stop your baby from moving so that the doctor may give the baby a blood transfusion. The drug is usually administered into the umbilical cord after the initial blood sample is obtained. The effects of the drug usually last between three and four hours. At that time you will begin to feel the baby move again. By giving this medication, blood transfusions to the baby are much easier for the doctor and much safer for your baby. If the initial blood count shows the baby to be very anemic (hematocrit of less than 30%), your doctor will typically begin an **intravascular transfusion**. This is a type of intrauterine transfusion where the blood is injected directly into the umbilical cord (see Diagram 4). Once the correct amount of blood is injected, the needle is removed. Often an additional amount of blood will be placed into the baby's abdomen (belly) as

part of the same procedure. This is called an **intraperitoneal transfusion**. The blood placed into the abdomen is absorbed slowly into the baby's blood vessels over a ten-day to two-week period. This allows the baby to have a better blood count when the next intrauterine transfusion is scheduled.

Because the baby will continue to destroy many of his/her own red blood cells, the baby will likely need several transfusions before birth. The number of transfusions varies but generally ranges between two and eight. These procedures are usually performed two to three weeks apart until approximately 35 weeks of gestation (eight months and three weeks).



6. *Are there any other forms of treatment for hemolytic disease of the fetus/newborn other than intrauterine transfusion?*

On rare occasions because of an extremely high antibody titer or a previous history of a very sick fetus early in pregnancy, your doctor may feel that specialized treatments may be required before the first intrauterine transfusion. At about 10 weeks' gestation (two and one half months) you may be scheduled for **plasmapheresis**. In this procedure, a tube will be placed into a vein and your blood will be washed with a specialized machine. This machine removes the liquid part of your blood (**plasma**) that contains the antibodies. The liquid portion is then replaced with a sterile protein solution. The plasmapheresis is usually done three times (every other day) in the tenth week of the pregnancy. The major risk to plasmapheresis involves a low blood calcium level. This may cause some tingling in your lips, but rarely requires treatment. Typically, your antibody titer will drop by half after the three plasmapheresis procedures.

Because your body will realize that there is not as much antibody present after plasmapheresis, it will try to replace the antibody. In an effort to prevent this, your doctor may prescribe **intravenous immune globulin**. This medication is made from antibodies from many individuals. It will fool your body into thinking that you do not need to make more anti-red cell antibody. In addition it may prevent the remaining bad antibody from crossing over to your baby. Intravenous immune globulin is administered intravenously over 6 to 8 hours. The first treatment is given the day of your last plasmapheresis and repeated the following day. Treatments are then given once each week until 20 weeks of pregnancy (five months). The major side effects of intravenous immune globulin appear to be severe headache, nausea, and rash. Your doctor will probably ask you to take two extra-strength acetaminophen tablets (Tylenol®) before each injection of intravenous immune globulin.

7. *Will I have to be admitted to the hospital for intrauterine transfusions?*

No. You will be asked to come to the hospital as an outpatient within 24 hours of your scheduled procedure to have a tube of blood drawn to match blood for the transfusion. This must be repeated every time your baby has a transfusion. You will then be required to come to the hospital approximately one hour before the procedure is scheduled to begin the next day. The intrauterine transfusion itself is performed on Labor & Delivery and lasts approximately one hour. You will be observed for two to three hours after the procedure, then allowed to go home. Your doctor will ask you to come to the office the following day to look at your baby with ultrasound and make sure everything is fine.

8. *Will I be put to sleep for the intrauterine transfusion?*

No. You will be awake during the procedure. A medication will be injected into your skin where the needle will be inserted to prevent any discomfort. This will be performed twice for the two parts of the intrauterine transfusion. A mild sedative will also be given intravenously to decrease your anxiety.

9. *Are there any risks to the procedure?*

Yes. When a needle is inserted into the womb, the risk of uterine contractions increases. On occasion, contractions may occur after the procedure requiring the use of a medication called **terbutaline**. This is given in the form of a shot under the skin. On rare occasions, you may have to be admitted to the hospital for observation and further treatment of your preterm contractions. Additional risks to the procedure involve the risk of introducing infection into the bag of waters around the baby as well as the risk of premature rupture of the bag of waters. You will be given an intravenous antibiotic after the procedure to prevent infection.

Your doctor may also recommend steroid injections due to the risk of premature labor and/or delivery associated with intrauterine transfusion. Research studies have demonstrated that administration of steroids (**betamethasone**) to the mother increases the rate of development of an unborn baby's lungs and also helps to prevent additional complications of prematurity such as bleeding into the baby's brain (**intraventricular hemorrhage**) and spontaneous perforation of the baby's intestine (**necrotizing enterocolitis**). Steroid injections are generally administered as an intramuscular injection in your shoulder or buttocks between 24 and 34 weeks of gestation.

10. *Does giving blood to the baby increase the chance that either I or the baby may get an infection from using someone else's blood?*

Many parents have voiced concern involving the use of blood products. Blood banks today thoroughly screen for infections such as hepatitis and AIDS making the chance for an infection in your baby very unlikely.

