Hemolytic Disease of the Fetus and Newborn

(Erythroblastosis fetalis)
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**Introduction**

Hemolytic Disease of the Fetus and Newborn is a disease that often confuses many parents expecting a baby. It is caused when red blood cells between the mother and the baby cannot exist together due to a condition called red cell alloimmunization. The purpose of this booklet is to discuss the causes and treatment of Hemolytic Disease of the Fetus and Newborn as well as to answer any questions you may have. By better understanding Hemolytic Disease of the Fetus and Newborn, you may find the treatment easier to understand as well as less stressful. Below are the answers to frequently asked questions about this disease.

1. **How do blood types, antigens, red cell alloimmunization and Hemolytic Disease of the Fetus and Newborn relate to each other?**

Hemolytic Disease of the Fetus and Newborn is caused by red cell alloimmunization. To understand red cell alloimmunization, you must first understand about different blood types. Blood types are determined by the kinds of antigens (substances that help your immune system make antibodies) on the surface of your red blood cells. The most common of these result in the human blood types A, B, AB or O. Other common blood group antigens include RhD, Rh(c) and Rh(E). These Rh antigens are either present (positive) or absent (negative) on human red blood cells. RhD is the most common antigen involved in red cell alloimmunization. When a patient is Rh negative, she does not have the RhD antigen on her red blood cells, whereas if an individual is Rh positive, the RhD antigen is present. Different kinds of blood types are A+, AB- and O+, for example. The + and – signs refer to whether the blood is positive or negative for the RhD antigen on the surface of red blood cells.

There are a variety of other red blood cell antigen systems found in humans such as Kell, Duffy, Kidd, and MNS. In general, much like the Rh system, these antigens are either present, and the person is called positive for the antigen, or absent, and the person 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 determine your baby’s hair color, body build, ABO blood type and Rh factor, among many things.
Red cell alloimmunization, also known as Rh disease if the RhD antigen is involved, happens when a mother’s body forms antibodies (a protein substance that reacts to unrecognized proteins in the body) in reaction to antigens different from her own (see Diagram 1).

**Diagram 1**

These antibodies are usually formed when your (the mother’s) blood circulation comes in contact with blood from another person, such as when receiving blood cells different from your own during a blood transfusion, or more commonly during a miscarriage, abortion, or after the delivery of a child, when the baby’s blood mixes with your own. If your blood is negative for a certain antigen and the baby’s blood cells are positive for that antigen, you may form antibodies against your baby’s red blood cells. During future pregnancies, these antibodies cross the placenta (afterbirth) and attach to the red blood cells of the baby. The amount of antibodies can be measured in your blood through a test called a titer or indirect Coombs test.

If enough of these antibodies are present in your blood (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 (a condition where the baby’s tissues, including the skin and eyes, turn yellow). The disease process that happens in the fetus or baby is known as Hemolytic Disease of the Fetus and 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 or her body), also known as hydrops fetalis. In the most severe cases, heart failure or even fetal death in the womb may occur.

2. **Can red cell alloimmunization and Hemolytic Disease of the Fetus and Newborn be prevented?**

Cases of Rh disease, a kind of red cell alloimmunization, can be prevented. All Rh-negative women should receive a medicine called Rhesus immune globulin after an abortion, miscarriage or delivery of an Rh-positive infant. Rh-negative women should also routinely receive this medicine at 28 weeks of pregnancy. Other rare
times when the medicine is required include ectopic (tubal) pregnancy, amniocentesis and after car accidents. This medicine is injected through a needle into the arm or hip. If given correctly, Rhesus immune globulin is over 99 percent 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 protection.

A similar-acting 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 begin to cross to the unborn child until approximately ten weeks of pregnancy.

