Hemolytic Disease of the Fetus and Newborn (HDFN)

A GUIDE FOR PREGNANT WOMEN WITH RED CELL ANTIBODIES

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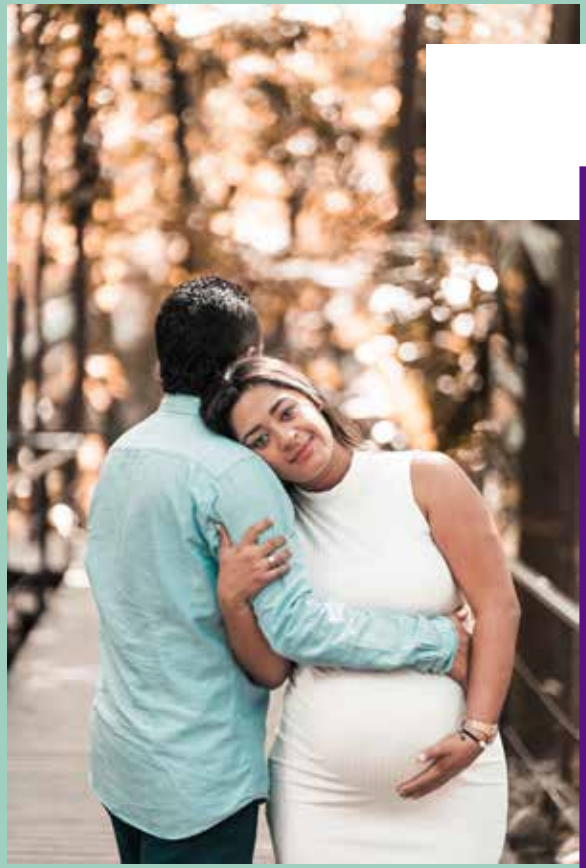

Welcome

Dear Families,

If you have been diagnosed with red blood cell antibodies during your pregnancy (alloimmunization), you may have a lot of questions. Our goal is to answer some of the common questions and concerns that parents have.

With close monitoring and timely treatment, babies with HDFN have a very high survival rate. Unfortunately, due to the rarity of alloimmunization and the variation in care practices around the world, well-managed pregnancies and ideal infant outcomes are not universal - but they can be.

Parents who learn about the condition and understand the monitoring and treatment options are better able to advocate for their babies. This pamphlet provides the most recent evidence-based management guidelines for alloimmunized pregnancies. Please discuss the appropriate treatment options with your provider.

What is HDFN?

Maternal alloimmunization occurs when a woman makes red blood cell antibodies as a result of foreign blood mixing. These alloantibodies can cross the placenta and attack the unborn child, a disease called **Hemolytic Disease of the Fetus and Newborn (HDFN)**. Once the antibodies have crossed the placenta, they can destroy the baby's red blood cells, causing fetal anemia.

ALLOIMMUNIZATION IN THE MOTHER CAN CAUSE HDFN IN HER BABY.

If you tested positive for **red blood cell antibodies**, it means you were exposed to a blood type that is different from your own.

Your body developed antibodies against one or more red blood cell antigens. For example, if you have anti-D antibodies, this means that your antibodies look for and attack blood cells that have the D antigen on them. If your baby has the matching antigen for your antibodies, the antibodies can bind to the baby's red blood cells and destroy them. If your baby does not have enough red blood cells, he or she develops anemia.

How Is HDFN Diagnosed?

During your initial prenatal blood work, your blood was checked for antibodies. If you tested positive for antibodies, your doctor should investigate whether the antibody is known to cause HDFN and whether your baby is at risk for inheriting the antigen in question from their father. If the baby is determined to be at risk for HDFN, you will have a blood test to check your titer levels. These titers determine how much antibody is in your blood and if your baby is at risk for developing severe anemia and hydrops. Your titers may need to be tested on a regular basis throughout the pregnancy. If your titer reaches the critical level, 4 for anti-K and 16 for all other antibodies, then you will have regular ultrasounds called MCA scans instead of titers. These MCA scans check the baby for fetal anemia.

What are the risks to the mother?

