Hemolytic Disease of the Fetus and Newborn (HDFN)

A Guide For Pregnant Women with Red Cell Antibodies

Updated to reflect the new HDFN Clinical Practice Guidelines

ALLO HOPE
FOUNDATION

ALLOHOPEFOUNDATION.ORG

Welcome

Keep an eye out for the

Advocacy in Action

tips throughout the booklet to help you advocate for the best care

Dear Families,

If you have been diagnosed with red blood cell antibodies during pregnancy (alloimmunization), you may be feeling overwhelmed or unsure about what this means for you and your baby.

With proper monitoring and timely treatment, babies affected by Hemolytic Disease of the Fetus and Newborn (HDFN) have an excellent chance of a healthy outcome. However, because alloimmunization is rare and care practices vary widely throughout the world, not all families receive the same level of guidance and treatment. Our goal is to change that.

Knowledge is one of the most powerful tools you have. When parents understand HDFN and know their monitoring and treatment options, they can advocate more effectively for the best possible care. This guide provides up-to-date, evidence-based information and management guidelines to help you navigate your alloimmunized pregnancy with confidence. We encourage you to discuss these options with your healthcare provider.

You are not alone in this journey. We are here to support you every step of the way.

With Hope,
The Allo Hope Foundation

Table of Contents

What is HDFN?

Maternal alloimmunization occurs when a woman's immune system produces red blood cell antibodies (alloantibodies) after being exposed to a foreign blood type. These antibodies can cross the placenta during pregnancy and attack the baby's red blood cells, a disease called **Hemolytic Disease of the Fetus and Newborn (HDFN)**. Destruction of the baby's red blood cells can lead to fetal anemia and other complications.

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.

This exposure usually happens during a previous pregnancy or blood transfusion.

Your immune system developed antibodies against one or more red blood cell antigens. For example, if you have anti-D antibodies, this means that you were exposed to D antigen positive blood. Your anti-D antibodies target and destroy red blood cells that carry the D antigen. If your baby inherits the antigen from their father, your antibodies can bind to and break down your baby's red blood cells, causing anemia and reducing their ability to carry oxygen to vital organs.

What are the risks to the mother?

Thankfully, HDFN does not pose a direct risk to your physical health during pregnancy, but it often comes with a heavy mental-emotional burden for the mother (see pg. 24). Let your healthcare providers know about your antibodies before medical procedures. If you need a blood transfusion, the donor blood must be matched to your specific antibodies to prevent a **hemolytic transfusion reaction**- a complication that occurs when your immune system attacks incompatible donor red blood cells. For example, if you have anti-K antibodies, any transfused blood should be K antigen negative.

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 12-15 weeks of age.

How can I protect my baby?

Find the Right Specialist- Establishing care early with a Maternal Fetal Medicine (MFM) Specialist (perinatologist) who is knowledgeable about HDFN is crucial. If you don't already have one, request a referral. Work with your provider to develop a plan in case an intrauterine transfusion (IUT) becomes necessary in the future.

Educate Yourself- Learn about alloimmunization and HDFN and make sure you understand timing of care (see pg. 7). Ask questions when you aren't sure about something.

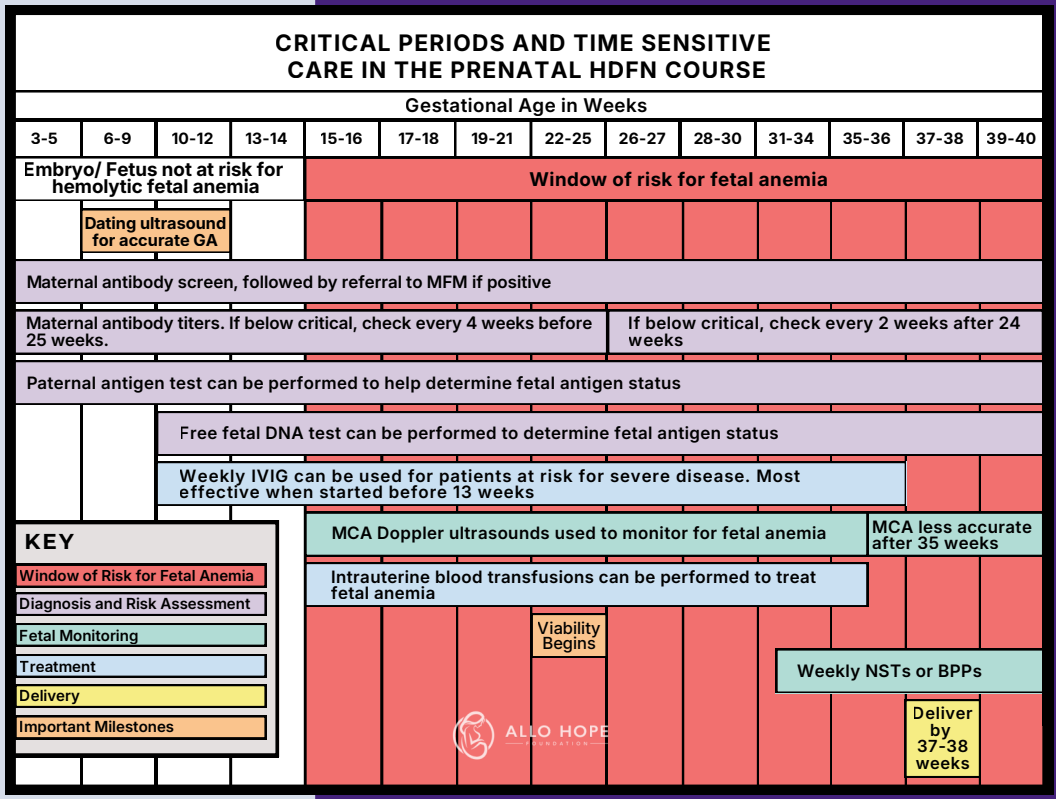
Advocate for the Right Care- You are your baby's voice. Make sure you receive the proper tests, monitoring, and treatments. If you have concerns or feel uncertain about your care, don't hesitate to seek a second opinion.

