Hemolytic Disease of the Fetus and Newborn: Cutting Edge Strategies for Diagnosis and Management

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Here is Dr. Lee Shulman.

Dr. Shulman:
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. HDFN occurs when maternal red blood cells or blood group antibodies cross the placenta during pregnancy and cause fetal red cell destruction. The physiologic consequences of severe anemia in the fetus can lead to edema, ascites, hydrops, heart failure, and death.

Dr. Shulman:
Dr. Moise, could you tell us a little bit about the alloimmune diseases of the fetus and newborn with a focus on HDFN?

Dr. Moise:
Alloimmune diseases involve the production of antibodies in a pregnant patient against fetal antigens. These antigens can be platelet antigens, or they can be red cell antigens. Today, we’ll concentrate on antibodies that cross the placenta and attach to red cell antigens. The most common of these, of course, will be the rhesus antigen, or RhD antigen, but other red cell antigens, like the Kell antigen or the little c-antigen, can also be the culprit in the disease.

When a mother develops antibodies, usually after her first pregnancy, these antibodies can be actively transported across the placenta, attach to the fetal red blood cells. These cells are removed from circulation by the fetal reticuloendothelial system causing fetal anemia, and this anemia can be progressive, leading to hydrops fetalis and ultimately leading to fetal death.

Dr. Shulman:
Dr. Moise, do all of these blood group antigens lead to a similar state of anemia and disease, or are some more serious than others?

Dr. Moise:
I believe the 3 antigens we are most concerned about for fetal disease, that is the fetus becomes anemic during course of the...
pregnancy, would be RhD, RhC, and the Kell, or K1 antigen.

Dr. Shulman:
Thank you. Now that we have a better grasp on HDFN, how do we diagnose it? And what algorithms are available for us to use to facilitate diagnosis and follow-up therapy?

Dr. Moise:
So we usually begin with a diagnosis when we find a positive antibody screen in the pregnant patient. This usually can occur when the patient books into the pregnancy at the first prenatal blood work. When an antibody is detected that can cause a disease, one then should request a titer, which is a measure of the amount of antibody in the maternal circulation. Usually, these titers are followed monthly until a critical value is reached, which is, depending on the particular antigen, somewhere between 16 and 32. When a critical titer is reached, we then look to the father to see if he, in fact, has the particular antigen on his red cells. So we would do a typing of the dad, and we would determine his zygosity to see if he is heterozygous or homozygous. If he’s homozygous, we know the fetus can be affected in every case. If he’s heterozygous, we have a 50/50 chance of an affected fetus, and we can proceed with either free DNA testing in the case of Rh or amniocentesis to determine the fetal blood type. If dad is homozygous or we find the fetus to be antigen-positive through DNA testing, we would proceed with specialized ultrasound called MCA, or middle cerebral artery Doppler. And we would measure the systolic velocity using specialized Doppler ultrasound. When that value exceeds 1.5 multiples of the median, or 1.5 times normal for a particular gestational age, we would be concerned about fetal anemia. And in that situation, we would proceed with cordocentesis to obtain blood from the fetus to evaluate its final blood count. This type of algorithm is available at many of the college documents, both from the American College of Ob-Gyn as well as the Society for Maternal-Fetal Medicine.

Dr. Shulman:
While your answer speaks volumes as to how we now approach the at-risk pregnancy, I have to mention the fact that finding out that initial antibody titer is such an important and critical issue.

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

Dr. Moise:
In the typical pregnancy, as I mentioned, once the MCA Doppler is elevated, we would proceed to cordocentesis to assess the fetal hematocrit, and if it’s found to be less than 30%, which is a number most centers use, we would proceed with an intrauterine transfusion. Once we begin intrauterine transfusions, we have to continue to do those on intervals somewhere between 10 days and 3 weeks. At our center, we continue those until 35 weeks’ gestation, and we begin induction at approximately 38 weeks. And that would be the typical management of a patient with intrauterine transfusions.

In very severe cases of Rhesus disease, sometimes the fetus can be anemic before we can technically do intrauterine transfusions, which would be somewhere between 18 and 20 weeks of gestation. So if a patient presents at that initial booking exam with a very high titer—let’s say as an example a titer of 2,048—that fetus is going to become anemic long before we can technically start intrauterine transfusions. In that situation, we’ve had some success with instituting plasmapheresis between 10 and 12 weeks to lower the maternal titer and following the plasmapheresis with weekly intravenous immune globulin and continuing that on a weekly basis until we detect an elevation in the MCA Doppler. Now, that protocol doesn’t negate the need for transfusions; it simply prolongs the interval until the transfusions are necessary. But that interval can be important because it can prolong the gestation until technically one can assess the cord and the vessels in the cord and perform a successful cordocentesis and transfusion.

