Hemolytic disease of the fetus and newborn (HDFN), also known as erythroblastosis fetalis, is a blood disorder that occurs when the blood types of a mother and baby are incompatible. For reference, “Hemolytic” means breaking down of the red blood cells and “Erythroblastosis” refers to the making of immature red blood cells. This is a disease that often confuses many expectant parents and 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.

What is red cell alloimmunization, also known as Rh Disease, and how does one get it?
Red cell alloimmunization, often called Rh (Rhesus) disease, is a type of HDFN. To understand red cell alloimmunization, one must first understand 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 from her egg are combined with genes from her partner’s sperm to form a unique embryo carrying 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, or Rh disease, occurs in response to an antibody – a protein substance that reacts to unrecognized proteins in the body – that is formed by the mother. These antibodies are usually formed in response to receiving blood during a blood transfusion that was different from the mother’s own, or more commonly during a miscarriage, abortion, or after the delivery of a child, when the baby’s blood mixes with the mother’s.

If the mother’s blood is negative for a particular antigen and the baby’s blood cells carry the antigen, the mother may form antibodies against the baby’s red blood cells. During subsequent pregnancies, these antibodies cross the placenta and attach to the red blood cells of the baby. These antibodies can be measured in the mother’s bloodstream through a test called a titer or indirect Coombs test. If enough of these antibodies are present in the mother’s 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, causing the baby to become anemic (have a low blood count) or become jaundiced. The disease process that occurs in the fetus or baby is known as hemolytic disease of the fetus/newborn (HDFN). 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 hydrodrops fetalis. In the most severe cases, heart failure or even death in the womb may occur.

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Checking the Father’s Blood Type
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 Rh disease, the father of your unborn baby will be Rh negative (like your blood type) in 13 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 approximately a 50 percent 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. In cases of Rh disease, a partner can be tested through a DNA blood test performed at a special laboratory. In the case of red cell alloimmunization due to other red cell antigens, a partner can be tested to see if he is heterozygous or homozygous through a simple blood test performed at most hospital blood banks.

Free Fetal DNA
If the father of the baby is found to be heterozygous or if a patient’s partner is not available for testing, a free fetal DNA test can be done on the mother’s blood to detect the baby’s Rh type. Free fetal DNA is found in the pregnant woman’s bloodstream as early as 10 weeks of gestation due to leakage of DNA material from the placenta. Currently the free fetal DNA test is only available for determining the Rh type of the fetus; testing for other red cell antigens is not yet available.

Ultrasound
A special type of ultrasound called Doppler can be used to measure the speed of your baby’s blood as it moves through a particular blood vessel in the baby’s brain. This vessel is called the middle cerebral artery (MCA). As babies become anemic, they increase the speed of the blood that moves through their body in order to deliver more oxygen to their tissues. The top speed of the blood moving through the MCA is then compared to a normal value for the point in pregnancy when it is being measured. The test result is reported as the multiples of the median or MOM’s. A test result more than one and a half times higher than the usual value (> 1.5 MOM’s) indicates that the baby is likely to be anemic. MCA measurements can be started as early as 16 weeks of pregnancy and are usually repeated every 1 – 2 weeks.

Cordocentesis
This test is typically not performed unless the MCA Doppler is abnormal. It involves drawing blood from your baby while the baby is still inside your womb. This procedure is known as Cordocentesis or Umbilical Blood Sampling. The procedure is very much like amniocentesis with the exception that instead of inserting the needle into the bag of waters around the baby, your doctor will direct a needle with ultrasound into the umbilical cord to get a sample of blood. 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), 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).
Treatment

If your unborn baby’s count is very low, your doctor may suggest a blood transfusion for your baby – an intrauterine blood transfusion. This procedure is typically done at the time of the first cordocentesis in an effort to minimize the risk or 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 likely administer a medication – usually a drug called vecuronium – that will temporarily keep your baby still during the procedure 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 less than 30%), your doctor will typically begin an intravascular transfusion, which is a type of intrauterine transfusion where the blood is injected directly into the umbilical cord. 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 in a type of procedure 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 fight 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).

Are there any other forms of treatment for Hemolytic Disease of the Fetus and 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 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 albumin, a sterile protein solution made from human blood. 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 in 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 (IVIG). 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 antibody from crossing over to your baby. Intravenous immune globulin is administered intravenously over six to eight hours. The first treatment is given the day of your last plasmapheresis and repeated the following day. Treatments are then given once a week using a home health care agency until 20 weeks of pregnancy. The common side effect of intravenous immune globulin is severe headache. This can usually be prevented by taking two extra-strength acetaminophen tablets (Tylenol®) before each injection of intravenous immune globulin. In some cases the headache can be as severe as a migraine and may require admission to the hospital. The highest chance for this is when you receive the first two doses of the IVIG after the plasmapheresis. After these doses, the chance for developing a severe headache is much less. Other side-effects of IVIG include nausea or a mild rash on the palms of your hands.
**Will I have to be admitted to the hospital for intrauterine transfusion?**

No. You will be asked to come to the hospital as an outpatient the day prior to your scheduled procedure to have a tube of blood drawn to crossmatch 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 several hours before your scheduled procedure. The intrauterine transfusion itself is performed in the operating room 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.

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

No. You will be awake during the procedure. A local “numbing” 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. An anesthesiologist will also give you medications through your IV to induce drowsiness during the procedure.

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

Yes. When a needle is inserted into the womb, the risk of uterine contractions increases. You will probably be given a medication in the form of a shot that is injected under the skin called terbutaline. This medication will cause your heart rate to increase and may make you feel very shaky. On rare occasions, you may have to receive a second shot of terbutaline in the recovery room if preterm contractions are noted after the procedure. Additional small risks to the procedure involve the risk of introducing infection onto the bag of waters around the baby as well as the risk of premature rupture of the bag of waters. Finally, there is about a 5% chance that the baby’s heart rate could slow down during the procedure. If this would happen, the needle will be removed from the umbilical cord. This usually causes the heart rate to recover to normal. However in some cases, the baby’s heart rate may remain slow. Once you reach a point in pregnancy when the baby could survive in the nursery, your doctor may elect to deliver your baby by emergency C-section. You will be put to sleep in these cases by the anesthesiologist. A special pediatric team will be immediately available to care for your baby should this happen.

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 a shot in your buttocks between 24 and 34 weeks of gestation.

**Frequently Asked Questions**

For more information on Hemolytic Disease of the Fetus and Newborn (HDFN), including answers to frequently asked questions, visit childrens.memorialhermann.org/fetal/rh-disease.

**Referrals**

To refer a patient, call 832.325.7288 or visit childrens.memorialhermann.org/thefetalceter.
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