Thankfully, HDFN does not pose risks to you during your pregnancy. You should let your providers know about your antibodies before medical procedures. If you need a blood transfusion, the donor blood must be matched to your specific antibodies ahead of time. Otherwise, you could be at risk for a **hemolytic transfusion reaction**. This can result in a systemic inflammatory response, low blood pressure, diffuse bleeding, and shock. A medical alert card can be used to help remind you and your providers of your specific antibodies.

What are the risks to the baby?

➤ BEFORE BIRTH:

- Anemia
- Fetal hydrops
- Organ damage
- Heart failure
- Death

➤ AFTER BIRTH:

- Anemia
- High bilirubin
- Jaundice
- Brain damage
- Kernicterus
- Thrombocytopenia
- Neutropenia
- Death

With the proper monitoring and treatment, these risks can almost always be avoided. Not all babies born to alloimmunized mothers experience these issues. Thankfully, HDFN is a temporary disorder and should leave no lasting effects on your baby if treated properly. Infants usually recover from HDFN by 12 weeks of age.

How can I protect my baby?

Find a Maternal Fetal Medicine Specialist (perinatologist) who is knowledgeable about HDFN and ask for a referral if you do not already have one.

Educate yourself about alloimmunization and HDFN and ask questions when you aren't sure about something.

Advocate for the proper tests, monitoring, and treatments. Sometimes this means asking for a second opinion. Remember that you are your baby's voice.

Plasmapheresis and IVIG are two treatment options that take place in early pregnancy. They are used to protect the baby until he or she is big enough for an intrauterine transfusion (IUT).

Testing Dad

ANTIGEN PHENOTYPE

The baby's father should have his blood drawn to look at his antigen phenotype. The antigen phenotype will tell you and your doctor if your baby could inherit the antigen, or blood type, that your antibodies may destroy. This test is a simple blood draw which will show if he is homozygous, heterozygous, or negative for the antigen. Unfortunately, some labs will accidentally test the father for antibodies instead of testing his antigen status. Always double check to ensure that an antigen phenotype was run, not an antibody screen.

Homozygous = Each child has a **100%** chance of inheriting the antigen and is at risk for HDFN.

Heterozygous = Each child has a **50%** chance of inheriting the antigen and may be at risk for HDFN. Talk to your doctor about the option of amniocentesis or cffDNA testing to determine your baby's antigen status.

Negative = Each child has a **0%** chance of inheriting the antigen and is not at risk for HDFN.

REMEMBER: Anti**BODY** tests are run on mom's **BODY**. Anti**GEN** tests are run on **GEN**tlemen.

Testing Baby - cffDNA Testing

AMNIOCENTESIS OR CFFDNA TESTING? WHICH ONE IS RIGHT FOR YOU?

There are two options to determine the fetal antigen status: **amniocentesis or cell-free fetal DNA (cffDNA)** testing. Unlike the traditional amniocentesis, the cffDNA testing carries no risk of fetal- maternal hemorrhage, increasing titers, chorioamnionitis, or fetal loss. This simple blood draw is a noninvasive way to find out whether a baby is antigen positive or negative. Fetal DNA is extracted from your blood and tested for the antigen. CffDNA can be used for pregnancies complicated by anti-K, anti-D, anti-C, anti-c, anti-E, and anti-e antibodies.

WHAT IMPACT WILL THE RESULTS HAVE ON PRENATAL CARE?

A negative result can greatly relieve anxiety, while a positive result can help you prepare for increased prenatal appointments and the possibility of a longer hospital stay after birth. If the fetus is antigen negative, weekly MCA scans are unnecessary and your pregnancy can proceed as usual without an early induction of labor. This can save thousands of dollars in medical bills and hours of time for the family. If the fetus is antigen positive, the fetus is at risk for HDFN and weekly MCA scans may be required if titers reach the critical threshold. An at risk baby would be delivered at an earlier gestation (37-38 weeks).

IS IT ACCURATE?

Overall accuracy of the cffDNA test is over 99%. Occasionally, test results might come back as inconclusive. In these cases the test will need to be repeated.

Testing Baby - cffDNA Testing

HOW CAN I HAVE CFFDNA TESTING DONE?

Regardless of where you are located, you may have your blood drawn at any laboratory and shipped to one of the labs listed below for testing.

