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Innovations in the Management of Hemolytic Disease of the Fetus and Newborn: The Role of the Neonatal Fc Receptor (FcRn) Pathway

Announcer:
Welcome to CME on ReachMD. This activity, titled “Innovations in the Management of Hemolytic Disease of the Fetus and Newborn: The Role of the Neonatal Fc Receptor (FcRn) Pathway” is provided by Omnia Education.

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Dr. Markham:
Hemolytic disease of the fetus and newborn, also known as HDFN, is an alloimmune blood group disorder, leading to destruction of fetal red blood cells. Consequences of HDFN can be serious and are occasionally fatal, and prevention and treatment of HDFN continues to pose a clinical challenge.

This is CME on ReachMD and I'm doctor Kara Markham. I'd like to welcome my colleague, Dr. Kenneth Moise, to our discussion today where we'll address this clinical challenge.

Dr. Moise:
Well, thank you, Dr. Markham, glad to be here today.

Dr. Markham, I’d like to start out by asking the first question: HDFN is considered an alloimmune disorder occurring between the mother and fetus, one with significant risk for dire health consequences for both. Could you address for us the key alloimmune immune and pathophysiologic processes associated with HDFN?

Dr. Markham:
Sure. Thank you, Dr. Moise. So, red blood cell alloimmunization occurs when an individual is exposed to foreign red blood cell antigens and he or she develops antibodies against these proteins. This process, called sensitization, most commonly occurs during pregnancy or from a blood transfusion. In future pregnancies, some of these antibodies can cross the placenta to cause disease for the baby. With HDFN, the antibodies bind to corresponding proteins on fetal red blood cells, leading to deformation of the red blood cells, extravascular destruction, and anemia.

Now, we can prevent some HDFN, specifically disease occurring due to exposure to the Rh D antigen. This can be prevented using a medication called Rh immunoglobulin. And the prevalence of the disease has greatly decreased since this medication came on the market.

Despite this, though, about 2% of pregnant individuals will be found to have red blood cell antibodies, and HDFN will complicate approximately 5 out of every 100,000 pregnancies. Importantly, not all antibodies cause HDFN the antibodies that are most commonly associated with clinically significant fetal anemia include Rh D, Kell, and Rh little c. The response to these antibodies can vary significantly from baby to baby.

Some babies won't have many issues, while others will develop clinically significant anemia and/or jaundice after delivery. The ones we

worry about the most as obstetricians are the subset that become anemic during pregnancy. Babies that become anemic during pregnancy can become very sick, developing a form of heart failure called hydrops fetalis, and even dying. So, it is imperative that obstetricians and maternal fetal medicine specialists are familiar with this disease to minimize the morbidity and mortality that can occur secondary to HDFN.

Dr. Moise:
So, Dr. Markham, you make some important points about anti-D, big E, little C and Kell being the important antibodies. What about ABO? Does that ever cause a problem during the pregnancy?

Dr. Markham:
ABO is not thought to be a problem during pregnancy. It can cause jaundice, and even mild anemia after delivery, but during pregnancy it doesn't cause fetal anemia that needs treated.

Dr. Moise:
Thank you for clarifying that. Well, let's move on to our second topic about treatment strategies for HDFN. So, Dr. Markham, I'd like you to expand upon our first question. What are the current prevention and treatment strategies for HDFN and why is there continued need for a safer and more effective approach?

Dr. Markham:
So ideally, we'd love to prevent alloimmunization entirely. As mentioned earlier, Rh immunoglobulins can be given during pregnancy and in the postpartum period to prevent disease specifically due to Rh D antigens. And blood for transfusion should be cross matched as much as possible in women of reproductive age and younger. But unfortunately, not all sensitization can be prevented.

When a patient is found to have a red blood cell antibody in pregnancy, providers must determine if the baby is at risk for anemia. This can first involve serially estimating the amount of antibody in the patient's circulation, something called an antibody titer. It also involves screening or testing for the presence of the corresponding antigen in the father of the baby, or, more importantly, the fetus.

For the fetus, we can now screen for the status of many red blood cell antigens using something called cell-free DNA screening or non-invasive prenatal screening, and this is a highly useful tool in determining the risk that an alloimmunized pregnancy will be affected by HDFN. If the fetus is thought, or proven to be negative for the antigen, there's no risk of HDFN. But if the baby is positive for that antigen, those are the babies we worry about. If a fetus is found to be at risk for anemia because of their antigen status and because of the maternal antibody titer, screening for anemia should be initiated by monitoring the rapidity of blood flow in the baby's brain, something called the middle cerebral artery.

And finally, if concerns arise for fetal anemia, definitive diagnosis should be undertaken with treatment as indicated. This may involve delivery of the baby if the gestational age is far enough along, but in-utero intervention by a fetal blood sampling and intrauterine transfusion may be needed for earlier pregnancies. Unfortunately, these procedures are not without risk, including the potential for fetal death and/or pregnancy loss.

In pregnant individuals at risk for developing early HDFN, those who we worry we may need to intervene on prior to about 24 weeks. Adjuvant therapies, such as intravenous immunoglobulin, may lower the maternal antibody concentrations to delay the onset of clinically significant fetal anemia. Unfortunately, these treatments will not prevent the disease entirely. So, given the risks associated with in-utero treatment, we would love to find a way to better prevent fetal anemia.