Know All of Your Treatment Options- If you have very high antibody titers or a history of severe HDFN, ask your provider about plasmapheresis and intravenous immunoglobulin (IVIG). These treatments can help protect your baby in early pregnancy until they are big enough for an IUT.

Time Sensitive Care

Advocacy in Action

Understanding the timing of certain tests and treatments during your pregnancy can help you and your medical provider make the best care plan possible.



How is HDFN Diagnosed?

Maternal alloimmunization can be diagnosed with a simple blood test on the mother, called an antibody screen or ICT test (indirect Coombs test).

Diagnosing **HDFN** in the developing baby in utero is a bit more complicated, so the question shifts from, "Does the baby have HDFN?" to, "Is the baby at risk for HDFN?"

Antibodies Known to Cause HDFN:

- K, k (Kell blood group)
- D, E, C, c (Rh blood group)
- Fya, Fyb, Fy3 (Duffy blood group)
- Jka, Jkb, Jk3 (Kidd blood group)
- M, N, S, s, U, Mia (MNSs blood group)
- Mta, Vw, Mur, Hil, Hut (MSSs blood group)
- Lua, Lub (Lutheran blood group)
- Dia, Dib (Diego blood group)
- Xg PP (Tja), Yta, Ytb, Lan, Ena, Ge, Jra, Coa, Co1-b- (Public antigens)
- Batty, Becker, Berrens, Biles, Evans, Good, Gonzales, Heibel, Hunt, Jobbins, Radin, Rm, Ven, Wrighta, Wrightb, Zd (Private antigens)

IN ORDER FOR THE FETUS TO BE AT RISK FOR HDFN, YOU MUST HAVE A:

- ☑ Mother with antibodies known to cause HDFN
- ☑ Mother with critical antibody titer
- ☑ Antigen positive father
- ☑ Antigen positive baby

If you tested positive for red cell antibodies, your doctor can determine if your baby is at risk for HDFN by investigating:

-whether the antibody is known to cause HDFN
-what your antibody titer is (see pg. 12-13)
-whether your baby is at risk for inheriting the antigen in question from their father (see pg.9)
-whether your baby is antigen positive or negative (see pg. 10-11)

Is My Baby at Risk for HDFN?

TESTING THE BABY'S FATHER: Paternal Antigen

To help determine whether your baby is at risk for HDFN, the baby's father can have a blood test to check his antigen status (antigen genotype for D, antigen phenotype for all other antigens). This test will show whether he carries the specific antigen that your antibodies target, helping you and your doctor understand the likelihood that your baby has inherited the antigen.

This simple blood draw will show if the father is:

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

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

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

Advocacy in Action

Occasionally, an antibody screen will accidentally be ordered on the father instead of an antigen test. Always double check to make sure the correct test was run- an antigen phenotype/genotype (D), not an antibody screen.

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

Is My Baby at Risk for HDFN?

