ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Hemolytic Disease of the Fetus and Newborn

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H&O What are the causes of hemolytic disease of the newborn?

KM The primary cause, of course, is maternal antibodies to red blood cells. Their formation usually occurs at delivery, and in the following pregnancy, those antibodies cross through the placenta and can affect the next fetus. When the antibodies attach to the fetal red blood cells, the cells break down and the fetus becomes anemic. In the United States, the 3 antibodies that cause nearly all the problems in utero are anti-D, anti-Kell, and anti-c.

There are approximately 40 more antibodies, including Lutheran and Duffy, that have been reported to cause hemolytic disease of the newborn. This type of disease does not require treatment in utero, however—it is usually limited to problems like jaundice. I have only needed to perform an intrauterine transfusion in 1 patient with anti-Duffy antibody.

When hemolytic disease of the newborn was first recognized in the 1950s and 1960s, we saw the condition only after the baby was born, so the name made sense. But now that we can detect and treat the disease in utero, I have proposed that we refer to the condition as hemolytic disease of the fetus and newborn.

H&O What causes a pregnant woman to become sensitized to a fetus with Rh-positive blood?

KM Most of the time this occurs at delivery, when fetal cells are able to access the maternal system after the placental barrier is broken. Sensitization also can happen during the pregnancy if there is an event that breaks the placental barrier. For example, if the woman is in a car accident and she receives a blow to the abdomen, she could have fetal cells cross over. Another possibility is that cells could cross from the fetal side to the maternal side during amniocentesis or chorionic villus sampling. The placenta provides a good barrier against cells crossing, but we know that in some cases, a few cells cross for reasons we do not understand. In those situations, mothers can become sensitized.

We do not know why some people become sensitized more easily than others. I had 1 patient who was an intravenous drug user and had become sensitized through the use of shared needles. She had never been pregnant before; just being exposed to a few red blood cells from the needles was sufficient for her to get sensitized. In contrast, there are reports of other people who have received a whole unit of Rh-positive blood and not formed antibodies. Some women have a propensity to develop antibodies, and that propensity obviously plays a role in whether an event will sensitize a specific woman.

H&O How common is hemolytic disease of the fetus and newborn?

KM We are seeing less and less of this disease because one of the successes in women's healthcare since the 1960s has been the use of Rh immune globulin during pregnancy. We do not have good estimates of the number of

babies born with this in the United States; the Centers for Disease Control used to require that this be checked off on a person's birth certificate. The rate is likely 1 case per several thousand deliveries, at least for anti-D, which can be prevented with injections of Rh immune globulin. There is no injection to prevent the formation of the other antibodies, like anti-Kell and anti-c, so we will continue to see those indefinitely—no company is going to make an immune globulin to prevent those diseases. But anti-D is the most common and the most virulent, so there was a reason to develop an Rh immune globulin.

H&O Are there specific steps that the physician can take to prevent sensitization from occurring in the first place?

KM Yes; if the mother is in an automobile accident or she has an amniocentesis—any event that might cause fetal cells to cross—she receives an injection. She also routinely gets a shot at 28 weeks into her pregnancy in order to cover spontaneous bleeds in which cells might cross unexpectedly between 7 months of gestation and delivery. If the baby turns out to be Rh positive at delivery, the mother gets another injection after delivery. These steps have been recommended in guidelines from the American College of Obstetricians and Gynecologists since 1984, and we emphasize the importance of the 2 shots per pregnancy to our residents, so this is pretty standard. Adherence is likely 95%. The average Rh-negative patient receives 2 injections per pregnancy. If she gets those according to the schedule, her odds of developing Rh sensitization are low, on the order of 2 out of 1000.

H&O How common is it for women to have Rh-negative blood?

KM Caucasian women have about a 15% incidence of Rh-negative blood, and the incidence for African Americans and Hispanics is approximately 8%. As a result, approximately 13% of all patients in the United States have Rh-negative blood.

H&O How are physicians able to recognize hemolytic disease of the fetus and newborn?

KM The standard is to obtain an antibody screen as part of the blood tests we perform at the start of pregnancy. What is controversial is whether a second blood test is needed at 7 months, which is when the Rh immune globulin is administered. I recommend doing the second blood test because there are a few women who develop antibodies between the first blood test at the start of the pregnancy and the second one.

If the mother has antibodies, the next step is to determine how much she has in her system. This is called a titer, and it correlates with the risk to the fetus. If the titer is high enough—a critical titer is defined as a level of 32—we use ultrasound to begin to assess the risk to the fetus. Using a technique that we developed at Baylor College of Medicine here in Houston, we can measure the speed of the blood flow in the middle cerebral artery of the brain using Doppler ultrasound and compare it with normative data for the appropriate gestational age. This tells us whether the fetus is likely to be anemic. In simplistic terms, the faster the blood is moving, the more likely that the fetus has anemia.

