Transcript Details
This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/alloimmune-thrombocytopenia-in-the-fetus-and-newborn/13909/

Released: 11/23/2022
Valid until: 11/23/2023
Time needed to complete: 15 minutes

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

Alloimmune Thrombocytopenia in the Fetus and Newborn

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Alloimmune Thrombocytopenia in the Fetus and Newborn” is provided by Omnia Education.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Shulman:
Fetal and neonatal alloimmune thrombocytopenia, or FNAIT, is an uncommon disorder occurring in about 1 out of 1,000 births. This form of thrombocytopenia results from the formation of maternal antibodies due to parental platelet antigen incompatibility. Platelet function remains relatively normal, but in the setting of severe thrombocytopenia, intracranial hemorrhage is unfortunately not rare, and it's critical that we mitigate the risk of serious consequences.

This is CME on ReachMD, and I'm Dr. Lee Shulman. I'm here today with Dr. James Bussel, Professor Emeritus of Pediatrics and Obstetrics and Gynecology at the Weill Cornell School of Medicine in New York. Jim, welcome to the show.

Dr. Bussel:
Thank you, Lee.

Dr. Shulman:
Let’s dive right in. This disorder is uncommon but complicated. But I understand you have a case study that will demonstrate its pathophysiology and the supportive care standards.

Dr. Bussel:
When I started as an attending at Cornell, I was very interested in thrombocytopenia. And I quickly learned from doing consults that a lot of what happened to the babies, whether or not they had an intracranial hemorrhage, was determined by the time they were born.

So I was confronted in 1983 with a family who had had a previous child where the intracranial hemorrhage had occurred at 32 weeks. We knew this would be worse in the next pregnancy, or at least as bad. And therefore, we couldn't do what was the standard of care at the time, which was to do an elective Cesarean section at 37 weeks. Through a complicated path, we ended up giving the mother weekly IVIG and steroids, and the baby did well, and we delivered her early but with mature lungs based on amniocentesis. And she's now an Associate Professor of medieval French literature at Columbia.

So this has kind of illustrated what the problem can be, meaning that this is a disease, Lee, as you said, that has maternal IgG antibodies that recognize something the fetus inherited from the father. And these antibodies go across the placenta and not only attack the fetal platelets, but also attack the fetal megakaryocytes, thus making the thrombocytopenia even more severe.

A great majority of cases, as in fact was this one, are diagnosed in the neonatal nursery when a baby of an otherwise uncomplicated delivery is born, has bleeding signs, a blood count is done, and severe thrombocytopenia is seen. In the neonatal nursery, we can give platelet transfusions and IVIG to the newborn, and that will usually take care of things. We encourage sending blood tests to confirm

platelet antigen and antibody status in the mother and father, because it's important to know for female relatives of the mother and any future pregnancies the family may have. It's also important in case the thrombocytopenia doesn't resolve, say, within the first week, and there is a consideration you could be missing another diagnosis, which most commonly could be an inherited form of thrombocytopenia. If it is in fact, FNAIT, then we can talk to the family about what's entailed for the future, meaning how we would manage the next pregnancy. That basically involves giving IVIG and/or steroids at different times and doses to the mother during the pregnancy to increase the fetal platelet count. And that's been a very successful plan.

Finally, there is newer treatments that are being developed, including FcRn inhibition with the goal of blocking transmission of the mother's antibodies into the fetus, and thus avoiding the disease altogether.

Dr. Shulman:
But I think your story also highlights an important concept is that obstetrical providers need to do a good follow-up with the newborn. You know, frequently we hear Apgar scores, we get a nod of approval from the neonatologist or the nursing staff that's resuscitating the newborn. And then if we don't really hear important issues coming from the nursery, it's sort of somewhat out of sight, out of mind. And obviously, stories like this, it's critical that we as obstetrical providers follow up, not so much to impact the care, but to know about information that we're going to need in future pregnancies.

In that regard, Jim, what can you tell us about the clinical manifestations of FNAIT and how to make the diagnosis, and what is the actual management that is entailed in that nursery or by the pediatric specialists?