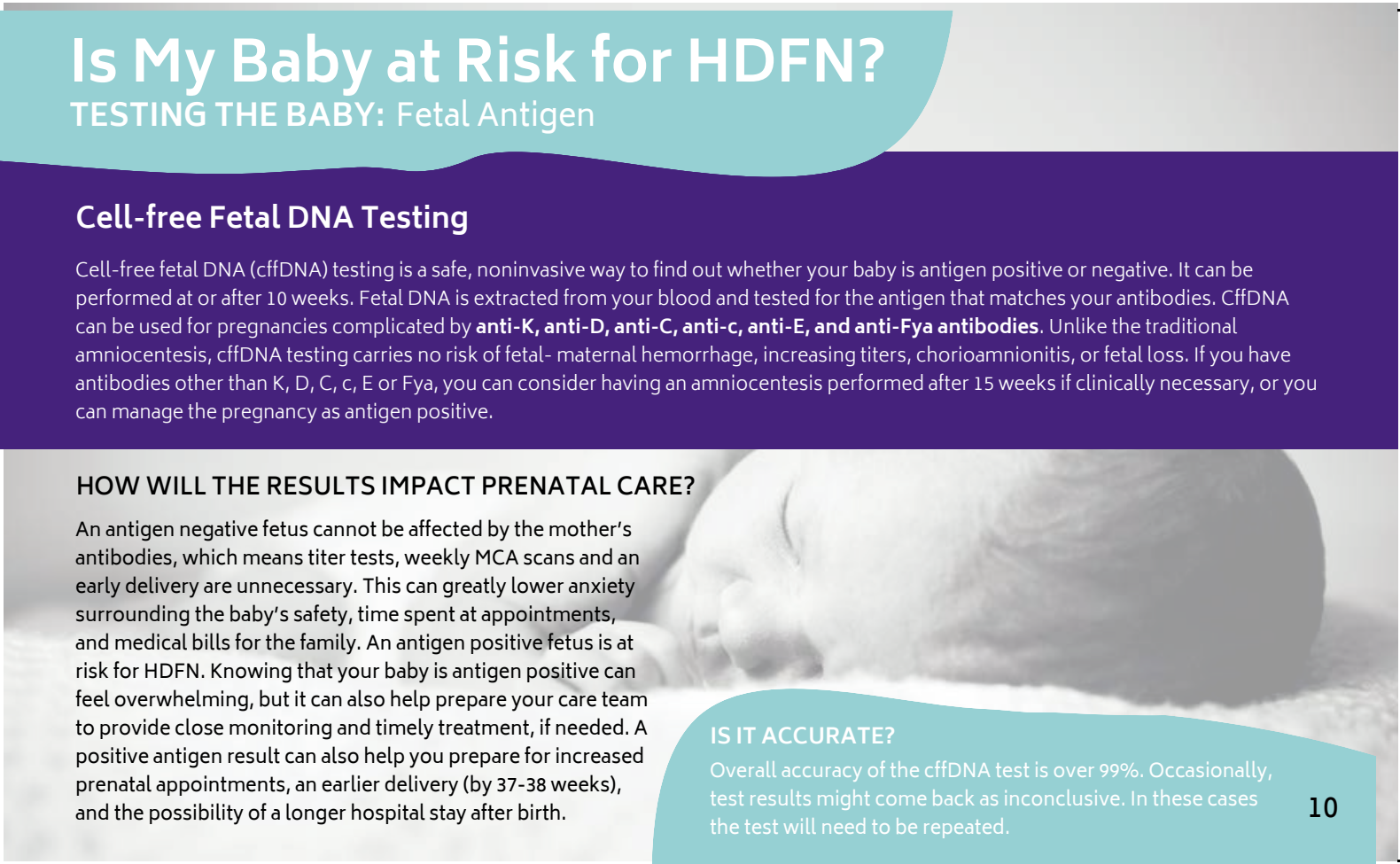
TESTING THE BABY: Fetal Antigen

Cell-free Fetal DNA Testing

Cell-free fetal DNA (cffDNA) testing is a safe, noninvasive way to find out whether your baby is antigen positive or negative. It can be performed at or after 10 weeks. Fetal DNA is extracted from your blood and tested for the antigen that matches your antibodies. CffDNA can be used for pregnancies complicated by **anti-K, anti-D, anti-C, anti-c, anti-E, and anti-Fya antibodies**. Unlike the traditional amniocentesis, cffDNA testing carries no risk of fetal- maternal hemorrhage, increasing titers, chorioamnionitis, or fetal loss. If you have antibodies other than K, D, C, c, E or Fya, you can consider having an amniocentesis performed after 15 weeks if clinically necessary, or you can manage the pregnancy as antigen positive.

HOW WILL THE RESULTS IMPACT PRENATAL CARE?

An antigen negative fetus cannot be affected by the mother's antibodies, which means titer tests, weekly MCA scans and an early delivery are unnecessary. This can greatly lower anxiety surrounding the baby's safety, time spent at appointments, and medical bills for the family. An antigen positive fetus is at risk for HDFN. Knowing that your baby is antigen positive can feel overwhelming, but it can also help prepare your care team to provide close monitoring and timely treatment, if needed. A positive antigen result can also help you prepare for increased prenatal appointments, an earlier delivery (by 37-38 weeks), and the possibility of a longer hospital stay after birth.



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.

Is My Baby at Risk for HDFN?

TESTING THE BABY: cffDNA Testing

HOW CAN I HAVE CFFDNA TESTING DONE?