After we have the results of that test, which is not 100% accurate but is still very good, we generally recommend referral of the patient to a center that can perform a transfusion in the uterus and give blood to the fetus that is compatible with the mother.

H&O When does the transfusion take place?

KM That depends on how severe the mother's disease is; I have given blood to fetuses at as early as 5 months' gestation. It also depends on when the disease is detected and when the fetus is found to be anemic. I have a patient right now who had 2 pregnancies, then lost a fetus at 32 weeks and then lost her next fetus at 20 weeks. She has a very high anti-D titer of 4000 and she is only 12 weeks pregnant. Obviously, I cannot transfuse her at 12 weeks, but we are trying some other therapies. We will be transfusing her fetus eventually, later in the pregnancy.

H&O What other therapies are used?

KM We have been using some innovative treatments at our institution. For example, last week we used plasmapheresis to filter the antibody out of this same patient's blood. In addition, yesterday and the day before that we gave her intravenous immune globulin. This medication, which is made from a variety of donors, seems to suppress the maternal immune system enough that it does not make more antibodies—although we do not know exactly how it works. Because this patient is only at 12 weeks' gestation, we are trying to buy more time. The fetus needs to be large enough that I can view the umbilical cord with ultrasound and give the fetus some blood. Once I can do that, the chances of survival are very good.

H&O At what point in the pregnancy can blood be administered to the fetus?

KM It depends on each patient. This patient is a little overweight, so it will be somewhat more difficult. I am hoping that I can get her past 20 weeks into the

pregnancy—which would be 5 months—to do the first procedure. The success rate at less than 5 months is very low because the fetus is so tiny and the anatomy is so difficult to see. The odds of survival are approximately 90% for a transfusion by an experienced practitioner. The question is, can I get her pregnancy far enough along to be able to get blood into the fetus on the first attempt?

The protocol that we have developed is to do the plasmapheresis 3 times the first week, followed by intravenous immune globulin every week until about 5 months' gestation. This is quite expensive; it costs close to $70,000.

H&O What are the complications if a baby is born with hemolytic disease?

KM That depends to some degree on whether the baby has been treated. Let us use this patient I have been talking about as an example. If this baby is born close to term and we oversee the delivery, the baby will do very well—the blood count will be normal and it will not have jaundice. It will, interestingly enough, be born with Rh-negative blood. This often confuses the people at the blood bank, but the fact is that all the cells that have been put in the baby during the transfusions have been Rh negative, and the baby stops making its own cells.

At about 1 month of age, before the baby has started making its own cells, some of the cells I have put in will begin to die off. Sometimes babies need to be readmitted to the hospital at this time for what we call a top-up transfusion. After the babies start making their own blood cells, they revert back to Rh positive.

Babies who do not get in utero treatment are at risk for anemia, of course, and usually need a transfusion shortly after they are born. Probably the most feared complication occurs when the red blood cells break down and create bilirubin, which is equivalent to yellow jaundice. Bilirubin in a newborn can cause a type of brain damage called kernicterus that leads to cerebral palsy.

That is a devastating outcome that should not happen in this day and place. These babies are watched closely for signs of jaundice, and we have effective ways to manage high bilirubin levels. We can place newborns under a special blue light to drop the bilirubin level, and in some cases we do an exchange transfusion to replace blood that is high in bilirubin with new blood.

H&O What steps should be taken regarding future pregnancies?

KM I recommend that before the patient attempts to get pregnant again, she should consult with a board-certified maternal-fetal medicine specialist. The specialist can advise the patient on the chances of a successful pregnancy, and refer her to a specialized center like ours that deals with these patients all the time. Most obstetrician-gynecologists, and even a lot of maternal-fetal medicine specialists, do not have the knowledge or the experience to deal with these pregnancies because they do not encounter them that often.

We have techniques now that were not available a couple of years ago. Notably, we can now use cell-free fetal DNA testing to determine the fetal blood type through a maternal blood sample. This is something that used to require an amniocentesis. We use this starting at 10 weeks of gestation for pregnancies in which the mother is Rh-negative and the father is heterozygous, so we do not know whether the fetus is affected.

H&O How might these cases be treated in the future?

KM I do not know if this will happen in my lifetime, but I think the day will come when we can downregulate the maternal immune system during pregnancy. If we could turn down the antibody, the fetus would make new blood cells and would not have a problem. This will be a much more sophisticated approach than what we are able to do now with plasmapheresis and intravenous immune globulin. There are some exciting new medications being developed in the transplant world that I think may end up moving to these patients. I think that in the future, we will see selective downregulation of the immune system, and the days of people putting needles in fetuses will thankfully come to an end.

Suggested Readings

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