Dr. Shulman:
For those just tuning in, you’re listening to CME on ReachMD. I’m Dr. Lee Shulman, and here with me today is Dr. Kenneth Moise Jr. We’re discussing evolving strategies in the diagnosis and management of hemolytic disease of the fetus and newborn.

I’d like to turn our discussion now to the potential role of the neonatal Fc receptor pathway in HDFN. What is that pathway, how is it related to HDFN, and how might it be therapeutically manipulated in the management of HDFN?

Dr. Moise:
So the receptor, the neonatal Fc receptor, is present on the placenta and is involved in actively transporting antibody from the maternal circulation to the fetus. In most cases this is a beneficial mechanism in that it is providing immunity to the fetus in a progressive fashion as the pregnancy continues so that when the fetus is born, it shares the maternal immunity as it comes into the world when it does not have a competent immune system yet. So this is a protective mechanism for the fetus to acquire maternal immunity. However, in the case of Rhesus disease, not only are beneficial antibodies transported across the placenta, but deleterious antibodies, and therein lies the problem of these antibodies crossing and causing red cell damage.

Of note, the neonatal Fc receptor is also present on the endothelial cells of the mother. So all of us have FcRn receptors on our
endothelial cells, and these receptors actually serve a different purpose of circulating our IgG between our serum, our bloodstream, and into the cell. So they basically maintain the pool of circulating IgG. So the Fc receptor has very important functions, both in normal individuals in the form of its role at the endothelial cell level and in placentas where it creates a transplacental passage of maternal immunity to the fetus.

Dr. Shulman: What you describe here with the Fc receptor is taking that immunological concept really to the next level, to the next state. How does this potentially play a role going forward in treating those fetuses that are at risk for HDFN?

Dr. Moise: Well, I think this is an exciting time, because if we can develop a monoclonal antibody to block the FcRn receptor, we could basically arrest the disease early in pregnancy where the deleterious antibody, in this case anti-D, could not affect the fetus because it would be stopped at the placental level. And so, in essence, the fetus would not suffer the consequences of maternal anemia. One of the agents that is currently under investigation as a monoclonal antibody for the treatment of HDFN is nipocalimab, and this probably will be the first agent that will be shown to be potentially successful in treating HDFN. This therapy has the potential to negate the need for needle-guided procedures, and my hope is that one day we look back on intrauterine transfusions as historical events, and we put our needles away because we now can treat our disease immunologically.

In addition, because an FcRn receptor would be blocked on the endothelial cell of the mother, there might be a second therapeutic mechanism of lowering the maternal titer since blockade of that FcRn receptor at the endothelial level will cause degradation of the circulating IgG pool and lower the anti-D level. Now, that would be the benefit at two different therapeutic sites, but we have to remember that lowering the maternal antibody level will lower all of the IgG pool, so that potentially could put the mother at risk for some infection, and we have to be concerned about that. Likewise, if we block the Fc receptor at the placenta, we prevent the beneficial antibody that the mother would normally pass on to her fetus—and her newborn, therefore—and so that could be a consequence that we would have to take into effect also since we might put the newborn at risk for infection if we have a total blockade of the Fc receptor.

Dr. Shulman: I must say this has been a fascinating conversation, truly cutting-edge information on a whole new approach to what is a somewhat well-recognized problem reduced because of obstetrical interventions that are part and parcel of routine obstetrical care. But before we wrap up, Dr. Moise, can you share with our audience your one take-home message?

Dr. Moise: I believe that the most important part of the care of these patients currently is to recognize the disease, but more importantly, for the maternal-fetal individual, to recognize their limitations of the major therapy we use today—that's intrauterine transfusion. We are seeing less experienced physicians performing these procedures, and because of that, mortality and morbidity is increased, and so I believe as maternal-fetal specialists, we should recognize our limitations, and in many cases these patients should be referred to specialized centers who perform these procedures quite frequently. Until we have some type of immunologic treatment, we still need to keep intrauterine transfusion in our back pocket and realize that it is a pretty difficult procedure, particularly early in pregnancy.

Dr. Shulman: Well, I agree 100% with you.

Unfortunately, that's all the time we have today, so I want to thank our audience for listening 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: I want to thank you, Dr. Shulman, for involving me in this podcast, and I want to thank the Omnia educational group also who organized it.

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