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Red Blood Cell Alloimmunization, Pathophysiology, Diagnosis, Treatment, and Prevention

Announcer:
Welcome to CME on ReachMD. This activity, entitled "Red Blood Cell Alloimmunization, Pathophysiology, Diagnosis, Treatment, and Prevention" is provided by Omnia Education.

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Dr. Shulman:
Previously known as erythroblastosis fetalis, hemolytic disease of the fetus and newborn, or HDFN, is a rare condition with an estimated 3 to 80 cases per 100,000 pregnancies annually in the United States. It's really an area of obstetrics that's not fully understood by many clinicians.

In this program, we'll contextualize red blood cell alloimmunization, specifically highlighting epidemiologic evidence, the pathophysiology of HDFN, and current and evolving management strategies that may impact your clinical practice.

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

It's now my pleasure to introduce Dr. Ken Moise, Professor in the Department of Women's Health at the Dell Medical School at the University of Texas at Austin, and the Director of their Comprehensive Fetal Care Center.

Dr. Moise:
Great to be here.

Dr. Shulman:
Dr. Moise, let's dive right in. Can you give us some background on alloimmune diseases of the fetus and newborn? Let's focus on HDFN so we can get everyone up to speed about the basic epidemiological information.

Dr. Moise:
So hemolytic disease of the newborn also usually known as HDN, or fetus and newborn HDFN, results from an alloantibody-mediated neonatal and fetal hemolysis caused by incompatibility between the fetus and its mother. It's not a very common condition, as Dr. Shulman pointed out, cases occurring only 3 to 80 per 100,000. So the practicing obstetrician may only see 2 or 3 cases in their entire career.

It has different impacts on different ethnicities. However, the 4 bad players or antibodies that cause the most problems in fetal life include RhD, Rhc, Kell, and RhE. Now, these particular antigens and their genes that cause them occur at different gene frequencies and with different zygosities throughout different ethnicities. We take, for instance, RhD negativity; it occurs in about 15% of Caucasians, but only about 8% of African Americans and Hispanics.

And if we take Kell, for instance, one of the other bad players, about 92% of Caucasians are Kell negative, and about 98% of African Americans are Kell negative.

So obviously, there are different problems that occur in different races and ethnicities.

Dr. Shulman:
You know, Ken, I think it's important for our listeners to understand that regardless of how often the patient has returned with ongoing pregnancies or what their ethnic or racial background is, absolutely no one is off the hook for being evaluated for their antibody status.

Now, I think you and I have many stories about paternity issues. Many of our listeners may have had situations in which the paternity of the putative father was not necessarily so. But regardless of that, it is critical for every clinician who cares for a pregnant woman to evaluate that antibody titer with every pregnancy, even if this is her fifth or sixth pregnancy and it's with the same partner. And also to follow up that evaluation at 28 weeks in those women who have Rh-negative pregnancies before one would administer Rh immunoglobulin.

What can you tell us about the basic pathophysiology of HDFN?

Dr. Moise:
So the pathophysiology of HDFN has been well described through the years. What we do know is that maternal IgG is transported actively across the placenta by attaching first to the FcRn receptor, and then it moves across into the fetal circulation. We know this begins at approximately 10 to 12 weeks of gestation, and there's an increasing amount of placental transport as the pregnancy progresses, to the point that at term, the levels in the fetus are about 125% of those of the mother.

Now in the case of the pathogenic antibody, for instance, anti-D or anti-Kell, once that crosses into the fetal circulation, this attaches to the fetal red cells. These cells are then sensitized, and they're then sequestered by the fetal spleen, causing fetal anemia. The fetus can respond to this by increasing the production of red cells from its bone marrow, and in more severe cases, even from the liver and from the spleen itself.

However, at some point, the system gets overwhelmed, and the fetus becomes severely anemic and can develop what we call hydrops fetalis. And what we see when the fetal hemoglobin is about one-third of normal, is that ultrasound will detect fluid in the abdomen, called ascites; around the heart, pericardial effusion; and around the lungs, called pleural effusion. And this represents congestive failure in the fetus and is the end stage of hemolytic disease of the fetus and newborn.

Dr. Shulman:
Let's now turn to diagnosis. Ken, what's involved in the diagnostic workup and evaluation? And what's the current thinking on amniocentesis?

Dr. Moise:
So, Dr. Shulman, as we talked about, any patient can be at risk. And so all patients should have an antibody screen no matter what their blood type at the beginning of the pregnancy. When the lab determines that there is a significant antibody present, the next step is to perform a titer to quantitate the amount of antibody. And these titers can be followed if they're fairly low until they reach a critical value. And normally, we would use a value of 16 for almost all of the antibodies with the exception of the Kell system. And we would use an antibody of 4 for the Kell system, because this seems to be a more virulent antibody.

And so when we reach a critical titer, we next look to see what can the baby be. And we'll look to dad; we'll look to zygosity. If dad's homozygous and paternity is assured, we know the baby can be affected. If dad's heterozygous, we can move on to additional testing. Now we shouldn't be doing CVS [chorionic villus sampling], because that disrupts the placental barrier, and that can make mom's disease a lot worse. So CVS is off the table.

Amniocentesis is a possibility, but is being supplanted today by free DNA, a sample from the maternal bloodstream that can tell us the baby's antigen status. In the US, it's only available for determining the D status. But there are several labs overseas that can perform free DNA analysis for Kell, little c, and E. So free DNA in the very near future, even in the US, will supplant the need for any amniocentesis to determine the baby's blood type. But remember, again, this is only done when dad's determined to be heterozygous. If he's homozygous, we know the baby's affected. We don't need to worry about free DNA.