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

AUSTRALIA

The Red Cross tests 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 and provides information on their website for international shipping.

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

Testing for the D, C, c, E, K, and Fya antigens can be done through BillionToOne's Unity test. Testing for the D antigen can also be done through Natera .

My Baby's Antigen Test Result Is:_____

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

HDFN Monitoring - Titers

The biggest risk to your HDFN baby in utero is fetal anemia. Fetal anemia happens when maternal antibodies destroy too many of the developing baby's red blood cells. Mothers with more antibodies in their blood are more likely to have babies who become anemic in utero (but not always). This is why we measure antibody titers in the mother. Titers show the amount of antibodies in a patient's blood and help the provider know when to start monitoring your baby for fetal anemia.

WHAT IS THE CRITICAL TITER?

The critical titer is the level associated with the risk of developing fetal anemia requiring intervention. If your titers reach the critical level, MCA Doppler scans should be used to monitor the baby for fetal anemia. Weekly MCA Doppler ultrasounds are typically started by 16 weeks once a critical titer is reached (or earlier in select, very high-risk situations).

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

If you have had a previously affected pregnancy with the same partner and your baby had HDFN, or if you ever had a critical titer in the past, MCA scans should be used for monitoring instead of titers.

REMEMBER: Titers give us information about the baby's environment. Titers don't tells us anything about the baby, including antigen status or fetal anemia levels.

HDFN Monitoring - 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 after that. Once your titer is critical, MCA scans should be performed weekly and titer tests are no longer necessary.

Advocacy in Action

It's important for you to know what your titers are. You can keep track of them in your phone, notebook or here in this booklet. 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?

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

ANTIBODIES ARE COUNTED IN MULTIPLES: 1, 2, 4, 8, 16, 32, 64, 128, 256, 512, 1,024, 2,048, etc.

HDFN Monitoring - MCA Doppler Ultrasounds

Your baby can be monitored for fetal anemia and treated if necessary. Untreated anemia can be fatal for the baby, and delayed monitoring can increase risks of complications. This is why consistent monitoring is essential if your titers are critical or you have had a previously affected child. Fetal anemia is detected with special ultrasounds called MCA Dopplers ("MCA scans"). These scans measure how quickly 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.

During your MCA Doppler scan your provider will measure the **Peak Systolic Velocity (PSV), which is the speed of your baby's blood flow** through an artery in their brain. The PSV number and your gestational age are used to calculate your MoM (multiples of median.) The MoM is used to diagnose fetal anemia.
You can calculate your MoM at:
medicinafetalbarcelona.org/calc/.

If your MoM is 1.5 or higher - This indicates moderate to severe fetal anemia. Your doctor should plan an intrauterine blood transfusion (IUT) in the next couple of days. Steroids should not be given until a decision to do an IUT is made because they can falsely lower MoMs.

WHEN TO START MCA SCANS

Start weekly MCA scans at 16 weeks if:

- You've reached a critical titer OR
- You've had a previously affected baby

Start weekly MCA scans at 15 weeks if:

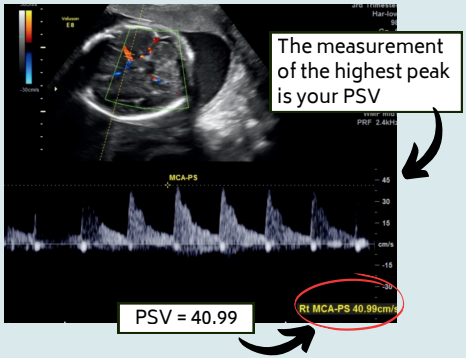
- You have highly immunogenic antibodies (anti-D, C, c, E, K, or Jka)
- You've had a severely affected baby in the past OR
- You have a high antibody titer

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

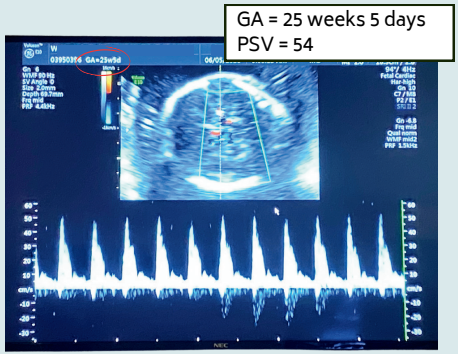
HDFN Monitoring - MCA Doppler Ultrasounds

HOW CAN I CALCULATE MY BABY'S MoM?

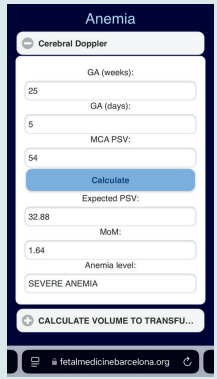
1. Ask your doctor for your PSV during or after your MCA scan. Your PSV is often visible on ultrasound as well, so you can look for it on the screen.



