# Hemolytic Disease of the Fetus and Newborn

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## Acknowledgment

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## Disease Overview

Hemolytic disease of the fetus and newborn (HDFN) can occur in an unborn baby or newborn if the mother has red cell antibodies (a diagnosis known as maternal red cell alloimmunization). During pregnancy, these antibodies can cross through the placenta and enter the unborn baby's blood and destroy the baby's red blood cells causing anemia (low blood count). The child is at risk for HDFN if their blood type matches the mother's antibody. Symptoms can be mild or severe. Maternal-fetal incompatibility with ABO, Rhesus factor (Rh) and/or other red blood cell antigens, RhD, Kell, and other non-ABO alloantibodies are the primary cause of moderate to severe HDF whereas ABO HDFN is typically mild and occurs after birth.

## Synonyms

- maternal alloimmunization
- Rh disease
- isoimmunization
- erythroblastosis fetalis
- fetal erythroblastosis
- HDFN

## Signs & Symptoms

In the unborn baby (fetus) symptoms may include:

- Anemia, which can be seen using specialized ultrasounds called middle cerebral artery (MCA) Doppler ultrasounds
- In severe cases, untreated anemia can progress to hydrops (condition in which large amounts of fluid buildup around organs cause extensive swelling), organ damage and death

In the newborn baby symptoms may include:

- Anemia which is measured by a blood draw for hemoglobin/hematocrit and sometimes noticeable as paleness, lethargy, fussiness or rapid breathing or heart rate
- High bilirubin (hyperbilirubinemia) which his measured by blood draw for total serum bilirubin and sometimes noticeable as yellowing of skin or eyes
- Bilirubin encephalopathy which can be noted by high pitched crying or seizures (in severe untreated cases; rare in developed countries)
- Low white blood cell count (neutropenia) in some cases
- Low platelet count (thrombocytopenia) in some cases

If untreated or if not treated quickly, HDFN can progress to hydrops, organ failure and death.

Hyperbilirubinemia is not a concern while the baby is inside the uterus, but it can become serious in newborn babies. If not managed well, hyperbilirubinemia can cause brain damage, developmental delay, hearing impairment or death. With proper management, survival rates of 92-98% have been reported in skilled referral centers.

After birth the child remains at risk of HDFN until maternal red cell antibodies are cleared from the child's blood, usually by 12-15 weeks of age. Long-term health problems are rare. Challenges with development (like cerebral palsy and hearing issues) have been reported in 4.8% of children who required intrauterine transfusion (IUT) for HDFN, but this was mostly in cases of severe hydrops, which is almost always preventable with close monitoring and timely, skilled treatment.

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## Causes

A female can develop red cell alloimmunization after exposure to blood that is not her own through blood transfusion, needle drug use, or pregnancy when mother and baby's blood may mix due to bleeding, miscarriage, delivery or other procedures. Once she develops antibodies, they remain in her bloodstream forever, though antibody levels can drop to undetectable levels at times. In order for the baby to have HDFN, the mother must have red cell alloimmunization.

The most common form of alloimmunization is the development of anti-D antibodies to the D antigen (i.e., a mother with an RhD negative blood type develops antibodies to a baby with an RhD positive blood type), which is why HDFN was once called "Rh disease". The development of Rh immune globulin (RhIG, trade names:  RhoGAM, Rhophlac, HyperRHO and WinRho) in the 1960's has greatly reduced the number of women with anti-D alloimmunization in developed countries. The RhIG injection is given to RhD negative mothers after any pregnancy bleeding, routinely at 28 weeks of pregnancy and then within 72 hours of birth. This prevents the mother with a Rh-negative blood type from developing anti-D antibodies when pregnant with a child with a Rh-positive blood type.

While RhIG prevents most cases of anti-D alloimmunization, it can still occur when doses are missed. Having access to RhIG is also very limited in some countries. Alloimmunization is now considered a rare disease but cases of D alloimmunization still happen. In addition to anti-D, there are more than 50 red cell antigens which can

cause HDFN. There is no preventative treatment for the development of these antibodies, most commonly anti-K, anti-E, anti-C and others in the MNS and Duffy blood group systems. In a recent U.S. survey among alloimmunized females with previous alloimmunized pregnancies, multiple antibodies were present in 47%. Their specific antibodies included anti-D (44%), anti-E (38%), anti-C (21%), anti-c (21%), anti-K (16%), anti-Fya (8%), anti-Jka (7%), followed by anti-G, anti-S, anti-k and others.

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## Affected populations

In the United States, a nationwide Rh HDFN estimate of 106 per 100,000 births in 1986 was obtained from analysis of the nationwide Birth Defects Monitoring Program.  Since then, alloimmunization rates from 740 to 1200 per 100,000 births and HDFN rates from 3 to 150 per 100,000 births have been estimated from single-center studies of Rh, ABO, or other significant red cell antibodies. Variability in estimated rates may be due to small sample size and differences in HDFN severity reported. A recent study utilized the National Hospital Discharge Survey (NHDS) from 1996 to 2010 to identify newborns with HDN and estimated similar rates.