4. How is Hemolytic Disease of the Fetus and Newborn diagnosed?

Physicians take several steps to diagnose this disease. They can:

- Check the father’s blood type
- Perform an amniocentesis (the process of getting a fluid sample from the amniotic sac) to check the baby’s blood type
- Perform a free fetal DNA test on your blood to check the baby’s Rh blood type
- Conduct an ultrasound to check the baby’s level of anemia
- If necessary, conduct a cordocentesis (the process of getting a blood sample from the unborn baby’s umbilical cord) for more information

**Checking the Father’s Blood Type**

One of the first steps in finding out whether your unborn baby may be affected by your antibodies is to check the blood type of the baby’s father. In cases of Rh disease, the father of your unborn baby will be Rh-negative (like your blood type) in about 15 out of 100 cases. This will result in the baby not being affected at all.

If the father of the baby is Rh-positive, your doctor will check to see if his blood is heterozygous (of a mixed variety) or homozygous (of a pure variety). If his blood is heterozygous, it means that half of this children will be Rh-negative (will have no problems) and the other half will be Rh-positive (may develop anemia, also known as low blood count). This occurs by chance, like a roll of the dice, when the sperm and egg meet. If the father of the baby is found to be homozygous (a pure Rh-positive blood type), then all of his children will be Rh-positive. This means his children have the chance to be affected by your antibodies. 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.
Amniocentesis

If the baby’s father’s blood is heterozygous, the next step in diagnosis is to determine the baby’s blood type by taking a sample of amniotic fluid to test it. Amniotic fluid is the fluid your baby lives in while inside the womb. Your doctor will get this fluid by performing an amniocentesis, a procedure often conducted after about 15 weeks of pregnancy. With the aid of ultrasound, your doctor will insert a needle through your abdomen (stomach) and guide it into the amniotic sac (bag of water) around the baby (see Diagram 2). Your doctor will then draw some fluid and send it to the laboratory. The laboratory will test the genetic material (DNA) of the fluid in order to tell the baby’s blood type. The chance of fetal loss after amniocentesis is about one in 200 procedures.

A sample of your blood and the baby’s father’s blood must also be sent to the laboratory with the amniotic fluid sample to verify the results. The results are typically available in about one week. If the results show that the baby doesn’t have the red cell antigen for which your blood has developed antibodies, there is no further risk to your pregnancy and you will be referred back to your primary care physician for the rest of your prenatal care. If, however, the results show that the baby does carry the antigen for which you (the mother) have antibodies, then additional testing will be required later in the pregnancy.

Your doctor may also test the baby’s amniotic fluid to check the level of bilirubin (a substance produced by the breakdown of red cells that causes jaundice, a yellowing of the skin and tissues). The higher the level of bilirubin in the amniotic fluid, the greater is the chance that your baby could be sick. If your doctor decides to do a series of amniocentesis to check bilirubin levels, they will usually happen at one-week to three-week intervals. This older test is rarely used today.

Free Fetal DNA

If the father of the baby is heterozygous for the red cell antigen causing your antibodies, a free fetal DNA test can done on your blood to detect the baby’s Rh type. Free fetal DNA is a common occurrence in all pregnancies where some of the baby’s genetic material (DNA) leaks into the mother’s blood stream through the placenta. That means your blood can be tested for information about the baby’s blood. Currently the free fetal DNA test can only be used to find the RhD type of an unborn baby; it will not work for other red cell antigens like little “c” or Kell.
Ultrasound

In most situations, your doctor will use a special type of ultrasound to detect the baby's anemia. This is important in cases of Kell alloimmunization, where the usual amniocentesis test for bilirubin cannot predict when a baby is becoming anemic. The ultrasound measures the speed of the baby's blood, which is related to its level of anemia. As babies become anemic, they increase the speed that their blood moves through their bodies in order to provide more oxygen to their tissues. To do this, they increase the efficiency of how their hearts pump. A Doppler (ultrasound) measures the speed of the blood by creating a color image of the baby's head, including a special blood vessel called the middle cerebral artery. The medical staff determines the speed of the blood and compares it to the median (middle range) of other babies that are the same age in pregnancy. The test result is called a multiple of the median (MoM). Depending on the results, the test is usually repeated every one to two weeks. If the study reveals a very high blood speed over time (more than one and a half times normal or 1.5 MoM), your baby may be anemic and your doctor will typically consider cordocentesis to measure the baby’s blood count directly.

