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Released: 07/28/2021
Valid until: 08/31/2022
Time needed to complete: 15 minutes

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HDFN: New Understandings of Risk, Diagnosis, and Therapeutic Approaches

Announcer:
Welcome to CME on ReachMD. This activity, entitled "*Hemolytic Disease of the Fetus and Newborn—New Understandings of Risk, Diagnosis, and Therapeutic Approaches*" is provided by Omnia Education.

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Dr. Shulman:
Hemolytic disease of the fetus and newborn, or HDFN, occurs when maternal red blood cells or blood group antibodies cross the placenta during pregnancy and cause fetal red cell destruction. The consequences of severe anemia in the fetus can be life-threatening. And timely detection and close follow-up of this condition are critical. In this program, we will highlight new epidemiologic evidence, the underlying pathophysiology, and current and evolving management strategies that may impact your clinical practice.

This is CME on ReachMD, and I'm Dr. Lee Shulman.

Dr. Robinson:
And I'm Dr. Chris Robinson.

Dr. Moise:
And I'm Dr. Ken Moise.

Dr. Shulman:
I'd like to welcome both of you to the program.

Dr. Moise, let's dive right in. Could you tell us a little bit about the alloimmune diseases of the fetus and newborn with a focus on HDFN? What is the epidemiology, and how does it present in your clinical practice?

Dr. Moise:
Hemolytic disease of the newborn, also called HDN, or when we talk about fetus and newborn, or HDFN, results from alloantibody-mediated neonatal and/or fetal hemolysis caused by an incompatibility between the fetal and maternal red cell antigens. Often, it's due to ABO or Rh incompatibility or sometimes other blood group antigens, including Kell, Kidd, and Duffy. There are short- and long-term consequences in the newborn including icterus, kernicterus, anemia, thrombocytopenia, and even serious neurodevelopmental outcomes. In addition, there can be edema, ascites, and heart failure, particularly in the fetus, and with that, anemia and hydrops or even fetal demise.

Now recently, we authored an abstract at the last annual SMFM meeting in early January of this year, and we looked at the National Hospital Discharge Survey between 1996 and 2010 and identified newborns using ICD-9 coding with HDN but not HDFN. What we found is that the rate of HDN remained fairly stable over the 15-year period, from about 1,700 cases per 100,000 newborns. The rate of Rh HDFN declined on average from 85 to 60 cases for every 100,000 newborns. ABO incompatibility and other unknown antigens remained fairly stable. The majority of HDN cases involved White newborns. Yet the rate of HDN was observed to be higher among

Black individuals at about 2.3%, compared to White individuals at 1.6%. Compared to healthy newborns, HDN newborns stayed in the hospital longer, 3 days versus 2 days, were less likely to be routinely discharged, and their mothers had higher cesarean section rates, 30.6% versus 20.9%. There was also a higher percentage of cases that occurred in larger hospitals with more than 100 beds, in government hospitals, and in the South versus the Midwest and West. The most utilized therapy in the newborn was phototherapy, in about 22% of cases, while simple transfusion and exchange transfusion, or IVIG were used only in 1% and 0.5% of patients with HDN, respectively.

Dr. Shulman:
Well, Ken, I think your data clearly shows that there is a profound impact on HDFN with regard to limited resources, and that in a very strong way contributes to underdiagnosis and under-management. It's interesting that the rate of Rh-related disease has gone down, but some of the other causes of HDFN have been maintained.

More recently, the American College of OB/GYN echoed this in stating that they were "committed to eliminating disparities in women's health and to confronting implicit and explicit bias and racism. This means recognizing and examining our own prejudice and bias and addressing the way in which health care systems perpetuate inequality."

The Society for Maternal-Fetal Medicine, or SMFM, has also issued an equality statement. Chris, what can you tell us about that?

Dr. Robinson:
Absolutely, Lee. Thanks for bringing this up. SMFM is deeply concerned about racial and ethnic inequalities and health outcomes, as well as healthcare during pregnancy, childbirth, and the postpartum period. These same periods affect the hemolytic disease of the fetus and newborn that we're talking about today. So we're very, very committed to eliminating these disparities and advancing equity through the society's activities of research as well as access to maternal-fetal medicine care.

Dr. Shulman:
Chris, I really couldn't agree with you more.

Dr. Robinson, can you briefly describe the pathophysiology of HDFN? Do all of these blood group antigens lead to a similar state of anemia and disease, or are some more serious than others?