2. Write down your baby's gestational age (GA) and PSV



3. Go to medicinafetalbarcelona.org/calc/ Click "Anemia" then "Cerebral Doppler" to access the right calculator. Plug in your GA and PSV to calculate MoM.



*This baby's MoM is 1.64, which indicates severe anemia. He received a successful intrauterine transfusion (IUT) the following day with a starting hematocrit of 25 and ending hematocrit of 45.

Advocacy in Action

Try to write down your PSV and/or MoM each week so you can track your baby's anemia risk. If you notice a rising trend or if your MoMs are 1.5 or higher you can discuss treatment with your doctor.

HDFN Monitoring - MCA Doppler Ultrasounds

TRACKING MY BABY'S MoM

Gestation	PSV=1.0 MoM	PSV=1.5 MoM	My PSV or MoM	Gestation	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			

Advocacy in Action

You can estimate the PSV that roughly calculates to a 1.5 MoM by doubling your gestational age.

HDFN Treatment-
Intrauterine Transfusions

Fetal anemia caused by HDFN can be treated with an intrauterine blood transfusion (IUT). While the idea of an IUT may seem overwhelming, in the hands of an experienced specialist, it is a safe and highly effective procedure.

Talk to your doctor about your baby's MoMs and any treatment that may be required. It's important to have a care plan in place before your baby needs treatment. IUTs are time sensitive and have better outcomes when performed **before** fetal anemia progresses to fetal hydrops. Being prepared can also help you feel more at ease with what is happening.

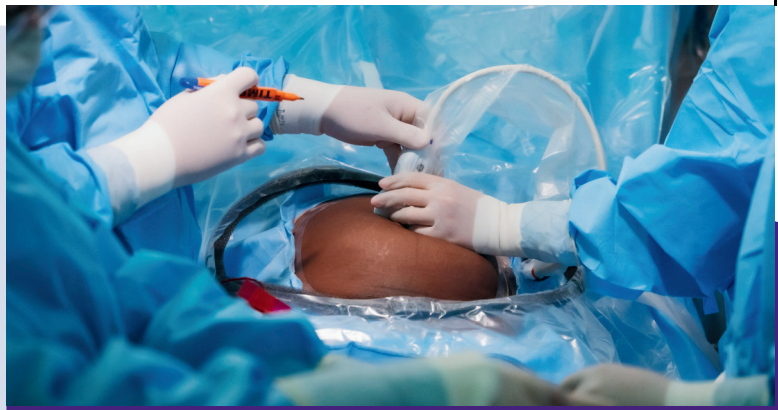
You may want to ask your doctor questions such as:

- Where would an IUT be performed if I needed one?
- Who would perform the IUT?
- Does that provider perform IUTs on a somewhat regular basis? Roughly how many per year?
- What is the earliest IUT you have performed successfully?
- Can you walk me through your IUT procedure??
- How will you keep me comfortable during the procedure?
- Will the doctor temporarily paralyze the baby for the IUT?
- What was my baby's starting and ending hematocrit?
- When is my next IUT?

HDFN Treatment-
Intrauterine Transfusions

WHAT HAPPENS DURING AN IUT?

- You may receive medication to help you relax.
- The doctor will clean your abdomen with an antiseptic and use ultrasound guidance to carefully insert a thin needle through your uterus into your baby's umbilical cord vein, abdomen (peritoneum), or hepatic vein.
- A small sample of your baby's blood will be tested to determine how much blood needs to be transfused.
- The doctor will then deliver carefully matched donor red blood cells to your baby through the needle.
- After the transfusion, another sample is taken to check the baby's hematocrit (red blood cell levels) and ensure the procedure was a success.



WHAT TO EXPECT AFTER THE IUT

After the procedure, you will be monitored in a recovery room where your medical team will check:

- Your baby's heart rate
- Fetal movements
- Any contractions

IUTs are typically performed every 2-3 weeks until delivery, depending on your baby's specific needs. IUTs can be performed by experienced providers as early as **15 weeks.** The last IUT should be planned for **35 weeks** when possible.

HDFN Treatment-
Severe Disease

If your baby is at risk for early onset severe HDFN, you do have preventative treatment options that could delay the need for IUTs. These treatments are called plasmapheresis and IVIG. IVIG should be considered if you have an anti-D titer ≥512, or anti-K titer ≥64, or a prior pregnancy with fetal loss, or a prior pregnancy with fetal anemia <24 weeks.

PLASMAPHERESIS

Plasmapheresis is a procedure that removes the antibody-rich plasma from the mother's blood. This can decrease the amount of antibodies in the blood and lower the antibody titer.

Plasmapheresis may make IVIG more effective. While IVIG is sometimes used on its own, plasmapheresis is rarely used without IVIG.