11. *What is the chance my baby will survive if intrauterine transfusions are required?*

Our experience indicates that 85 out of 100 babies survive intrauterine transfusions. Babies that are very sick early in pregnancy (less than 24 weeks' or 6 months' gestation) seem to have more problems with the first transfusion. If it is found that your baby has a very low blood count at this point in the pregnancy, your doctor may transfuse only a small amount of blood. Then you

will be asked to return one or two days later to repeat the intrauterine transfusion. At the second procedure your baby would be given enough red blood cells to raise his/her blood count to normal.

12. *When can I expect to have my baby delivered?*

If all goes well, the last intrauterine transfusion would be performed at about 35 weeks' gestation (eight months and three weeks). You may then be asked to take a medication called phenobarbital to help the baby's liver mature more rapidly. This medication works in a similar fashion to the steroids used to help the baby's lungs mature more rapidly. Our center has found this medication to be useful in preventing jaundice after the baby is born. The phenobarbital is given by mouth three times a day. During the first few days of taking this medication, you may experience some sleepiness. In addition, the medication may cause your baby to slow its movements. These effects will go away after several days. Delivery is usually planned for two to three weeks after the last intrauterine transfusion (37-38 weeks' gestation).

13. *Does having hemolytic disease of the fetus/newborn mean I will have to have a Cesarean Section?*

Not necessarily. If all goes well and you are able to carry the baby to term, chances are you will be able to have a normal vaginal delivery. Your doctor may, however, elect to induce labor.

14. *Will my baby need special attention after he/she is born?*

When it is time for you to have your baby, your doctor will ask a special baby doctor to attend the delivery. This doctor is called a **neonatologist**. These doctors are specially trained to care for newborn infants with special problems such as hemolytic disease of fetus/newborn. It is very likely that your baby will be taken to a nursery specially designed to meet his/her health needs. There, the baby will be closely monitored for any possible complications that may arise. On some occasions the baby may need additional blood transfusions to maintain his/her blood count. Additionally, your baby may be placed under special blue lights often called **bililights** that reduce the amount of bilirubin being formed in the baby's bloodstream. Occasionally, the baby may need to have an **exchange transfusion**. During this type of transfusion, the baby's blood is removed in small amounts, discarded, and replaced with new blood. This procedure is usually performed to drop the level of bilirubin in the baby's bloodstream before it can cause problems. The father of the baby cannot donate blood because he carries the same red cell antigens for which you have antibodies.

15. *When will my baby get to come home?*

The amount of time your baby will need to be hospitalized is variable. This depends on many different factors and can best be answered by your baby's doctor. Generally, babies born to mothers with Rh disease do well but may need to be hospitalized a little longer than babies without the disease.

16. *Will my baby require any other treatment after it comes home?*

Yes. Your baby has a 1 in 2 chance of needing a **top-up transfusion** at about four to six weeks of life. This is necessary because the baby may not start making its own red blood cells until it is this old. You will be asked to have your baby see a pediatrician each week for a blood count. If

your baby's blood count becomes too low, then a top-up transfusion will be required. Generally, only one transfusion is necessary but on rare occasions, two or three transfusions may be required several weeks apart. Your pediatrician may decide to put your baby in the hospital for one or two days for each transfusion. Other pediatricians are comfortable giving the baby a blood transfusion as an outpatient.

17. *Will my baby have any long-term problems as a result of its hemolytic disease of the newborn?*

Research studies to date have shown that approximately 90 to 95% of babies that survive intrauterine transfusions have no developmental problems. Five to ten percent of babies have been found to have evidence of cerebral palsy, but many times this is felt to be related to problems with prematurity itself. Studies have not shown a relationship between how sick the baby is in the womb and the chance for long-term developmental problems. Babies affected by hemolytic disease of the fetus/newborn have a slightly higher chance for hearing loss. Most state laws require that the baby's hearing be tested before he/she is discharged from the hospital. We also recommend a second hearing test by two years of age. Female Rh babies do have a slightly higher chance to develop an umbilical (belly button) hernia. Male Rh babies have a slightly higher chance of developing a groin (inguinal) hernia. Some of these may require surgery at a later date to be repaired.

CONCLUSION

It is sincerely hoped that this booklet has answered many of the questions that you or your family may have concerning **Hemolytic Disease of the Fetus/Newborn**. Your doctor or nurse will be happy to answer any further questions that you may have. Again, our goal is to assist you to deliver a healthy baby and have a safe and enjoyable pregnancy.

Kenneth J. Moise, Jr., MD. Copyright, University of North Carolina at Chapel Hill, 2005.

REFERENCES

Knuppel RA and Drukker JE. **High Risk Pregnancy: A Team Approach**.
W.B. Saunders, Philadelphia, 1993.

March of Dimes. **Public Health Education Information Sheet (9-0179), Rh Disease**, 1984.

Moise KJ. **Changing Trends in the Management of Red Blood Cell Alloimmunization in Pregnancy**. Arch Pathol Lab Med 1994; 118:421-428

Quilligan EJ and Kretchmer N. **Fetal and Maternal Medicine**. John Wiley & Sons, New York, 1980.

Ross Laboratories. **Clinical Education Aid No. 9 Teaching Reference, Erythroblastosis Fetalis** (Hemolytic Disease of the Newborn), 1983.