Transcript Details

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Hemolytic Disease of the Fetus and Newborn (HDFN): What Pediatric Providers Need to Know When Managing Hemolytic Disease in Newborns (HDN)

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Hemolytic Disease of the Fetus and Newborn: What Pediatric Providers Need to Know When Managing Hemolytic Disease in Newborns” is provided by Prova Education.

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Dr. Markham:
During a recent satellite symposium at the 2022 American Academy of Pediatrics National Conference in Anaheim, California, my colleagues and I explored the evolving care of neonates with hemolytic disease of the fetus and newborn, otherwise known as HDFN. Dr. James Bussel, Bethany Weathersby, and I presented the latest data regarding current and emerging practice patterns, highlighting the critical need for improved understanding and multidisciplinary collaboration in the area of HDFN. Today I’m here to provide a recap of that symposium.

This is CME on ReachMD, and I’m Dr. Kara Markham.

In the first presentation, Bethany Weathersby provided a patient perspective that set the stage for our discussion. She discussed her personal history of having a daughter die in utero secondary to severe HDFN, followed by the successful delivery of her son August following plasmapheresis, IVIG, multiple intrauterine blood transfusions and coordinated neonatal care.

Bethany highlighted the fact that HDFN is a rare, complex disease, and women experience heavy psychosocial burdens related to this. As is a common theme throughout the symposium, she stressed the importance of collaboration amongst care providers. Without this multidisciplinary care, babies can sadly fall through the cracks. As an example, Bethany provided pictures of a child born to another mother, whose pregnancy was complicated by HDFN. I hope you can appreciate how pale Silas is in these pictures. Without proper follow-up, he became very anemic. Fortunately, his mother advocated for him, and he received the transfusions that he so desperately needed. Ideally, though, this degree of anemia should have been prevented through appropriate coordination of care in the first 3 to 4 months of life.

Next, I provided a historical overview of HDFN. Sir William Liley, pictured here, pioneered the field of fetal medicine when he successfully performed the first intrauterine transfusions for mothers and babies with severe HDFN.

Alloimmunization is an example of the immune system behaving how it is designed to behave. We’re exposed to a foreign entity, and we form antibodies to clear this from our system. But pregnancy is unique, because half of the fetus is derived from the father, and is thus foreign to the maternal host. When the mother is exposed to these paternally derived antigens from the fetus, she can’t distinguish these from any other foreign source. The body acts like it was designed to act by forming antibodies.

The problem is that these antibodies, specifically IgG antibodies, can cross the placenta to cause disease for the baby. Now we’re

talking about red blood cell alloimmunization here, but the inciting event of HDFN is the same as it is for neonatal alloimmune thrombocytopenia and other antibody-mediated diseases. With HDFN, the antibodies cross the placenta to bind to corresponding antigens on fetal red blood cells, leading to RBC deformation, destruction and ultimately anemia, the occurrence of which can be fatal for the fetus or the newborn.

Not all babies at risk for HDFN will develop clinical sequelae. In fact, about 80% of fetuses will compensate through a variety of mechanisms. 20% cannot compensate, though. We know that adequate compensation is less likely with certain antibodies and with multiple antibodies, but we are unable otherwise to assess what's called the fetal reserve, making it very hard to predict which fetuses will get into trouble. On the severe end of the spectrum, some fetuses will develop hydrops fetalis, a form of diffuse organ failure, usually seen when the hemoglobin is less than 5 g/dL.

In pregnancy, we use a tiered approach to managing women with red blood cell antibodies. The first tier involves screening for whether or not the fetus is at risk for anemia. All women go through this tier when we do antibody screening as part of the routine prenatal battery. Additional relevant questions include the titer of that antibody or the amount, whether or not the patient has a history of a prior pregnancy affected by HDFN, and whether or not the father of the baby and, more importantly, the baby itself has the corresponding antigen. If the fetus is determined to be at risk for anemia, we move to Tier 2, and this involves serial ultrasounds to screen indirectly for fetal anemia. We can't automatically start in Tier 2, because those ultrasounds are not perfect in identifying anemia, and there's a 10%-12% false positive rate. Finally, though, if we suspect anemia, we move to Tier 3, in which we diagnose and treat anemia directly. This can occur in utero. If the pregnancy is early in gestation, we can perform intrauterine transfusions, or IUTs. Or treatment can be provided directly to the neonate.

Ideally, though, we would like to prevent HDFN entirely. Attention has recently turned to the neonatal Fc receptor, FcRn, our manipulation of which may prevent diseases like HDFN. The FcRn is expressed throughout the human body, where it serves 2 primary functions. First, this receptor transports IgG across epithelial cells including those in the placenta, which is very important. Second, the receptor protects IgG from catabolism, so it extends these antibodies' half-lives in both the pregnant and the nonpregnant individual.