AUSTRALIA

The Red Cross is testing for the D antigen, and enrolling women in a study testing for the c, C, e, E, and K antigens.

CANADA

The Canadian Blood Service does testing for the c, C, D, e, E, and K antigens.

THE NETHERLANDS

Sanquin laboratory accepts blood samples from around the globe to test for the c, C, D, e, E and K antigens.

UNITED KINGDOM

The NHS tests for the c, C, D, e, E, and K antigens. They also accept blood from outside of the UK for testing.

UNITED STATES

The Unity test for the D antigen is available in the USA. Testing for the c, C, e, E and K antigens can be done by shipping samples to Sanquin laboratory in the Netherlands.

My baby's cffDNA test result is:

*See https://www.sanquin.org/products-and-services/diagnostics/non-invasive- fetal-blood-group-genotyping for the requisition form.

Know your levels - Titers

It is important for you to know your antibody titer. Titers are a measure of the amount of antibodies in a patient's blood.

WHAT IS THE CRITICAL TITER?

The critical titer is the titer level associated with a risk of developing severe anemia and hydrops (fluid collections in the baby indicating evidence of fetal heart failure.) Below the critical titer, the fetus is at risk for developing mild to moderate, but not severe anemia. If your titers reach the critical level, then weekly MCA scans should be used to monitor the baby for fetal anemia. These scans can start at 15-18 weeks of pregnancy.

The critical titer for all antibodies except anti-K is 16. The critical titer for anti-K is 4.

If you have had a previously affected pregnancy with the same partner and your baby had HDFN, then your care should not be based on titers alone. MCA scans should be used for monitoring instead of titers.

Know your levels - Titers

HOW OFTEN ARE TITERS DRAWN?

If your titer is below critical, your titer will be checked every 4 weeks until 24 weeks, then every 2 weeks until 36 weeks. Titers are drawn weekly from 36 weeks until delivery at 37-38 weeks. Once your titer is critical, MCA scans should be performed weekly and titer tests are no longer necessary.

Having a care plan in place before your baby needs treatment is key. What will happen if your titer level increases? Will your MFM perform weekly MCA scans? Does your local office or hospital have an online patient portal where you can check your results? Ask your doctor about your prenatal care plan.

Titer:	Date:	Titer:	Date:
Titer:	Date:	Titer:	Date:
Titer:	Date:	Titer:	Date:
Titer:	Date:	Titer:	Date:

Know your baby's levels - MCA-PSV

Fetal anemia is one of the complications of HDFN and can be treated as long as the anemia is detected early enough. Untreated anemia can be fatal for the unborn baby, so consistent monitoring is essential if your titers are critical or you have had a previously affected child. Anemia is detected with special ultrasounds called MCA-PSV Dopplers ("MCA scans"). These scans measure how fast the baby's blood is flowing through the middle cerebral artery in the brain. If the blood is flowing too fast, it could be an indicator that the baby is anemic.

As part of your child's MCA scan for anemia, you will be given a Peak Systolic Velocity (PSV) number (also called Vmax). This number is plugged into a calculator and converted into an MoM number. You can find a calculator for this at: medicinafetalbarcelona.org/calc/.

If your MoM is...

- **1.3 - 1.49** - Your baby could be mildly anemic. No treatment is needed at this time, but the baby needs to be monitored closely.
- **1.5 or higher** - This may indicate moderate to severe anemia. Your doctor should discuss scheduling a repeat scan and/or an intrauterine blood transfusion (IUT) in the next couple of days.

Remember: Titers show the amount of antibodies in your blood. MCA scans check to see if your baby is anemic.