Dr. Bussel:
Lee, I think one thing that you brought up that's very important is maybe as an obstetrician, somebody else delivered the baby or you weren't involved and the family moved. But as you were highlighting, if there's thrombocytopenia in the baby, this FNAIT needs to be considered because it's the primary diagnosis of neonatal thrombocytopenia that would recur in the next pregnancy and be worse.

The clinical manifestations, we talked about bleeding. If there's a low platelet count, a head sono is required to be sure that there wasn't a silent intracranial hemorrhage, because this would have major implications for how to manage the next pregnancy. The key used to be that there wasn't another cause of thrombocytopenia in the newborn, for example, not sepsis, not asphyxia, et cetera. But probably even more important is identifying a platelet count less than 50,000 in the first day of life. So even if, for example, you had a baby born with a count of 15- or 20,000, or 10,000, and you thought they might have been septic, they still should have a workup for fetal and neonatal alloimmune because of the possibility that it would recur in the next pregnancy and because some of the cases can have multiple causes.

We strongly recommend sending blood on the parents to the Versiti Lab, which used to be the Blood Center of Wisconsin, because they're by far the premier laboratory in the country and will be able to identify not only unusual incompatibilities, but also whether the mother has antibody and, importantly, whether it's specific to the platelet antigen in question. Otherwise, if the next pregnancy occurs, if there wasn't an intracranial hemorrhage, we would recommend giving IVIG, 1 g/kg/week, starting 20 to 24 weeks, and we would add 0.5 mg/kg of prednisone. We're on the extreme of wanting to have 99+% well babies, and since fetal blood sampling is too dangerous to really use in this setting, especially with the thrombocytopenic fetus, we would overtreat many of the mothers in order to ensure that the next baby is fine, and that would involve adding a second IVIG per week at around 32 weeks and delivering at, say, 37, 38 weeks, perhaps by elective C-section.

Dr. Shulman:
You know, it's interesting that you mentioned the diagnostic testing that you would potentially use.

Jim, how can you delve a little deeper into counseling patients and couples? And how is this tied to risk stratification and ultimately treatment?

Dr. Bussel:
Let me say that, in the course of the studies that we've done in this setting, meaning treating the mother for her next affected pregnancy, I've worked closely, as you know, with Dick Berkowitz, who was at Mount Sinai and now is at Columbia. And we've treated over 300 pregnancies to try to achieve this.

Usually, the issues in counseling are to convince them that if they do what's needed, and this is a fair amount of putting up with stuff, if you want to call it that, for the mother, the IVIG treatments, et cetera, that, as I indicated, there's a 99+% chance that they will do well. We talk about things like asking the mother to give up rodeo. We ask the husband to make sure that the potholes on their street are fixed. In other words, obviously, to avoid any kind of trauma to the mother that could trigger an intracranial hemorrhage in a thrombocytopenic baby.

Unfortunately, we don't have a biomarker, so we can't say for one woman, you know, you're going to do fine, we don't have to give you this extra treatment, and to another woman that you're at really high risk, you need to be treated as much as possible. The only biomarker that we have at the moment is whether the previous sibling had an intracranial hemorrhage. And that's something that hopefully studies will sort out in the future.

I think, as you know, Lee, you require a specialist in maternal-fetal medicine [MFM] to do this. And most of them will need to arrange to give the mom IVIG, and that might involve either talking to a hematologist or, in our setting, we try to arrange this after the first infusions to be done by homecare.

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. James Bussel. We're just about to transition our discussion about FNAIT into what the community obstetrician needs to know.

And I think, Jim, before I do that, I think it's important to emphasize what you've already mentioned, is that this diagnosis does not fall upon the obstetrical provider to make.

This is something that the pediatrician, the neonatologist is going to be making that diagnosis of thrombocytopenia and then initiating the evaluation of the mother. But it is important for that community-based obstetrician or even academic-based obstetrician to know about this condition, to know about the evaluation of neonatal thrombocytopenia, and also to be aware of those issues that are going to impact future pregnancies.

And I think in that regard, I'm going to ask you to talk a little bit about the Rallybio trial because it is hopefully going to provide us with important information regarding the ongoing screening going into the future.