Cordocentesis

Another way to tell how well your baby is doing is by drawing some blood from your baby while he or she is still inside your womb. This procedure is called cordocentesis. The procedure is very much like amniocentesis except 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 allows your doctor to perform a variety of tests to predict the level of disease in your baby. These tests 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). Usually a cordocentesis isn’t performed 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 one percent.

Diagram 3

Diagram courtesy of Contemporary OB/GYN, June Special Issue, 1997 and Beth Willert Studios, Roselle, New Jersey
5. How is Hemolytic Disease of the Fetus and Newborn treated?

If your unborn baby’s red blood cell count is very low, your doctor will probably suggest an intrauterine blood transfusion for your baby (a blood transfusion that happens inside the uterus, or womb). This procedure is typically done at the time of the first cordocentesis so that the umbilical vein does not need to be tapped again.

There are usually two parts to an intrauterine transfusion. The first part is the intravascular transfusion (for babies in the womb, this means when blood goes right into the umbilical cord). See Diagram 4. The second part is the intraperitoneal transfusion (when blood goes into the baby’s stomach to be slowly absorbed).

![Diagram 4](image)

At the time of the first cordocentesis, a small sample of blood is taken from the baby’s umbilical cord; the baby’s hematocrit (blood count) will be measured immediately in the operating room. If the blood count shows the baby to be very anemic (hematocrit less than 30 percent), your doctor will typically begin an intravascular transfusion.

Since most babies are generally very active inside the womb, your doctor will probably give your baby medicines to keep him or her from moving during the procedure. Your baby will receive this medicine in his or her umbilical cord after the initial blood sample is drawn. This medicine helps make blood transfusions to the baby easier for the doctor and much safer for your baby. The effects of the medicine usually last between three and four hours. At that time you will begin to feel the baby move again.

Once your baby receives the correct amount of blood from the transfusion, the needle is removed. Often, doctors place some blood into the baby’s abdomen (stomach) in a procedure called an intraperitoneal transfusion. The baby’s body slowly absorbs this blood into his or her 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 or 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. Your doctor will typically perform these procedures two to three weeks apart until about 35 weeks of pregnancy.
6. What other forms of treatment for Hemolytic Disease of the Fetus and Newborn are there besides blood transfusion?

Plasmapheresis is another kind of treatment your doctor may suggest if there is a very high antibody level or a history of a very sick fetus early in your previous pregnancy. If this is the case, your doctor will schedule plasmapheresis at about ten weeks of pregnancy. Plasmapheresis helps remove the antibodies in your blood that are causing red cell alloimmunization. In this procedure, the medical staff will place a tube into your vein to withdraw blood. A special machine will then remove the plasma (the liquid part of your blood) that contains the antibodies. The liquid portion is then replaced with sterile salt water and your red blood cells are transferred back into your body. Plasmapheresis is usually done three times (every other day) in the 10th week of pregnancy. The procedure may lower your blood calcium level which may cause some tingling in your lips, but rarely requires treatment. Typically, your antibody level will drop in half after three plasmapheresis procedures.

Because your body will realize that there is not as much antibody in your blood after plasmapheresis, it will try to replace the antibody. In an effort to prevent this, your doctor may prescribe intravenous immune globulin, which you will receive in a vein. This medicine is made from antibodies from many people. It will fool your body into thinking that you do not need to make more anti-red cell antibody. It may also prevent the remaining antibody from crossing over to your baby. It takes six to eight hours to receive intravenous immune globulin through your veins. The first treatment is given the day of your last plasmapheresis and repeated the following day. You will then receive treatments once each week until 20 weeks of pregnancy. The major side effects of this medicine appear to be severe headache, nausea and rash. Your doctor will probably ask you to take two extra-strength acetaminophen tablets (Tylenol®) before you receive this medicine.