Dr. Robinson:
So the pathophysiology of the hemolytic disease of the fetus and newborn really involves the interaction between the fetal red blood cell and the maternal immune system. So if we look at how this happens, the fetal red blood cell can cross the placenta and enter the maternal circulation where the mother then has immune response to that foreign fetal cell, especially if there are antigens that are not common between the fetus and the mother. This would then result in the maternal immune system recognizing those foreign antigens and forming antibodies against those fetal antigens.

Now, in the first exposure, we would have the formation of IgM class antibodies which cannot cross the placenta, but in that subsequent exposure, what we would anticipate, maybe in the next pregnancy, for instance, that a pregnancy that does carry that specific antigen, the immune system in the mother would be activated with only a small exposure due to memory B cells being present. And these memory B cells can then produce very large amounts of antibody, and those antibodies are IgG class antibodies which have the ability to cross the placenta and enter the fetal circulation. When those IgG antibodies cross the placenta, they can actually attach themselves to the fetal red blood cells, and those fetal red blood cells would then undergo erythroblastosis, destruction, leading to anemia and hemolysis. And that also results in many other changes, things like increased bilirubin from the load of losing those red blood cells, the response of the baby to try to produce additional erythrocytes through extramedullary erythropoiesis, as well as hydrops if it's not attenuated by transfusion or intervention. So there's many different things that can happen.

When we look at the antigens themselves, the antigens that are usually involved are RhD and Kell, which both can be very severe antigens producing antibodies, and those antibodies can be very aggressive at causing fetal anemia. There are also minor antigens, such as anti-E, -C, or Duffy, which have less, but still can have significant impact in some of those pregnancies, as well. So they're not to be ignored, but they can cause more milder disease and less aggressive disease. And certainly, Kell has a secondary mechanism where it can actually suppress the production of new erythrocytes by the destruction of red cell progenitor cells and that leads to two mechanisms of anemia, both the destruction of the fetal cells as well as the inability of the fetus to respond to that anemia. So I think remembering that Kell is a very significant and very severe antigen is also important.

Dr. Shulman:
Let's now turn to diagnosing HDFN. What do you use in your practice, and do you have any clinical tips for our listeners?

Dr. Robinson:

Yeah, so I think the first thing to remember is when pregnancy is diagnosed, one of the first things we begin with is an antibody screen. And the antibody screen is really routine for all pregnancies to screen for red blood cell antigens, as well as ABO testing hopefully at the first prenatal visit and hopefully early in pregnancy. And by doing this, what we're actually doing is an indirect antiglobulin or a Coombs method screen. It's a very accurate and inexpensive screen that can be done by most labs. And so we can actually, in early pregnancy, begin to detect whether there are any clinically significant antibodies that may be present.

If we do see that one or maybe more alloantibodies are actually detected, the next step is really to consider what is the significance of those alloantibodies? Are they alloantibodies that can be implicated in hemolytic disease of the fetus and newborn? And if so, then we are going to begin talking about confirmation as to whether the current pregnancy that the mom is carrying could be at risk as a result of having those antibodies present on her antibody screen. This then turns to paternity and also the consideration of the mother's history. Looking back, what has her previous pregnancy history been like? Thinking about things, were any of her previous babies born with anemia? Did any of them have severe hyperbilirubinemia, maybe even requiring exchange transfusion after delivery? Were any of her infants kept in the hospital for a prolonged period after delivery or require referral to a hematologist after delivery? We usually start with that, and then we attempt to get records to look at what the course of some of those deliveries were like.

We also discuss paternity because if the mother has the same father for all of her pregnancies, then we would have at least a pattern of understanding if that father has fathered other pregnancies that may have had antibodies in the past, or was there any clinical history that fit with that. And then testing the father to determine whether he carries the antigen that we are seeing in the antibody in the mother. And the second piece of that is does he carry that as a homozygous or a heterozygous condition to determine whether there is a 100% chance this fetus is actually going to carry the offending antigen, or is it possible that it is a 50% chance that the baby will not carry it. So there are options there to begin to look.

When we talk about the assessment and diagnosis of the fetus, one of the things that we consider is, do we want to provide invasive testing? And invasive testing is generally avoided by chorionic villus sampling but may be considered by amniocentesis by avoiding the placenta and avoiding transplacental approach if we are going to type the fetus. There are some new novel methods that are coming about that have been used clinically looking at cell-free fetal DNA to make some of these diagnoses, and that's very exciting because that would give us a noninvasive way to potentially look at that in the future. But I think the primary method still requires examination of that pregnancy for whether the fetus actually carries the antigen of interest.

