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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

A Deeper Understanding of Maternal Alloimmunization and Hemolytic Disease of the Fetus/Newborn

Announcer:
You're listening to ReachMD. This medical industry feature titled, "A Deeper Understanding of Maternal Alloimmunization and Hemolytic Disease of the Fetus/Newborn" is sponsored by Janssen Pharmaceutical Companies of Johnson & Johnson.

Here's your host, Dr. Charles Turck.

Dr. Turck:
This is ReachMD. I'm Dr. Charles Turck, and today I'm joined by Dr. Kenneth Moise, who's a Professor in the Department of Women's Health and Director of the Comprehensive Fetal Care Center at Dell Children's Medical Center. We're honored to have his expertise in hemolytic disease of the fetus and newborn to bring to today's interview. Thank you for joining us, Dr. Moise.

Dr. Moise:
Well, thank you for having me today. I look forward to our discussion.

Dr. Turck:
Let's begin with a brief overview of this disease. Dr. Moise, what can you tell us about hemolytic disease of the fetus and newborn?

Dr. Moise:
So hemolytic disease of the fetus and newborn, also referred to as HDN, or HDFN, is a rare condition in which the fetus or the newborn baby can suffer from potentially very serious anemia as a result of maternal antibodies that attack the red blood cells of the fetus. This happens when the red blood cell antigens of the fetus are not a match to the mother. Or to be more specific, the red blood cells of the fetus express one or more antigens that the mother's red cells do not have. The pregnant woman's immune system, if sensitized, recognizes these red blood cell antigens as foreign and develops antibodies against them, which leads to the destruction of the red blood cells of the fetus.[1]

A few potential adverse outcomes of HDFN include fetal hydrops and fetal and neonatal demise. Infants born after an affected pregnancy may have complications, such as hyperbilirubinemia or anemia requiring a simple or exchange transfusion.[1]

Dr. Turck:
With that overview in mind, can you give us more insight into how HDFN is diagnosed?

Dr. Moise:
The evidence of antibodies in the woman's blood would signify that alloimmunization has occurred, and thus, the risk for HDFN may be present. We monitor the maternal antibody titer, or the level of the alloantibodies in the woman's blood. If the titer gets to be too high, and crosses an established value, we often try to assess the red blood cell antigens of the father in order to help predict the risks to the fetus.[1]

In other words, if the father has a red blood cell antigen that the pregnant woman has developed alloantibodies against, then the fetus may also have the same red blood cell antigen present as in the father, and therefore, would be a target for the maternal antibodies.

We can also determine the father's zygosity to see if he has one or two copies of the genes that result in the antigen. If he's found to be heterozygous, there's a 50:50 chance that the fetus can be affected. It's also possible to perform cell free fetal DNA testing, or amniocentesis to assess the red blood cell antigens in the fetus more directly.

If the fetus is found to have the red cell antigen that the maternal antibodies could target, then we monitor the fetus using the middle cerebral artery, or MCA, Doppler ultrasound. This method provides a means to evaluate if anemia is developing in the fetus. An MCA value greater than 1.5 multiples of the median is an indicator that fetal anemia is present. A cordocentesis is then performed to assess the blood count of the fetus.[1]

Dr. Turck:
Now can you tell us more about how common HDFN is and which patient populations may be at the greatest risk for this condition?

Dr. Moise:
Approximately 2 percent of women in the U.S. were found to have red blood cell alloantibodies present in their blood, nearly 19 percent of whom had more than one type of alloantibody.[2] About 20 percent of infants have been found to have a red blood cell antigen that is incompatible with the mother.[3] But in many of these cases, the type of antibodies the pregnant woman has in circulation are of the IgM type, most of which do not cross the placenta and do not target the fetal red blood cells and cause hemolysis.[4] However, HDFN may result when maternal IgG alloantibodies against red blood cell antigens cross the placenta.

HDFN is estimated to effect 3 to 80 women per 100,000 patients per year in the United States.[4] If we look a little closer at this patient population, we will find that pregnant women may develop these antibodies in a few different ways. Multiparity, operative removal of the placenta, a previous major surgery, or a red or platelet transfusion, are all factors that may be associated with the risk of maternal alloimmunization.[4]

It's important to keep in mind that while HDFN is considered a rare disease, the outcomes can be devastating. So, it's still important to determine who may be at risk for developing HDFN.

Dr. Turck:
Let's dig a little deeper into how HDFN happens. Can you tell us how maternal antibodies access the red blood cells of the fetus?