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

No. Your doctor will ask you to visit the hospital the day before your scheduled procedure to have a tube of blood drawn to prepare the blood for the transfusion. This must be repeated every time your baby has a transfusion. Your doctor will then ask you to go to the Labor and Delivery Unit at St. Luke’s Episcopal Hospital two hours before your scheduled procedure. You should not eat or drink anything for at least eight hours prior to your scheduled procedure. Your family may come with you to the hospital and wait for you during your procedure in one of our labor and delivery waiting rooms. The medical staff will insert an intravenous line (IV) by needle stick and draw tubes of blood for pre-operative lab tests. This IV will also allow you to receive fluids and medicine during and after surgery. An obstetrics and gynecology resident will perform a brief history and physical exam and then you will talk with an anesthesiologist. If you are far enough along in your pregnancy, you may talk with a neonatologist (high risk pediatrician). A maternal-fetal medicine specialist will use an ultrasound to locate your baby’s placenta and umbilical cord. The nurse will give you a shot of terbutaline under your skin to prevent preterm contractions. This medicine may make your heart beat fast and may make you feel jittery. A specially trained nurse coordinator who will assist in the procedure and an anesthesiologist will come with you to the operating room at Texas Children’s Hospital.
After the procedure, the hospital staff will take you back to the recovery room or a labor room at St. Luke’s. The hospital staff will observe you for several hours before you go home. The next day, your doctor will schedule you to come to the Baylor Clinic for an ultrasound to make sure everything is fine.

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

No. You will be somewhat awake during the procedure (this is called conscious sedation). An anesthesiologist will inject medicine through the tube in your vein to make you sleepy. In addition, the fetal intervention physician will inject local “numbing” medicine to prevent discomfort where the transfusion needle will go into your stomach. This will be performed twice for the two parts of the intrauterine transfusion.

9. Are there any risks to the procedure?

Yes. When a needle is inserted into the womb, the risk that your uterus will contract increases. If your uterus contracts after the procedure, you will receive a shot to help it stop. On rare occasions, you may have to be admitted to the hospital for observation and further treatment of your contractions. Additional risks to the procedure involve the risk of infection in the amniotic sac (bag of waters around the baby) as well as the risk of breaking the amniotic sac.

Your doctor may also recommend steroid injections due to the risk of premature labor and/or delivery associated with intrauterine transfusion. Research studies show that betamethasone (steroid) injections to a mother increase the rate of development of an unborn baby’s lungs. They also help to prevent other complications of prematurity such as intraventricular hemorrhage (bleeding into the baby’s brain) and necrotizing enterocolitis (spontaneous perforation of the baby’s intestine). Steroid injections are given as two injections generally in your shoulder or buttocks muscles between 24 and 34 weeks of pregnancy. On occasion, the two injections are repeated if several weeks have gone by since the first injections and you have not yet delivered.

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 about the use of other people’s blood for intrauterine transfusions. Today’s blood banks thoroughly screen for infections such as hepatitis and AIDS so that the chance that you and your baby could contract these diseases is very, very rare.

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

Our experience at Texas Children’s Fetal Center shows that three out of four babies survive intrauterine transfusions. Babies that are very sick early in pregnancy (fewer than 24 weeks) seem to have more problems with the first transfusion. If 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 your doctor will ask you to return one or two days later to repeat the intrauterine transfusion. At the second procedure your baby will be given enough red blood cells to raise his or her blood count to normal.
12. When can I expect to have my baby delivered?

Your doctor will usually plan to deliver your baby two to three weeks after your last intrauterine transfusion (37 to 38 weeks of pregnancy).