Once we know the baby is positive for the antigen involved, and we know in fact the titer has reached a critical value, the next step is MCA Doppler, or middle cerebral artery Doppler. We do that every 1 to 2 weeks, starting as early as 15 and 16 weeks in some cases, looking for the speed of the blood in the baby's brain. And when it exceeds 1.5 times the normal rate, or 1.5 MoMs, we're concerned about fetal anemia. And that's a case where we move on to cordocentesis to evaluate the actual level of anemia in the fetus.

Dr. Shulman:
You know, I think that's a really important point. And that is that for many clinicians who maybe grew up in a residency or early practice where amniocentesis was the mainstay of evaluating and following these fetuses, amniocentesis is really no longer an integral part of

this ongoing care for a sensitized pregnancy.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Lee Shulman, and here with me today is Dr. Ken Moise. We're just about to delve deeper into alloimmune disorders, focusing on HDFN and current treatment strategies.

Ken, what's the main course of treatment if the clinician is concerned about fetal anemia?

Dr. Moise:
When we determine that the MCA peak systolic velocity is 1.5 multiples of the median or higher, we're significantly concerned about fetal anemia. And at that point, we would proceed with cordocentesis. We would obtain a sample of the fetal blood, and if the baby is confirmed to be anemic, we would then perform an intrauterine transfusion of compatible red blood cells to obtain a final fetal hematocrit in the range of 40% to 45%. That's the normal range for the fetus.

Once we start these, we continue to do serial transfusions every 2 to 3 weeks. And we'll stop these at 35 weeks' gestation with the plan to induce the patient at 38 weeks.

Now one caveat is that sometimes we determine the fetus to be anemic even as early as 15 weeks. And we know that the loss rate from intrauterine procedures performed in the umbilical cord prior to 22 weeks is about 20%. And that's due to technical problems with doing cordocentesis that early. So some centers will use intraperitoneal transfusions as a bridging method to span the gestational age until the cord is bigger and can be accessed through an intravascular technique. In any event, after serial intrauterine transfusions, we'd stop those at 35 weeks with the plan to deliver at around 38 weeks' gestation.

Now, we're not done yet; those babies typically do pretty well in the nursery. Sometimes they need some phototherapy, but rarely do they need additional transfusions. However, these babies need to be followed very carefully on a weekly basis, every week or so after delivery, because they can bottom out their hematocrit and need additional top-up transfusions during neonatal life. So we have our patients see a pediatric hematologist prior to delivery so that they can be available to go to their clinic soon after the baby's born and get careful follow-up.

Dr. Shulman:
I think it's important to recognize that while amniocentesis has been, in a sense, overtaken in its role in the evaluation of such pregnancies, the intrauterine transfusion has remained the mainstay of therapy and really has provided a way of getting these fetuses to a point where they can in fact survive and thrive once delivered.

Can you touch on the treatment option selection in the case of a patient with a previous loss? What do we currently have in our tool kit, and what's on the horizon?

Dr. Moise:
So occasionally, the clinician is faced with a patient who, say, had an attempted intrauterine transfusion at 20 weeks' gestation for, say, hydrops fetalis. And this is usually a very difficult pregnancy for this patient to undergo, and the next pregnancy where we expect the disease to even be worse. That is, have onset of fetal anemia prior to the gestation of the previous pregnancy.

So what we have in our tool kit is some immunomodulation techniques. And those are done in one of 2 ways. Some centers, somewhere between 10 and 12 weeks of gestation, remember that's when the IgG begins to cross, will perform plasmapheresis on several different time settings to attempt to decrease the maternal titer. This might be done when the patient's titer is, say, 2,000 or 4,000 and astronomically high. The idea would be to get the titer down by about half with 3 sequential plasmaphereses performed every other day.

Subsequent to that, most centers facing these pregnancies will incorporate intravenous immune globulin [IVIG], given typically on a weekly basis to these patients.

And data more recently in one of the studies, the PETIT trial, would show us that we can buy time with IVIG, usually several weeks, but ultimately, we'll still have to do transfusions. So even though we're doing weekly IVIG therapy, we're still following the MCA Doppler, knowing that eventually, we'll probably have to resort to intrauterine transfusions. So it's not a cure, but it sure buys us time until we technically can perform the procedure.

What I hope is on the future is targeted FcRn receptor therapy. So if we can develop a monoclone that will target the FcRn receptor of the placenta, we can perhaps decrease the passage or maybe stop the passage of this pathogenic antibody to the fetus, and therefore negate the need for intrauterine transfusions.

Dr. Shulman:
Do you have a take-home message that you'd like to share with our audience?

Dr. Moise:
I believe that any patient or obstetrician faced with these difficult pregnancies should obtain some consultation from a maternal fetal medicine specialist, preferably one who deals with these type of patients on a frequent basis.

In addition, we have pretty good data that the experience with intrauterine transfusion is waning as we see fewer these patients in recent years, and therefore, I would ask that the patient do their homework and make sure that they're dealing with a maternal fetal specialist who has experience in these procedures, preferably doing maybe 10 a year, so that they have a team approach to have the best clinical outcome. And data from experienced centers would say survival rates are on the order of 95% with intrauterine transfusion in experienced hands.

Dr. Shulman:
I think it is critical that whenever somebody does an antibody test on that pregnant patient, that if it comes back positive, to contact a maternal-fetal specialist for assessment.

I want to thank our audience for listening in. And thank you, Dr. Moise, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Moise:
Thank you. It's been an honor.

Announcer:
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