IVIG

IVIG is a weekly infusion administered slowly through an IV or a port. IVIG should be started by 12 weeks to be most effective. It can be administered at the hospital, outpatient infusion center, doctor's office or at home by a home care nurse. IVIG has been shown to **delay** fetal anemia but is not used to **treat** fetal anemia once the baby is already anemic.

Advocacy in Action

You might experience side effects from IVIG such as migraine, nausea, vomiting, body aches and fatigue.

To help lessen side effects you can:

- Ask your healthcare provider to give medications for symptom relief.
- Ask your infusion nurse to run the infusion slowly.
- Try to stay well hydrated before and during your infusion.
- Receive an antihistamine and acetaminophen before your infusion.

Antenatal Testing

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

Birth

- If you are alloimmunized but your baby has not needed IUTs, delivery should be scheduled between **37w0d and 38w6d**, regardless of titer, UNLESS your baby is known to be antigen negative through prenatal testing.
- If you are having IUTs, your provider should try to time the last IUT for 35 weeks if possible. Delivery is usually scheduled 2-3 weeks after your last IUT, based on your care team's assessment.
- 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

DO THE RISKS END ONCE THE BABY IS BORN?

Your antibodies that were in the baby's blood before birth will stay in his system and can continue to destroy his red blood cells for up to 12 weeks (occasionally longer if the mother has had IUTs). The two main risks to the infant are hyperbilirubinemia (jaundice) and anemia. 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. Thankfully, these complications are treatable and the risks are preventable in most cases with close monitoring and timely treatment.

WHAT TESTING DOES THE BABY NEED AT 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 and will show if your baby needs immediate treatment after birth. 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.

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.

Can I Have More Children?

Yes! While you will always have antibodies—even when you are not pregnant or when your titer is low—they do not have to limit your family size.

Advances in monitoring, treatment, and care have greatly improved outcomes, giving families more options than ever before.

HDFN does not have to limit your family size.

If you wish to have more children, there are several paths to consider:

- Natural conception with proactive monitoring and treatment
- In vitro fertilization (IVF) with preimplantation genetic diagnosis (PGD) to select an antigen-negative embryo
- Sperm donation from an antigen negative donor
- Embryo adoption to select an antigen negative embryo
- Surrogacy using a gestational carrier that does not have red cell antibodies

If you are considering another pregnancy, it's important to plan ahead. Talk to your doctor before conceiving to discuss the best ways to prepare and ensure the safest possible outcome for you and your baby. With the right care and support, many families affected by alloimmunization go on to have healthy pregnancies and thriving children.

Caring for your
Mental and Emotional Health

Learning that your pregnancy is high-risk and that your baby may develop HDFN can feel overwhelming. Women going through an alloimmunized pregnancy are at higher risk of developing anxiety, depression and Post Traumatic Stress Disorder (PTSD), and report high levels of isolation and stress.

YOU MIGHT FEEL:

- Grief over the loss of a typical pregnancy experience and birth
- Anxiety and fear about your baby's health and the unknowns of the disease
- Emotional and physical exhaustion from frequent appointments, tests, and treatments
- Stress from advocating for proper care and always feeling on guard
- Guilt—even though this is not your fault, many mothers carry an unfair burden of self-blame

COPING STRATEGIES AND ENCOURAGEMENT:

- Take it one step at a time. Instead of worrying about the entire pregnancy, try to focus on getting to the next milestone.
- Lean on support. Talk to your partner, family, trusted friends, counselor or faith community about your stressors and need for support. Come join the AHF patient community on Facebook, "Antibodies in Pregnancy: An AHF Support Group"
- Anxiety, depression and PTSD are treatable conditions. Reach out to your doctor or a mental health professional for more information about treatment options.
- Allow yourself to grieve. It's okay to mourn the loss of a "normal" pregnancy experience.
- Keep a journal. Writing down your thoughts, questions, positive affirmations, meditations or prayers can help process emotions.
- Educate yourself about HDFN, listen to The Allo Podcast, ask questions, and don't be afraid to seek second opinions.
- Remember: YOU ARE NOT ALONE. The Allo Hope Foundation is here for you every step of the way.

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. Try to keep all of your prenatal appointments.
- Titers below critical are drawn every 4 weeks until 24 weeks, then every 2 weeks after that..
- 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 should deliver by 37-38 weeks unless you have confirmed that your baby is antigen negative.
- After birth, your baby will need regular blood tests for at least 6 weeks.

Glossary & Abbreviations

Alloimmunization - When a person makes antibodies after being exposed to a foreign blood type. 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 - Proteins made by the immune system to recognize and attack foreign substances.

Antigen - Markers found on the surface of red blood cells that determine a person's blood type. These markers are inherited from our parents. Antigens help the immune system recognize which red blood cells belong in the body and which are foreign. The term antigen comes from "antibody generating".