If all goes well, your last intrauterine transfusion will be performed at about 35 weeks of pregnancy. Your doctor may then give you a medicine called phenobarbital to help the baby’s liver mature more rapidly. This medicine works in a similar fashion to the steroids used to help the baby’s lungs mature. Texas Children’s Fetal Center has found this medicine to be useful in preventing jaundice after the baby is born. You will take this medicine three times a day by mouth. During the first few days of taking phenobarbital, you may feel sleepy and your baby may slow his or her movements. These effects will go away after several days.

13. Does having Hemolytic Disease of the Fetus and Newborn mean I will have to have a cesarean section?

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

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

When it is time for you to have your baby, your doctor will ask a neonatologist to attend the delivery. This is a doctor who is specially trained to care for newborn infants with health conditions such as Hemolytic Disease of Fetus and Newborn. It is very likely that your baby will be taken to a nursery specially designed to meet his or her health needs. There, the baby will be closely monitored for any possible issues that may arise. On some occasions, the baby may need more blood transfusions to maintain his or her blood count. Nurses may also place your baby under special blue lights, often called bililights, which reduce the amount of bilirubin forming in the baby’s bloodstream. Sometimes, the baby may need to have an exchange transfusion. During this type of transfusion, the baby’s blood is removed in small amounts and replaced with new blood. This procedure is usually performed to drop the level of bilirubin in the baby’s blood.

15. Can I breastfeed my baby?

There is no reason why you cannot breastfeed your infant. If your baby needs specialized treatment in the intensive care nursery, you may be asked to “pump” your breast milk to store it for later use. A lactation consultant can help you with either breastfeeding or pumping.

16. When will my baby get to come home?

Your doctor will be able to let you know how long your baby will stay in the hospital after delivery. The amount of time depends on many factors concerning your baby’s health. Generally, babies born to mothers with Rh disease do well, but may need to be hospitalized a little longer than babies without the disease.
17. Will my baby require any other treatment after it comes home?

Yes. If your baby required several intrauterine transfusions, most of his or her red blood cells are those received during the transfusions. Often the transfusions have worked so well that the baby is no longer independently making any of his or her own red blood cells because his or her bone marrow (the place where new red blood cells are made) has gone to sleep. For this reason, your baby’s pediatrician will check your baby’s blood count each week. If the blood count becomes too low, your baby’s pediatrician will suggest a “top-up” transfusion, which means your baby receives blood and none is removed. Your baby has a one in two chance of needing a “top-up” transfusion at about four to six weeks of life. Some babies with Hemolytic Disease of the Fetus and Newborn may not start making their own red blood cells until this age, which is why they might need this transfusion.

Generally, only one transfusion is necessary but on rare occasions, your baby may need two or three transfusions 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 during a single day hospital visit.

18. Will my baby have any long-term issues because of Hemolytic Disease of the Fetus and Newborn?

Research studies to date have shown that about 90 to 95 percent of babies that survive intrauterine transfusions have no developmental issues. Five to ten percent of babies have been found to have evidence of cerebral palsy, but this may 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 issues. Rh babies are more likely to have umbilical (belly button) hernias than babies who do not have the disease; some hernias may require surgery at a later date to be repaired.

Hearing loss may occur more often in infants affected by Hemolytic Disease of the Fetus and Newborn than those not affected. This may be related to the high bilirubin (jaundice) levels that the fetus experiences in the womb while its hearing ability is developing. Most states require newborn hearing testing soon after birth before the baby leaves the hospital. We recommend a repeat hearing test at one and three years of age.
Conclusion

We hope this booklet has answered many of the questions that you or your family may have concerning Hemolytic Disease of the Fetus and Newborn. Your doctor or nurse coordinator will be happy to answer any further questions at any time. Again, our goal is to help you deliver a healthy baby and have a safe and enjoyable pregnancy.

Kenneth J. Moise, Jr., M.D.

References


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