Know your baby's levels - MCA-PSV

Gestation Age	PSV=1.0 MoM	PSV=1.5 MoM	My PSV or MoM	Gestation Age	PSV=1.0 MoM	PSV=1.5 MoM	My PSV orMoM
14	19.3	28.9		27	35.2	52.8	
15	20.2	30.3		28	36.9	55.4	
16	21.1	31.7		29	38.7	58.0	
17	22.1	32.3		30	40.5	60.7	
18	23.2	34.8		31	42.4	63.6	
19	24.3	36.5		32	44.4	66.6	
20	25.5	38.2		33	46.5	69.8	
21	26.7	40.0		34	48.7	73.1	
22	27.9	41.9		35	51.1	76.6	
23	29.3	43.9		36	53.5	80.2	
24	30.7	46.0		37	56.0	84.0	
25	32.1	48.2		38	58.7	88.0	
26	33.6	50.4		Modified from G Mari et al.[1] New England Journal Medicine. 2000: 342:9			

Talk to your doctor about your baby's MoMs and any treatment that may be required. Having a care plan in place before your baby needs treatment is key. How often will you have MCA scans? What will happen if your baby's MoM is high? What if it is the weekend or a holiday - will your MCA scans be delayed? Ask your doctor about your care plan.

Treatment Options – IUTs

Fetal anemia can be treated with an **intrauterine blood transfusion (IUT)**. IUTs often seem scary to patients, but in the hands of a skilled physician IUTs are a safe, effective treatment for fetal anemia.

During an IUT, you may receive medication to help you relax. The doctor will clean your abdomen with an antiseptic prep and he or she will use an ultrasound to guide the needle through your uterus, into your baby's umbilical cord or abdomen. Once there, the doctor will take a sample of your baby's blood and test it to determine how much blood to transfuse. After the procedure, you will be monitored in a recovery room.

Once IUTs are started, they are usually continued every 1-3 weeks based on how your baby is responding. This means you will typically receive 3-4 procedures during the pregnancy. IUTs are usually not performed after 35 weeks of gestation.

Talk to your doctor about your baby's levels and any treatment that may be required. Having a care plan to monitor and treat your baby will help you to feel more at ease with what is happening. You may want to ask questions such as:

- Where would an IUT be performed if you needed one?
- What is the procedure like?
- What medications will you be given?
- Will the doctor temporarily paralyze the baby during the procedure?
- Will you receive an antibiotic to prevent infection?
- What was your baby's starting and ending hematocrit?
- How much blood did your baby receive?
- When is your next IUT?

Antenatal Testing

Once you reach 32 weeks gestation, you should have biophysical profiles and non-stress tests 1-2 times per week. A biophysical profile (BPP) is an ultrasound that checks amniotic fluid levels, fetal breathing, movements, and tone. A non-stress test (NST) is a procedure where two bands are placed on the mother's abdomen to monitor contractions, fetal movement, and fetal heart rate.

Birth

Women with antibodies usually give birth between 35 and 38 weeks, but the exact timing of delivery depends on your specific situation and what is safest for your baby. Even if titers are low, the majority of alloimmunized women deliver early due to increased risk of stillbirth and increased difficulty monitoring the baby. Babies who have had IUTs are often born earlier (24-37 weeks) than those who did not need IUTs. ACOG, RCOG, and SMFM all recommend delivery by 37-38 weeks regardless of titer level and MoM values. Having antibodies does not mean you must have a c-section.

Women with alloimmunization usually deliver at a hospital with a neonatal intensive care unit (NICU). Babies with HDFN may need treatment directly after birth such as exchange transfusions or phototherapy. You can ask your doctor ahead of time if your hospital is capable of providing these treatment options for your baby or if your baby would need to be transferred to another hospital.

After Birth – Are there risks?

DO THE RISKS END ONCE THE BABY IS BORN?

Your antibodies that were in the baby's blood stream before birth will stay in his system and can continue to affect him for up to 12 weeks (occasionally longer if the mother has had IUTs).

Risks to the infant include anemia, hyperbilirubinemia (jaundice), neutropenia (low white blood cell count) and thrombocytopenia (low platelet count.) Just like during pregnancy, untreated anemia can be fatal. If the newborn's bilirubin levels are not managed appropriately, there is a risk of neurological damage. Neutropenia can make an infant more susceptible to infections, while thrombocytopenia can make the infant bruise or bleed more easily. Most of these complications should not have lasting effects on the infant if they are detected with the necessary lab tests and treated appropriately.

After Birth – Monitoring the Baby

WHAT MONITORING DOES THE BABY NEED AFTER BIRTH?