This illustration depicts the role of the FcRn in transporting antibodies from mother to baby across the placenta. Syncytiotrophoblasts in the placenta internalize maternal IgG into endocytic vesicles, where they bind to the FcRn. The FcRn-bound IgG is then transported across the placenta and released into the fetal circulation. There is ongoing research using an agent called nipocalimab, that aims to block these processes, so if we add nipocalimab to this illustration, as indicated by the red structures, this will block or bind to the FcRns on the maternal side of the placenta, blocking their ability to transport maternal IgG into fetal circulation. If there's no anti-RBC IgG in the fetal circulation, there's no red blood cell destruction and therefore no anemia. The initial research using nipocalimab has been very encouraging, and we are continuing to study both the efficacy and the safety profile of this in ongoing multinational trials.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Kara Markham, and I'm just about to delve a little deeper into the pathophysiology of HDFN.

Next, in his talk entitled, "Neonatal and Infant Late Anemia in HDFN – The Role of the Pediatrician," Dr. Bussel presented a historical perspective and emphasized significant aspects of pathophysiology. This was of particular interest to the audience. Dr. Bussel described 3 time periods in the history of HDFN management. First, prior to the advent of prophylaxis and prior to intrauterine transfusions, or IUTs, HDFN was very common, occurring in about 1% of all deliveries, with up to a 25% mortality rate. Management centered around the care of the neonate by exchange transfusions. This was a common enough procedure that general practitioners were expected to know how to perform exchange transfusions. Second, HDFN related to anti-RHD antibodies in particular, greatly decreased in prevalence following the advent of prophylaxis with RH immunoglobulin, but we still see HDFN secondary to other antibodies, and due to inadvertent admission of RH immunoglobulin.

We are now in a time period after the advent of prophylaxis and intrauterine transfusions. With proper obstetric care, we expect the vast majority of babies, even with severe HDFN, to survive to delivery. The risk, though, is that practitioners can incorrectly assume that the baby is cured, but these babies remain at risk for morbidity and even mortality.

Now I've previously mentioned that delivery is the recommended intervention for babies further in gestation who are suspected to be anemic. These neonates may require simple transfusions, exchange transfusions, IVIG, and phototherapy, but the hemoglobin will usually stabilize within the first week or 2 of life.

Babies who require 2 or more intrauterine transfusions, though, are at risk for delayed anemia. These babies will display pronounced depression of erythropoiesis, with research showing marked depression of erythropoietin levels despite significant anemia. These babies may look clinically well, with hemoglobin levels initially that depend largely upon when the last intrauterine transfusion was performed. It is critical, though, that pediatric providers recognize the risk of delayed anemia, with recommendations for management

protocols that include the following: avoidance of iron replenishment, weekly CBC monitoring, and administration of high-dose erythropoietin prior to discharge from the hospital in an effort to promote RBC production.

Finally, in the last presentation, Bethany Weathersby returned to the patient perspective. She brought it home by providing us more details about why understanding HDFN matters. She focused on the patient perspective, describing these journeys as an HDFN relay race, in which there are 2 to 3 baton passes from one group of providers to another – passes that, if they don't occur seamlessly, can result in worsening disease for the baby. By the time the mother gets to the pediatrician, they've been through a lot. There is significant prenatal burdens for the mother, including mental or emotional burdens, logistical burdens, and physical burdens. These burdens persist after delivery. In addition, the mother is at increased risk for perinatal or postpartum anxiety, depression, and post-traumatic stress disorder. The mother herself is really not in any shape to participate further in the HDFN relay race. Despite this, many women find themselves needing to advocate for post-birth HDFN management. The mother often serves as the baby's prenatal medical record, being asked to explain how prenatal interventions affect her baby's post-birth needs.

So what is the solution to this problem? Well, the Allo Hope Foundation serves as a great resource for patients on these journeys, and we hope to soon provide information for medical providers as well. Again, though, we stress the importance of coordinated, multidisciplinary care. The mother should never be given the baton. The providers should carry this burden, passing the baton smoothly to the next provider until the babies cross the finish line and can live long, healthy lives, unaffected by their HDFN journey. So you have the power to keep these babies safe and ease the burden for the mothers.

So to wrap up, I'd like to share these key take-home messages with our audience. A range of clinicians play a critical role in ensuring the continuity of care for the fetus, the newborn, and mother, and this collaboration of care is absolutely imperative to ensure the best outcome for these babies.

Core problems and consequences include the following: HDFN is a rare, complex disease; HDFN requires multiple providers and subspecialists to care for the mother and the baby; many providers don't have a chance to become experts through day-to-day experience; patients don't always receive consistent, high-quality care; there's little continuity of care; consequences for the mother are heavy; and consequences for the baby can also be heavy, including preventable harm, even death, and lifelong health issues.

I want to thank our audience for listening in, and I'd like to thank my colleagues, Dr. Bussel and Bethany Weathersby, for their insight, expertise, and participation in this symposium.

Announcer:
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