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 substance formed 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-Fya 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.

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

Fetal Hydrops (hydrops fetalis) - A condition in which large amounts of fluid build up in a baby's tissues and organs, causing extensive swelling (edema). This is a sign of advanced fetal anemia. Survival rates decrease upon development of hydrops.

Hematocrit - The percentage of the volume of whole blood that is made up of red blood cells. Normal hematocrit range for infants 0-6 months is 37.4 - 55.9% for females, and 43.4 - 56.1% for males. Low levels indicate anemia.

Glossary & Abbreviations

Hemoglobin - A protein in red blood cells that carries oxygen. Normal hemoglobin range for infants age 0-6 months is 12.7 - 18.3 g/dL for females and 14.7 - 18.6 g/dL for males. Low levels indicate anemia.

Hemolytic Disease of the Fetus and Newborn (HDFN) - A fetal/neonatal blood disorder that is caused by Maternal Alloimmunization. The mother's antibodies cross the placenta during pregnancy and destroy the baby's red blood cells.

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.

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.

Intrauterine Transfusion (IUT) - A life-saving procedure used to treat fetal anemia. 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 that can be treated with an IUT.

Plasmapheresis - A procedure where the blood is removed from the mother, processed to remove the plasma, then returned. This can decrease the antibody titer.

Titer - A 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.

New Clinical Practice Guidelines

for the Management of Red Cell Alloimmunized Pregnancies

Full publication detailing systematic review and guidelines development methodology and accompanying rationale available at:

Moise KJ, Markham KB, Spinella PC, et al. A Clinical Practice Guideline for the Management of Pregnancy Alloimmunized to Red Blood Cell Antigens. JAMA Network Open. 2025;8(11):e2544649.

Recommendation 1 - We recommend the use of maternal free DNA to accurately determine the fetal red cell antigen status drawn after 10 wGA in pregnancies complicated by RhD, RhC, Rhc, RhE, Kell or Fya alloimmunization.

Practice Points

1.1 A patient case review with a Maternal-Fetal Medicine specialist should be strongly considered soon after red cell alloimmunization is diagnosed in a pregnancy. In some cases, a pre-conceptual consultation with a Maternal-Fetal Medicine specialist may be beneficial prior to the patient considering another pregnancy. In the case of a previous transfusion with Rh-positive RBCs or LTOWB, a preconceptual consult in the Rh-negative patient is also indicated.

1.2 cffDNA testing should be collected any time after 10 wGA. In many situations it can be included as part of the NIPT (noninvasive prenatal testing) assay for genetic screening offered by some laboratories.

1.3 If cffDNA testing reveals an antigen negative fetus, no further surveillance including repeat titers or middle cerebral artery Doppler measurements are indicated for the remainder of the pregnancy.

Recommendation 2a- **We recommend the use of IVIG in patients with a documented antigen-positive fetus with a history of either fetal anemia or a fetal loss due to HDFN before 24 wGA in a previous pregnancy.**
2b: **We suggest the use of IVIG in patients in a pregnancy with a documented antigen-positive fetus and a titer for anti-D of ≥512 or a titer for Kell ≥64 regardless of prior pregnancy history.**

Practice Points
2.1 A positive fetal antigen status should be documented as early as possible, preferably through maternal free DNA testing prior to initiation of IVIG. However, in some circumstances IVIG may be started while antigen status is pending.
2.2. Patients should be made aware of the complications of IVIG therapy prior to its initiation including risks for malaise, fatigue, headache, aseptic meningitis, hemolytic anemia, and thrombosis.
2.3. The initial dose of IVIG should be administered in an acute care setting such as a hospital or infusion center to monitor for adverse reactions.
2.4. Dose calculations should be based on the patient's baseline weight with no escalation in dose. A commonly employed dose used is 1 gr/kg weekly.
2.5. Ideally IVIG should be initiated prior to 13 wGA or as early as possible thereafter.
2.6. Patients with blood type A, B or AB should be followed with serial hemoglobin measurements to monitor for maternal hemolysis.
2.7. Cessation of IVIG therapy should be considered after the initiation of intrauterine transfusion therapy.
2.8. Plasmapheresis can be considered prior to IVIG in patients with high initial maternal titer (anti-D of ≥ 512 or a titer for Kell ≥ 64).

Recommendation 3 - **We recommend that surveillance with middle cerebral artery peak systolic velocity measurements be initiated when the maternal Kell titer is 4 or greater OR there is a history of an affected fetus/neonate in an antecedent pregnancy.**

Practice Points
3.1. If an initial titer is below critical, repeat titers should be performed monthly until 24 wGA, increasing to every 2 weeks thereafter. In some clinical circumstances, a repeat titer may be indicated earlier than this interval if obstetrical circumstances indicate a risk for enhanced alloimmunization (example: genetic amniocentesis, abdominal trauma or placenta abruption).
3.2. Serial titers should be performed at the same laboratory since there are variations in methodology. Preferably titers should be run in tandem with the patient's previous titer to detect increases.

