Episode 42 Transcript: Preventing Rh Disease, the evolution from discovery to ongoing challenges

Tony Casina: Welcome to QuidelOrtho Science Bytes. We're proud to sponsor this podcast as a continuing commitment to transform the power of diagnostics into a healthier future for all.

Today, our topic is preventing Rh Disease: the evolution from discovery to ongoing challenges. I am Tony Casina, your moderator. And today we have a very special guest, I am joined by Doctor Steven Spitalnik. Dr. Spitalnik is a Professor in the Department of Pathology and Cell Biology, Vagelos College of Physicians and Surgeons of Columbia University, and a member of the Medical Staff at New York Presbyterian/Columbia. He has authored over 250 publications and served as an investigator on more than 30 grants and contracts including Principal investigator on more than 20 of those grants. Additionally, he has sponsored more than 15 Training Grants. Dr. Spitalnik is a member of multiple professional societies, including the Association for the Advancement of Blood and Biotherapies (AABB) and the International Society for Blood Transfusion (ISBT). He has served on multiple committees within these organizations and was on the Board of Directors for the AABB. He has received multiple society awards and was elected to the Hall of Fame of the AABB Foundation (previously the National Blood Foundation). Dr. Spitalnik is the Founding Member and Executive Director of the Worldwide Initiative for Rh Disease Eradication, otherwise known as WIRhE.

Thank you very much, Dr. Spitalnik for being here with us today. It is truly an immense pleasure and honor for us. And just on a personal note, I had the pleasure of working with Dr. Spitalnik earlier on in both of our careers in transfusion medicine.

Dr Spitalnik: Thank you, Tony. It, it's lovely to be here with you today.

Tony Casina: OK. Our first question of the podcast is, we should probably start with, what is Rh disease?

Dr Spitalnik: Ok. Thank you. So, Rh disease occurs when a woman who is Rh negative and who becomes sensitized to Rh D antigen and develops antibodies against Rh D gets pregnant again with an Rh-positive fetus. In that case, her antibodies can cross the placenta, bind to the fetal red blood cells and cause hemolysis in utero. And also after the baby is born, ongoing hemolysis can continue. This can lead to anemia, sometimes very severe anemia, and hyperbilirubinemia. And if those to particular conditions are not treated effectively and rapidly, this can either lead to the death of the baby or the death of the fetus or to severe chronic outcomes like kernicterus, which is a learning disorder.

Tony Casina: Thank you. So, how do these anti Rh antibodies develop?

Dr Spitalnik: So, classically, they're found in women and classically, they occur when Rh negative women have children with Rh-positive fathers and the woman becomes sensitized to the Rh either in utero when fetal red blood cells can cross the placenta and enter the maternal circulation typically in the second and third trimesters or more commonly during delivery when there can be a significant fetal maternal hemorrhage and fetal red cells can enter the maternal circulation during delivery.

And so that in a sense is a transfusion and an incompatible transfusion if you will and the mother can develop antibodies to the Rh D antigen. That's the most common scenario. However, it can also occur in men or women can develop anti D when they're exposed to Rh-positive blood cells. For instance, in a transfusion either in a massive transfusion setting where there may not be sufficient units of O-negative red blood cells available can also occur in individuals who abuse intravenous drugs, illicit drugs, and if they share needles, they can introduce foreign red blood cells into their own circulation, but by far the most common scenario is in pregnancy.

Tony Casina: Ok. Thank you. So, what are the common risks involved in development of anti Rh D antibody? And are there uncommon risks that can result in development?

Dr Spitalnik: Yes. So, I'm sorry if I'm being a little redundant but the most common risk is pregnancy, an Rh-negative woman having an Rh-positive fetus, particularly if she's pregnant more than one time.

So classically, she becomes allo immunized during or after the first pregnancy and then the titers increase with each subsequent pregnancy. So typically the first child is unaffected and subsequent children are more severely affected as time goes on. That's the most common. The uncommon occurrences are either an inappropriate transfusion of Rh-positive red cells into an Rh-negative recipient in men or women or those kind of transfusions that are not necessarily inappropriate, but because there's a shortage, typically of O-negative red cells and an uncommon but relevant situation is with IV drug abuse where people share needles and if an Rh-negative person uses a needle that was previously used by an Rh-positive person, there's a risk of introducing Rh positive red cells into their circulation and becoming allo immunized to Rh D. They're even more uncommon if you will but can potentially occur during pregnancy is if a woman is carrying an Rh-positive fetus but has a miscarriage more likely in the second trimester than the first trimester or if a woman is pregnant and needs chorionic villus sampling or has abdominal trauma. By for instance, being in a car accident, these can potentially sensitize her to Rh D. Although those situations are uncommon and actually somewhat controversial as to whether they're clinically relevant or not.