HDFN affects an estimated 3 in 100,000 to 80 in 100,000 patients annually.

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## Disorders with Similar Symptoms

Other disorders can cause anemia and hyperbilirubinemia in the fetus or newborn. Fetal anemia requiring intrauterine transfusion is most often necessary due to HDFN but can also be needed in cases of parvovirus B19, significant bleeding between the mother and baby (called fetal-maternal hemorrhage) or twin-to-twin transfusion syndrome.

After birth, anemia and hyperbilirubinemia are common issues for babies and not always related to HDFN. However, anemia and hyperbilirubinemia due to HDFN present in different patterns than typical neonatal/breastmilk jaundice or iron deficiency anemia. Anemia due to HDFN can have a delayed start (1-3 weeks of age and continuing up to 12-15 weeks of age) and may require so called “top-up’ red cell transfusions. These usually involve an overnight admission for the baby. Anemia due to HDFN after birth is not related to lack of iron and will not improve with iron

medication (this can cause iron overload in newborns with HDFN). Hyperbilirubinemia due to HDFN can include a rapid and persistent rise in bilirubin and often peaks at days 4-6, whereas newborn or breastmilk jaundice can rise more slowly and can last longer.

Other antibody-related pregnancy and neonatal diseases that are not related to HDFN include platelet alloimmunization (causing fetal/neonatal alloimmune thrombocytopenia, FNAIT) and anti-SSA/SSB antibodies, most commonly seen in mothers with lupus or other autoimmune disorders, which can cause a slow heart rate (called congenital heart block) and permanent cardiovascular damage to the fetus.

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## Diagnosis

In developed countries, screening for red cell alloimmunization is standard in the first trimester of pregnancy. After a positive antibody screen, the antibody is identified, and the level (titer) should be checked with a blood draw on the mother. If the antibody is known to cause HDFN, it is necessary to find out the baby's antigen status to understand whether the baby is at risk of HDFN.

In order for red cell antibodies to affect the baby and cause HDFN, the child must have the matching antigen that the mother's antibody attacks. This can be determined in three ways. The simplest and lowest-risk method is to do cell free fetal DNA (cffDNA) testing on the mother by collecting blood from the mother and using laboratory testing to find small amounts of the baby's DNA floating in her blood. This is currently offered in many countries including the U.S. with >99.9% accuracy.

The second option is paternal antigen phenotyping, a blood test done on the father of the baby. The father's antigen phenotype tells whether the father has zero (homozygous negative), one (heterozygous) or two (homozygous positive) copies of the antigen in question. A homozygous result indicates that the baby has a 100% chance of inheriting the father's antigen phenotype. A heterozygous result indicates a 50% chance that the child will inherit the offending antigen (e.g., if the mother has anti-E antibodies and the father's antigen phenotype is Ee, he is heterozygous, and the child has a 50% chance of inheriting the E antigen from the father and being affected by the mother's antibodies).

While it should be avoided, if possible, because of the slight complication rate and the possibility of increasing the maternal antibody levels (titers), a third option is amniocentesis when the first two options are not available or do not give a result with certainty. Chorion villus biopsy (sampling the placenta for genetic diagnosis) should be avoided at all costs since this is often associated with an increase in the maternal titer after the procedure. Once a baby is determined to be antigen positive by any of the above methods or if the methods are not available and the baby must be assumed to be antigen positive, close monitoring and on-time treatment should be planned.

For antibody titers below 16 (16 is considered a “critical titer”), checking titers every four weeks in the first and second trimester and every two weeks in the third trimester is the best way to monitor the pregnancy. An exception to this is for pregnancies where the mother has anti-Kell (anti-K) antibodies, which are known to be more aggressive than other antibodies and should be treated as critical at a lower titer than for other antibodies. Delivery in pregnancies with non-critical titers should take place at 37-38 weeks gestation (2-3 weeks before the anticipated delivery date).

For antibody titers at or above critical levels (16 or above; lower titer for anti-K), weekly MCA Doppler ultrasounds can begin as early as 15-16 weeks in experienced high-risk pregnancy and fetal centers with trained staff. MCA Doppler ultrasounds measure the rate of blood flow in the middle cerebral artery in the fetal brain. An increased blood speed (1.5 multiples of the median or higher, MoM) means that the fetus is probably anemic and may need an intrauterine blood transfusion (IUT) (see “Standard Therapies”). Usually, IUTs can be done until about 35 weeks gestation with a goal for delivery at 37-38 weeks gestation. Delivery as early as 35-36 weeks is sometimes indicated if the fetus is showing signs of anemia, and sooner if the treatment center is unable to safely conduct an IUT for any reason and/or the fetus is too sick to handle the IUT.

In addition to symptoms of anemia in combination with a positive maternal antibody screen, HDFN can also be confirmed using a direct agglutination test (DAT, or direct Coombs test) on the newborn’s cord blood. A positive test means that maternal antibodies are attaching to the newborn’s red blood cells, and they have HDFN.