So for now, in addition to Rallybio can you break down into actionable clinical tips what that community obstetrician needs to know about FNAIT?

Dr. Bussel:
Well, I think you and I agree that what the community obstetrician really needs to know about FNAIT is that if the previous baby has had low platelets, and again, especially if they were very low, they should refer to a maternal-fetal medicine specialist to consider the diagnosis.

I would say that in the neonatal and pediatric hematology world, this is a very well-known diagnosis, and hopefully it's relatively unlikely, though certainly not impossible, that testing might have been missed. So I think this is something that's up to the MFM to consider and do testing on the mom and the dad as necessary to ensure that this isn't the diagnosis. Because as we just discussed, there's a lot of considerations for antenatal management if it is FNAIT.

The Rallybio study, in essence, hopes to convert FNAIT into a disease that is very rare. It would involve screening all women if they're HPA-1bb or HPA-1a negative or, as it used to be called PlA1-negative, and therefore at risk, they would be screened for DRB3*01:01, which is an immunologic class 2 HLA marker for high risk of making antibodies to HPA-1a. So if they're in approximately the 1 in 200 women who are HPA-1bb and at high risk of making antibodies because they have DRB3*01:01, in the future, ideally, they would get prophylaxis.

I think it would be even easier to give prophylaxis to these women in one way, because it could be given via a monoclonal antibody that has not worked in Rh disease, because the Rh antigen D has too many forms to be completely covered by one monoclonal and, therefore, is still a hyperimmune gamma globulin plasma-based treatment.

Ideally, this would make things a lot better. As with Rh disease, it wouldn't eliminate other antigens which could cause FNAIT, and it wouldn't take care of ones that broke through, for whatever reason, and developed antibodies to HPA-1a anyway. Simultaneously, as you may know, from ClinicalTrials.gov, there is an ongoing study in hemolytic disease of the fetus and newborn using an inhibitor of FcRn, as we talked about before, and that might be an optimal way to treat any of the antibody disorders there that are based on the mother's IgG entering the fetus. So I think it's a great field, lots of progress. Really excited about it.

Dr. Shulman:
I'll have to add that our listeners have heard other presentations on different applications of FcRn therapies.

As we're getting towards the end of our time, Jim what are your main take-home messages for our audience?

Dr. Bussel:
I think the main take-home messages are that FNAIT should be a relatively straightforward diagnosis; it just has to be thought of. If testing goes to a top-notch reference lab for identification of platelet antigen typing in the mom and the dad, and whether the mom has an

antibody, and if necessary, based on the results, sometimes it can be a little confusing, consultation can be made with people who work at that laboratory. It ought to be possible to be very close to 100% on the diagnosis.

And second, and very important, treatment can be given to the mother in the next pregnancy if necessary. And basically, it should be possible between that screening and other factors to pretty much eliminate this as a disease, the way HDFN has been eliminated. So I think it's great, Lee, that we had this opportunity to talk about it. And again, the MFMs are the heart place of where this needs to go out of.

Dr. Shulman:
First and foremost, every obstetrical provider, midwife, obstetrician needs to find out about the neonatal outcomes, not just the baby is ostensibly healthy, but if there are any laboratory issues that are of any concern to the pediatricians who are taking care of that newborn. Because as we've heard today, the implications of low platelets can have profound ramifications.

If you do find out that the newborn has low platelets, even if there's no associated morbidity with that particular finding, get in touch with your maternal-fetal medicine provider, the folks who you refer your high-risk patients to, and ask them whether or not this woman that you've just taken care of really requires a referral if she becomes pregnant again in the future.

Well, unfortunately, that's all the time we have today. So I want to thank our audience for listening in. And I want to thank you, Jim, for joining me here today and for sharing all of your valuable insights. I learned an awful lot of information today, and I really appreciate you being here with us today. It was great speaking with you.

Dr. Bussel:
Thank you, Lee.

Announcer:
You have been listening to CME on ReachMD. This activity is provided by Omnia Education.

To receive your free CME credit, or to download this activity, go to ReachMD.com/Omnia. Thank you for listening.