And then finally, we also screen these pregnancies for what is going on with that antibody as pregnancy progresses. So is her immune system mounting an antibody response against an antigen by increasing the titer to a critical titer that could result in anemia in a fetus? That's specifically important in the RhD class antigens. In the Kell antigen class, it's a very controversial topic, and some individuals feel that there really is not an antibody critical titer that should be used and then some use titers of 4 or 1:8 in those situations. And then we monitor once the critical titer has been met. We generally use noninvasive ultrasound screening by the use of the middle cerebral artery Doppler to assess what the flow rate is like within the MCA [middle cerebral artery] artery within the fetal brain. This gives us a noninvasive methodology to assess whether a fetus is experiencing anemia in utero.

Dr. Shulman:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Lee Shulman, and here with me today are Dr. Christopher Robinson and Dr. Ken Moise.

Ken, once the risk for HDFN has been identified, what treatment options are available for our patients?

Dr. Moise:
So once we begin to follow the MCA peak systolic velocities, those are usually done every week, and when we reach a value of 1.5 multiples of the median, we're concerned about fetal anemia. So that's a scenario where a cordocentesis would be performed to obtain a fetal hematocrit, and if the fetus is anemic, we would proceed with intrauterine transfusions. That's the mainstay of therapy. And those are repeated at different intervals. Some people use the MCA Doppler to decide when to do the next one; other centers use empiric intervals. But once we start intrauterine transfusions, we have to continue those every week to two-week basis until about 35 weeks' gestation, and then we would deliver the patient a few weeks later. So intrauterine transfusion is the mainstay of fetal therapy.

Now, that being said, we are presented with cases where there's been, let's say, a previous history of a loss at 20 weeks, and these patients have demonstrated to us that they're going to have, in the next pregnancy, fairly sick fetuses. Transfusions prior to 24 weeks carry a mortality of up to 20%. And so in that scenario, we would consider starting some type of immunomodulation. And that needs to be started, based on a recent publication called the PETIT trial, as early as 10 to 12 weeks, because that's when the IgG begins to cross. And that will usually involve either IVIG alone or IVIG therapy with plasmapheresis to lower the titer. But again, the IVIG is given to the patient weekly, the MCAs are followed, and hopefully the intrauterine transfusions can be postponed in those cases.

Once the patient delivers, then we now turn to our neonatologists to take care of the patient. And the primary goal is 2-fold in their situation. One is to deal with hyperbilirubinemia, which can cause significant, neurologic outcomes in the newborn, particularly if the bilirubin is high enough, it can cross the blood-brain barrier and cause kernicterus, which can result in cerebral palsy. And so bilirubin is followed very carefully. The first form of therapy is phototherapy. That usually involves banks of lights, blue lights on top of the baby, and many times, what's called a biliblanket under the baby. If phototherapy alone does not resolve the rising bilirubin, the next step would be an exchange transfusion. Now, our babies are too small to be dialyzed, and so an exchange transfusion is simply take an aliquot of blood in and take an aliquot of blood out to, if you would, wash out the affected red cells but also to remove the bilirubin itself. Exchange transfusions are not done that often these days and they carry their own risk for morbidity and mortality, even in experienced hands.

Finally, if a baby has been transfused in utero, many times these babies do quite well in the nursery and go home in just a few days with their mother. But we're not done yet. These babies have suppressed marrows because of the intrauterine transfusions, and they need to be followed fairly closely by perhaps a pediatric hematologist because many of them will need a top-up transfusion at 3 to 4 weeks of age. Usually it's one top-up transfusion, but on some occasions, they may need several before the baby begins to form its own red blood cells, and then the process is pretty much ended.

Erythropoietin has been attempted in these babies with limited success to try to get that bone marrow to wake up, if you would. There is a clinical trial ongoing in Europe to see if this is effective at this point. We don't have any data to suggest it's necessary to use erythropoietin in these babies.

IVIG is used in babies also by neonatologists to prevent further hemolysis. However, recent studies showed that IVIG is unnecessary and ineffective in babies that have had intrauterine transfusions. And the reason for that is that the cells that the baby is born with are in fact compatible donor cells, so IVIG really is not indicated in the neonate in that situation. And, in fact, there is some concern for necrotizing enterocolitis in some babies treated with IVIG. So it would not be used in that situation.

Dr. Shulman:
We have just heard an excellent overview, not just of diagnosis, but also of evaluation and intervention.

Chris and Ken, thank you so much.

Dr. Robinson:
Thank you, very much. It's been a great discussion.

Dr. Moise:
Yep, thanks Chris and Lee, this has been great.

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