It is important to note that antigens are a normal part of the red blood cell. While the fetus is in the mother’s uterus and shortly after birth, their mother’s antibodies may attack their blood cells, but the child’s blood is not abnormal in any way. The mother’s

antibodies simply recognize the child's blood type as something unlike her own and attack the blood like they would attack a virus or other illness. Once the child is cleared of HDFN, the child is not at risk for this disease in their own life or any of the child's future pregnancies. The alloimmunized mother however will continue to have antibodies in all of her pregnancies and will require management as described below.

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## Standard Therapies

Early onset of severe disease, though uncommon, requires close monitoring with serial Doppler ultrasounds and rapid treatment with early IUTs and sometimes other medications such as intravenous immune globulin (IVIG).

The most common treatment for HDFN while the mother is still pregnant is intrauterine blood transfusion (IUT) which is necessary in about 22-23% of antigen positive fetuses with a critical titer. This is a needle procedure done by a maternal fetal medicine specialist (MFM) with specific and repeated experience in doing IUTs. During an IUT, a needle is inserted into the mother's belly and into the fetus' umbilical vein (IVT). Sometimes, the fetus is too small to reach the vein safely or is moving too much, and the needle is instead inserted into the fetal abdomen (IPT).

A small amount of blood is given to the fetus and a beginning and ending hematocrit is measured, when possible, to aid in the timing of the next IUT.  This usually happens every 2-3 weeks until delivery once the procedures are started. IUTs must be done quickly after finding that the fetus is anemic and before the development of fetal hydrops. Doing an IUT promptly after an MCA Doppler MoM of 1.5 even if hydrops is not visible is important to ensure the best chances of survival. In highly skilled centers, IUT complication rates can be as low as 2-3%. This depends on the doctor's skill and experience and the patient and doctor should work together to find an MFM/perinatologist for the procedure with consistent positive outcomes; referral out of state may be necessary.

In mothers with a history of early onset severe HDFN (requiring IUT before 24 weeks gestation or having a previous loss to HDFN) or with extremely high titers, some mothers may benefit from therapies to reduce their antibody titer and delay time to the first IUT. These treatments include intravenous immune globulin (IVIG), an IV therapy given to the mother weekly beginning around 10-13 weeks of pregnancy until

the first IUT.  In some cases of a very high titer in the mother, a procedure called plasmapheresis is used (the patient is attached to a line to remove the liquid part of the blood that contains the antibodies while the mother's red cells are returned to her body) three times in one week followed by IVIG.

Some studies have found that giving a pill to the mother called phenobarbital for 10 days before delivery can help the baby's liver develop more rapidly, allowing them to better process the broken-down blood cells after birth and reduce their chances of needing an exchange transfusion after birth for hyperbilirubinemia (jaundice).

After birth, the two most common treatments include aggressive light therapy (phototherapy) for hyperbilirubinemia and top-up transfusion for anemia. Exchange transfusion where the baby's blood is slowly removed and replaced with new donor blood is sometimes needed (in about 10% of cases). Intravenous immune globulin (IVIG) is sometimes given to the newborn and is thought to reduce the chances of needing transfusion.

After discharge, the use of erythropoietin in the first few months of life can encourage new red blood cells to be made. This has recently been shown to reduce the need for "top-up" transfusions in newborns with HDFN.

Newborns with HDFN need monitoring with weekly blood draws for hemoglobin/hematocrit and reticulocyte counts until both are increasing without transfusion. Most newborns with HDFN are cleared of their condition by 12-15 weeks of age and have no lasting effects from HDFN.

As commented before, after birth the child remains at risk of HDFN until maternal red cell antibodies are cleared from the child's blood, usually by 12-15 weeks of age and long-term health problems are rare.

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## Clinical Trials and Studies

Information on current clinical trials is posted on the Internet at https://clinicaltrials.gov/ All studies receiving U.S. Government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Tollfree: (800) 411-1222
TTY: (866) 411-1010
Email: prpl@cc.nih.gov

Some current clinical trials also are posted on the following page on the NORD website:
https://rarediseases.org/living-with-a-rare-disease/find-clinical-trials/

For information about clinical trials sponsored by private sources, contact:
https://www.centerwatch.com/

For information about clinical trials conducted in Europe, contact:
https://www.clinicaltrialsregister.eu/

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## Programs & Resources

## RareCare® Assistance Programs

NORD strives to open new assistance programs as funding allows. If we don't have a program for you now, please continue to check back with us.

## Additional Assistance Programs

### Rare Disease Educational Support Program

Ensuring that patients and caregivers are armed with the tools they need to live their best lives while managing their rare condition is a vital part of NORD's mission.

https://rarediseases.org/patient-assistance-programs/rare-disease-educational-support/

### Rare Caregiver Respite Program

This first-of-its-kind assistance program is designed for caregivers of a child or adult diagnosed with a rare disorder.

https://rarediseases.org/patient-assistance-programs/caregiver-respite/

## Patient Organizations

### The Allo Hope Foundation

*NORD Member*

Phone: 205-331-6430 | Email: info@allohopefoundation.org

https://rarediseases.org/organizations/the-allo-hope-foundation/

### Maternal Alloimmunization Foundation

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Email: contact@alloimmunization.org

https://rarediseases.org/organizations/maternal-alloimmunization-foundation/