Dr. Markham:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Kara Markham, and here with me today is Dr. Kenneth Moise. Our focus today is the rationale for evaluating the neonatal FcRn pathway as an emerging treatment target in the prevention and management of HDFN.

Dr. Markham:
Dr. Moise, the neonatal Fc receptor pathway has become a major investigational target in a number of conditions. This pathway appears to affect the recycling and transcytosis of IgG and albumin. How and why is that important as we consider new approaches to preventing and managing HDFN?

Dr. Moise:
Well, thank you, Dr. Markham, for that question. The neonatal Fc receptor, also called the FcRn receptor is an important receptor throughout the human body. First of all, it's present on the endothelial cells that line one's blood vessels, and its role there is to actually recycle IgG from inside the cell back to the surface of the cell. In other words, it works as a salvage mechanism to prevent the degradation of IgG. So, in fact, it allows for the IgG to be maintained at a certain level. The second part of the important mechanism of

FcRn is to take maternal antibody and transport it across the placenta. And in that situation, the antibody from the mother is particularly the beneficial antibody, is sent over to the fetus so that when it's born, it has a full complement maternal antibody.

Now, when a drug like nipocalimab comes on board, that blocks the FcRn receptor. So, that's going to do two things, and both of which are beneficial in the alloimmune disease case.

The first is it's going to lower the total circulating pool of IgG by as much as 85%. Now, that will lower all IgG, including the pathogenic IgG. So, in essence, the maternal titer will drop. And then the second thing, the nipocalimab will do is block the FcRn receptor at the placenta so that any antibody crossing to the fetus will be blocked, and there will be a decreased amount of the pathogenic antibody.

So, that's a two-edged sword. You're blocking the pathogenic antibody from getting to the fetus, but you're blocking the beneficial antibody at the same time. But if you think about this, nipocalimab has the possibility of blocking other pathogenic antibodies, for instance, congenital heart block associated with antibodies fetal neonatal alloimmune thrombocytopenia where there are other antibodies involved against platelets. So, this drug has the possibility of treating a variety of alloimmune diseases by its mechanisms.

Dr. Markham:
Thank you, Dr. Moise. Let's continue our discussion with a follow up to our last topic. What does the future look like in HDFN? Can you tell us more about data associated with use of nipocalimab, and what its impact should be when it – or if it eventually reaches the clinic?

Dr. Moise:
Yeah. Thank you for that question, Dr. Markham. So, recently in June of 2023, the initial data from the UNITY trial, which is a phase two open-label trial that was undertaken first through Momentum Pharmaceuticals and then through Johnson and Johnson and Janssen Pharmaceuticals, was presented in Valencia, Spain at the Fetal Medicine Foundation. So, the trial's admission was open-label, it was everybody knew if they were getting the drug, both the investigator and the patients. It was designed to administer it to patients who had early onset HDFN. So, they had to have either anti-D or anti-Kell with a significant titer, and their previous pregnancy yet to be affected by either the loss of the pregnancy or the need for transfusion before 24 weeks. And so, in total there were 14 patients enrolled in the trial. Now, the primary endpoint was, in fact, the number of patients who reached 32-weeks gestation without the need for intrauterine transfusion. Now remember, all of these patients had either loss or a fetal transfusion at the previous pregnancy. And so, adverse events were also looked forward during the trial, so this added a safety aspect to the phase two trial in both the mothers for 24 weeks postpartum, and for their babies up to 96 weeks after birth.

The important finding in the trial is that 54% of the patients, 7 of 13, ended up without the need for intrauterine transfusions before 32 weeks. And when compared to historical reference points of only 10%, this was clearly significantly increased as an improved outcome with the drug.

Of the patients that reached the primary endpoint, the median gestational age in these 7 patients was 37 and 1/7 weeks, so basically, term. The most frequent adverse events were thought to be related mostly to pregnancy or to HDFN itself. Two participants experienced live births associated with safety events thought to be related to nipocalimab. One had a subchorionic hematoma with IUGR and a fetal heart rate deceleration, and the second experienced preterm separation of the placenta after amniotomy for polyhydramnios. Because of these findings, nipocalimab was fast-tracked by the FDA in July of 2019.

Dr. Markham:
It sounds so promising. This has been a great discussion. Before our close, Dr. Moise, do you have a single key takeaway to share with our learners.

Dr. Moise:
Well, I think the thing that's important is that we've now completed a Phase 2 trial, and the data was significant enough, both on the efficacy side and the safety side to move on to a Phase 3 trial. This is the AZALEA trial. It is just starting to enroll patients and it will be a double-blind randomized controlled trial wherein both the investigator and the patient will not know if they are receiving the drug or placebo. The good news is, it's a 2 to 1 randomization, so the patients are twice as likely to get the drug as to be in the placebo arm.

Dr. Markham:
Unfortunately, that's all the time we have today. So, I want to thank our audience for listening in, and thank you, Dr. Moise, for joining me and for sharing your valuable insight. It was great speaking with you today.

Dr. Mosie:
And thanks for having us and it's been a great pleasure to do this.

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