Recommendation 4- We recommend that middle cerebral artery peak systolic velocity (MCA-PSV) measurements be initiated weekly by 16 wGA in patients with red cell antibodies associated with HDFN when there is an antigen positive fetus or antigen unknown fetus once a critical titer threshold has been reached. A critical titer is defined as 16 or greater for most antibodies and 4 or greater for anti-Kell.

Practice Points

4.1. cffDNA determination of the fetal antigen status should be considered before initiation and/or continuation of MCA-PSV Doppler measurements.

4.2. MCA-PSV measurements should be performed in consultation with a Maternal-Fetal Medicine specialist.

4.3. Cases involving alloimmunization with anti-D, anti-C, anti-c, anti-E, anti-Kell or anti-Jka antibody and/or a history of a severely affected fetus/ neonate in the antecedent pregnancy should be followed with weekly MCA-PSV measurements starting at 15 wGA. In some cases of alloantibodies other than -D, -C, -c, -E, -Kell, -Jka, the clinician and patient may mutually agree to conduct MCA Doppler measurements every two weeks with an intent to escalate to weekly MCAs with a rising trend. Consultation with a Maternal-Fetal Medicine specialist with expertise in red cell alloimmunization should be considered in these cases.

4.4. MCA-PSV Dopplers should be performed with proper technique by an experienced sonographer. A minimum of three measurements should be determined when the fetus is in quiescent state with no evidence of breathing movements. As close as possible to a zero-degree angle of insonation should be used. Manual calipers instead of onboard software should be used to calculate the peak systolic velocity. The best measurement should be considered the final value.

4.5. An MCA-PSV measurement of > 1.5 MoM is consistent with moderate to severe fetal anemia warranting cordocentesis and preparation for concurrent intrauterine transfusion within 24 – 48 hours if fetal anemia is detected. In some cases of a borderline elevated MCA-PSV value, a repeat measurement within 24 hours may be considered before intervention.

4.6. MCA-PSV measurements may be initiated as early as 15 wGA in cases of a high maternal antibody titer or a previous history of early prenatal onset of HDFN.

4.7. Antenatal steroids have been anecdotally associated with a reduction in the MCA-PSV. This effect may last up to 48 hours. For this reason, if a patient is to be referred to a fetal treatment center for possible intrauterine transfusion, steroids should be withheld until the patient arrives at the center.

Recommendation 5: We recommend for women undergoing intrauterine transfusions in pregnancy for the treatment of HDFN, intrauterine transfusions should be continued until the end of the 35th week of gestation unless there are technical limitations to undertaking the procedure.

Practice Points
5.1. Intrauterine transfusions should be performed proximate to resources for immediate delivery by Cesarean section when there is a shared patient/physician decision for immediate delivery for fetal indications.
5.2. Delivery should be scheduled 2–3 weeks after the final intrauterine transfusion.
5.3. Ideally cordocentesis and intrauterine transfusions should be undertaken by an experienced operator at a center with proper access to blood banking and neonatal services.
5.4. Delayed umbilical cord clamping at the time of delivery can still be practiced in pregnancies affected by HDFN.

Recommendation 6: We recommend that for women with a current or previous pregnancy with red cell antibodies known to cause hemolytic disease of the fetus and newborn (HDFN) regardless of titer who have not received an intrauterine transfusion, delivery should occur between 37 0/7 to 38 6/7 wGA.

Practice Points
6.1. Red cell alloimmunization is an indication for weekly antenatal testing which should begin by 32 wGA.
6.2. If the fetus is known to be antigen negative by prenatal testing, routine obstetrical care should be considered.
6.3. If the fetal antigen status is unknown, then delivery should occur between 37 0/7 to 38 6/7 wGA.
6.4. Due to the presence of maternal antibodies, performing a maternal crossmatch for red cell units prior to delivery may be advantageous if there is an acute need for maternal or neonatal blood. In some cases, this may involve a planned delivery where there is a higher level of obstetrical and neonatal care available.
6.5. Red cell alloimmunization is not an indication for Cesarean delivery.
6.6: Neonatal consultation prior to delivery should be considered to develop a plan of management for the newborn.
6.7: Evaluation of cord blood for blood type/cognate antigen, direct antiglobulin test, hemoglobin/hematocrit, reticulocyte count, and total bilirubin may be useful to guide the need for early phototherapy in the neonate.

ALLO HOPE
FOUNDATION

Join Our Patient Support Group

Listen/Watch The Allo Podcast

New HDFN Clinical Guidelines

For Additional Resources Visit:

AlloHopeFoundation.org

@allohopefoundation

info@allohopefoundation.com

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 case. 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.