Dr. Moise:
The neonatal Fc receptor, or FcRn, plays a critical role in that process. These receptors are responsible for the transplacental transport of IgG, which is an important process that provides neonatal immunity.[5] We know that it takes some time for the newborn to produce its own protective antibodies. So, the ones it receives from its mother are very important in early life. But when harmful alloantibodies are present, they too are transported across the placenta from the maternal blood supply to the fetus by these same receptors.[5]

For example, let's take the case of an RhD negative woman. Her red blood cells do not have the RhD antigen. She was exposed to blood with the D antigen through a prior pregnancy and delivery. But because that blood did not match her own type, she became sensitized and developed anti D antibodies. These antibodies are then at ready to identify and attack the red blood cells with the D antigen, if they are encountered in the future, as in another pregnancy. If the fetus too has the D antigen present, the maternal alloantibodies against the D antigen are transported across the placenta by the FcRn receptor.[4]

Dr. Turck:
Are all cases of HDFN the result of maternal antibodies against the D antigen?

Dr. Moise:
There are many red blood cell antigens, and there are many that can be the target of maternal alloimmunization and thereby risk of HDFN in pregnancy. There are five major antigens of the Rh blood group system and many variant antigens.[6]

RhD is the most common antigen leading to HDFN. However, other antigens are important too including the Kell antigen, little c-antigen, and others. This is why it's important to do a full antibody screening early in pregnancy, so even antibodies against less common antigens can be detected.[6]

Dr. Turck:
Are there certain groups of women who may be at higher risk for alloimmunization and the development of HDFN in pregnancy?

Dr. Moise:
To understand who's at greatest risk, we need to take a look at access to care, which is a significant challenge for preventing HDFN from adversely affecting pregnancy outcomes. The availability of rhesus immune globulin allows us to prevent HDFN when the RhD antigen is involved.

Current guidelines recommend using rhesus immune globulin, which is an immunoprophylaxis with IgG, anti RhD in non-sensitized RhD negative women. But despite these guidelines, the utilization of rhesus immune globulin worldwide falls well below the expected need.

The 3.6 million doses actually administered in one study fell short of the calculated need for nearly 13 million doses annually.[7]

Lower income regions of the world such as South Asia and Sub-Saharan Africa, were demonstrated to have utilization well below the expected need. Studies like these highlight the disparity in care. We have a highly effective prophylaxis method for patients who are RhD negative, but it is not universally accessible, putting patients at risk for potentially devastating outcomes for something that could have been preventable. In addition, there is no immune prophylaxis available for other red blood cell antigens such as Kell.[7]

Dr. Turck:
Given all of that information, how are women who have a pregnancy at risk for hemolytic disease of the fetus and newborn currently managed?

Dr. Moise:
Well, first, it's essential to recognize the risk. Knowing which women may be alloimmunized and ensuring they get the right expert care is essential. It's not only the D antigen, which is the one people most often think about; women can become alloimmunized against several other red blood cell antigens as we discussed earlier.[6] So awareness among physicians and detection of the condition is critical.

Next, we have to monitor risk to the fetus during the pregnancy. While assessing the titers of the maternal alloantibodies may be useful, we need to effectively monitor the developing fetus. Although assessing fetal hemoglobin would be a highly accurate method to monitor the development of fetal anemia, doing such invasive testing on a repeated basis for monitoring purposes is not preferable. Fortunately, we do have the ability to monitor the fetus with non-invasive methods. Specifically, an increase in the systolic blood flow velocity in the fetal middle cerebral artery is predictive of the risk for fetal anemia, which can be monitored with Doppler ultrasound.[6]

If the Doppler suggests risk for fetal anemia, then invasive procedures including an umbilical blood sampling for hematocrit/hemoglobin, and use of intrauterine transfusion, if necessary, should be considered. We want to delay the use of any invasive procedures as long as possible, but they may be unavoidable.[6]

Dr. Turck:
Dr. Moise, you've shared a lot of information with us already today on HDFN. As we come to a close, can you share with us what you think are the primary takeaways providers should keep in mind?

Dr. Moise:
Well, I appreciate the chance to share all of this information with you today. I think it's important the audience remember a few things. First, HDFN may be rare, but the consequences of unrecognized or poorly managed patients can have traumatic outcomes in the form of the loss or severe health consequences for the baby.

Second, while rhesus immune globulin is available, many patients in need do not have access to this prophylactic option and remain at risk. Also, rhesus immune globulin does not impact the risk in women who are alloimmunized to other red cell antigens other than RhD.

And lastly, I encourage providers to be familiar with the guidelines relating to alloimmunization in pregnancy, and the risk for hemolytic disease. And be sure to swiftly refer your patients to a maternal fetal medicine specialist because early management is essential.

I will just close by saying I remain hopeful. I've witnessed too many families suffer a great deal due to this disease. But I look forward to a time when we can all more effectively prevent and treat the condition for all affected women.

Dr. Turck:
Thank you for those reminders, Dr. Moise. And again, thank you for your time today.

Announcer:
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