At birth all infants born to alloimmunized mothers need to have their cord blood tested for:

- Direct Agglutination Test (DAT, also called a Direct Coombs Test)
- Hemoglobin/Hematocrit
- Bilirubin

These tests will help confirm or rule out the diagnosis of HDFN. If the baby's DAT is positive, or if the baby is antigen positive, he or she needs to be monitored for signs of HDFN. In some cases, a DAT negative baby may show signs of HDNF. If this happens, he or she should also receive close monitoring and timely treatment.

While in the hospital, the baby will have multiple bilirubin checks every 4-12 hours, especially during days 4-6 when hyperbilirubinemia due to HDFN tends to peak. You can also expect that the baby will have his hemoglobin, reticulocyte count, neutrophil count, and platelet count tested regularly.

If the doctor is considering giving iron supplements to the baby, a ferritin level must be checked first. Babies with HDFN have hemolytic anemia, not iron deficiency anemia, and they often have high iron stores. Giving iron to babies with HDFN without testing the ferritin levels first can be dangerous.

After Hospital Discharge – Monitoring Baby

WHAT MONITORING DOES THE BABY NEED AFTER BEING DISCHARGED FROM THE HOSPITAL?

Babies with HDFN are at risk for delayed onset anemia for up to 12 weeks after birth. Even if your baby was not anemic in the hospital, he or she may need a blood transfusion several weeks after birth. This is even more common in babies who have had IUTs. Your baby should have weekly blood tests to check hemoglobin and/or hematocrit to monitor for anemia. Once your child's hemoglobin or hematocrit is going up steadily on its own without a blood transfusion, your baby is safe and no longer has HDFN.

See our follow up booklet **Hemolytic Disease of the Fetus and Newborn—A guide for parents of infants at risk for HDFN** for additional information regarding after-birth care.

Can I have more children?

Absolutely! You will always have antibodies, even when you are not pregnant or when your titer is very low, but your antibodies do not have to limit your family size. It has been thought that subsequent pregnancies are affected at earlier gestations, and more severely, however this is not always the case. With improvement in care practices, and new treatment options, there are several choices available if you wish to have more children.

While there are many ways to grow your family naturally, there are also alternatives to natural conception that avoid the risk of HDFN altogether. These options include IVF with preimplantation genetic diagnosis (PGD) to select an antigen negative embryo, sperm donation, embryo adoption, or surrogacy. If you want to learn more about how to prepare for another alloimmunized pregnancy, talk to your doctor before you get pregnant again.

Alloimmunization does not have to limit your family size. You DO have options.

Key things to remember

- With the right monitoring and care, babies with HDFN recover and have no lasting effects.
- Regular monitoring is essential for babies with HDFN. Keep all of your prenatal appointments.
- Titers are drawn every 4 weeks until 24 weeks, every 2 weeks until 36 weeks, and weekly until delivery.
- If you have had a previously affected baby or if your titers reach a critical value, your baby will be monitored by weekly MCA scans.
- Women with antibodies usually give birth between 35 and 38 weeks.
- After birth, your baby will need regular blood tests for several weeks.
- You can have more children.

Glossary & Abbreviations

Alloimmunization - Alloimmunization is when a person makes antibodies as a result of foreign blood mixing. When this occurs in a pregnant woman, it is called maternal alloimmunization.

Amniocentesis - A procedure where a needle is inserted into the uterus to draw out some of the amniotic fluid which is tested for a variety of fetal health information including antigen status.

Anemia - An inadequate amount of red blood cells. Anemia in a fetus may present as an elevated MCA Doppler score (≥1.5 MoM). Untreated anemia may result in organ damage, heart failure or death.

Antibody - Antibodies are free-floating proteins in the blood plasma that bind to foreign antigens in order to destroy cells that have the foreign antigens.

Antigen - Antigens are protein surface markers located on red blood cells. The term antigen comes from "antibody generating". Everyone has antigens on their red blood cells.

Antigen phenotype - This test looks for the specific antigens on the red blood cell and will return a +/- or heterozygous or homozygous result. The antigen phenotype test can be done on the father to determine his antigen status and predict whether the fetus with inherit the problem red cell antigen.

Bilirubin - A product that is produced when red blood cells are broken down. Excess bilirubin can cause jaundice, hearing loss, tooth enamel problems, permanent brain damage or even death if left untreated.

cffDNA - This noninvasive test uses the fetal DNA that is found floating in maternal circulation to check the fetal red cell antigen status. It requires a blood sample from the mother. cffDNA can be used for pregnancies complicated by anti-K, anti-D, anti-C, anti-c, anti-E, and anti-e antibodies.

Direct Antiglobulin Test (DAT) - This test is sometimes called the Direct Coomb's Test. DAT looks for antibodies that are bound to red blood cells and is typically done on infants. With certain antibodies, this test can be negative even when the baby is still affected and needing treatment.

Delayed onset anemia - Anemia that is not present at birth, but happens between 2 and 12 weeks old.

Hemoglobin - A blood test that is used as an indicator of anemia.

Glossary & Abbreviations

HDFN - The official diagnosis for the fetus and for infants affected by maternal alloimmunization.

Hemolytic transfusion reaction - A serious complication that happens when a patient with alloantibodies is transfused with donor blood that is not properly matched to their antibodies. The patient's immune system destroys the donor blood. Alloantibodies are the second leading cause of fatal HTRs.

Heterozygous - This means that the patient's partner has two different antigens. If a partner is heterozygous, there is a 50% chance that the fetus will inherit the antigen.

Homozygous - This means that the patient's partner has two copies of the same antigen. If a partner is homozygous for the antigen, there is a 100% chance that the fetus will inherit the antigen.

IUT - This is a life-saving procedure where a needle is inserted through the abdomen and uterus into the baby's umbilical cord or abdomen to deliver antigen-negative blood.

Intravenous immunoglobulin (IVIG) - An infusion that is believed to lessen the mother's antibody response and delay fetal anemia.

Maternal Fetal Medicine Specialist (perinatologist) - A doctor who specializes in high risk pregnancies and complications. The MFM provides a care plan for your obstetrician (OB) to follow.

MCA Scan - A special ultrasound that measures how quickly the blood is flowing in the fetus' middle cerebral artery in the brain. If the blood is flowing too quickly, doctors know the baby may be anemic. A value of ≥ 1.5 MoM indicates moderate-severe anemia.

Neutropenia - This is a reduced level of neutrophils, a specialized kind of white blood cell. Approximately 45% of babies with HDFN develop neutropenia

Plasmapheresis - A procedure where the blood is removed from the mother, the antibody-rich plasma is removed, and blood cells are returned. This can decrease the antibody titer.

Thrombocytopenia - Thrombocytopenia is defined as a platelet count of less than 150 x 109/L. Approximately 25% of babies with HDFN develop thrombocytopenia.

Titer - Titers are a reciprocal measure of the amount of antibodies in a patient's blood. The critical titer for anti-K is 4, and 16 for all other antibodies.

Medical Alert Card

It is important that you notify your health care providers about your antibodies even when you are not pregnant, especially before any surgeries or blood transfusions. Women with maternal alloimmunization are at risk for a hemolytic transfusion reaction. Alloantibodies are the second leading cause of fatal HTRs. You can create your own medical alert card below to keep in your wallet in case of emergency.

TRANSFUSION ALERT

DOB:

BLOOD TYPE: ANTIBODIES:

HEMOLYTIC TRANFUSION REACTION RISK

This card was provided by

ALLO HOPE
FOUNDATION

TRANSFUSION ALERT

ALLERGIES: _____

_____

_____

EMERGENCY CONTACT: _____

_____

_____

This resource is for informational purposes only. It is not a substitute for advice from an experienced medical professional who is familiar with your specific treatment plan and condition. If you are unsatisfied with the quality of your care, please feel empowered to reach out to another provider for a second opinion or transfer your care. In an emergency, call 911 or go to the nearest emergency room.

For additional resources visit:

AlloHopeFoundation.org

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Protecting babies, supporting families.

Disclaimer: This booklet is partly funded by Janssen Pharmaceuticals. Content curated by the Allo Hope Foundation and reviewed by our medical advisory board.

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To find out how your antibody can help others, please contact Southern Blood Services, Inc.
southernbloodservices.com | 205-967-8189