Tony Casina: Thank you. OK. With that background, we are going to take a historical step back to look at the progression from a remarkable elucidation of the disease ultimately to delivering a solution to prevent Rh disease. So, let's start here, how did Dr. Philip Levine's momentous identification of the cause of hemolytic disease of the newborn and fetus influence the future development of a treatment to prevent Rh disease?

Dr Spitalnik: Yeah. So, Philip Levine was clearly and, and you're well aware, a giant in our field um and made many contributions throughout his long career, particularly in the setting of hemolytic disease of the fetus and newborn, particularly in the context of Rh disease. Although he made contributions to other sources of the disease of the fetus and newborn. So, I think in this context, his two major contributions were to help elucidate the pathophysiology of this disease which had in the early 20th century, went by four different names and were thought to be four separate diseases and Philip Levine along with other colleagues at the time in the 1930s and 1940s identified that these four separate diseases like erythroblastosis, fetal and hydrops, fetal were actually one disease and suggested the pathophysiology of maternal antibodies crossing the placenta and causing homolysis.

So, that was one major contribution of his and the second major contribution of his was with Alexander Weiner. Philip Levine discovered the Rh blood group system of which as we now know, is more

complicated than this. But at the time really was the discovery of Rh D and that elucidation of that blood group antigen and the tools to identify antibodies to that antigen, which were also contributed by Coombs with his, with his Coombs test in the 1940s allowed elucidation of Rh disease per se.

Tony Casina: Well, that leads us to the next question. Doctor John Gorman, Doctor Vincent Frieda and Doctor Bill Pollack were all involved in the concept of developing the treatment to prevent Rh disease. Can you tell us more about their approach, using an antibody to prevent an antibody from developing?

Dr Spitalnik: Sure. So it's actually an honor for me to be on the faculty at, at Columbia University because this is where John Gorman and Vince Freda worked in the 1960s to come up with their approach in collaboration with Bill Pollack at Ortho, I would be remiss if I didn't mention that they were, they were competing with a group in Liverpool in Great Britain, led by Cyril Clark, who had the same idea at the same time, of course, before the internet and rapid communications in the beginning, they weren't even aware of these two groups in the in New York and Liverpool were not aware that they were competing with each other, but they came up with similar ideas at the same time. John Gorman, who's still alive. He's the only member of either the British or the American groups who is still alive is quite an amazing individual. He's 93 and incredibly active and incredibly intelligent and still incredibly passionate about this disorder. He actually was studying to prepare to teach medical students at Columbia. He was a new faculty member at Columbia and in his studies, he came across and then read more deeply about some research that was done early in the 20th century and so this is when passive immunity was a therapeutic approach in bacterial diseases before antibiotics were invented. And ironically and somewhat sadly, came back into vogue during the COVID epidemic where the idea of infusing hyperimmune gamma globulin or plasma could be used to treat or prevent COVID.

This was used early in the 20th century when there were no other alternatives for bacterial diseases, particularly diphtheria. Indeed, the use of passive antibody therapy to treat diphtheria resulted in one of the first Nobel prizes in the early 1900s. So, John was reading to prepare to teach medical students and he came across a paper that at that time in the 1915, I think was trying to enhance antibody titers in guinea pigs or horses or whatever that were used as the source of this passive antibody therapy. And at that time, people were interested in increasing the antibody titers to make more effective therapeutics. But in one of these papers by a gentleman named Theobald Smith, he described that there was one way of increasing antibody titers by changing the ratio of antibody to antigen in the animal that was immunized. But there was an alternative approach which sadly, in the early 20th century would inhibit the formation of antibodies. And that was: if the ratio of antibody to diphtheria was very high compared to the amount of diphtheria antigen, it prevented the immune response. Whereas if the ratio of antigen to antibody was high, it enhanced the immune response. And John was very well aware of Rh disease because he and Vincent Freda were caring for those patients. And Vince Freda actually had a clinic for women with Rh disease. And this immediately struck John a potential therapeutic or prophylactic approach. If the woman who had fetal red cells circulating was overwhelmed, if you will with significant amounts of antibody to D, would that prevent her from making anti-D in the first place as a prophylaxis, not a treatment for Rh disease. And they first tried this approach in male volunteers and it was successful and then they moved into females. Now, the relationship with Ortho in particular with Bill Pollock was that Bill Pollock was an expert protein chemist in the 1960s, cutting edge protein chemistry involved things like precipitating proteins or precipitating gamma globulins, and so the approach that the American group took was to isolate high titer anti D by precipitating gamma globulins. And using that as a therapy where as or as the prophylaxis. Whereas in Great Britain, they were using plasma that

contained high titers of antibodies as the prophylaxis. As you might imagine, if you could have high titers of a small amount of antibody, you could use a intramuscular injection, which is what was pioneered in the United States. So it was really Vince Freder was the OB taking care of these patients. John was the blood banker who was identifying and titering anti D and Bill Pollock was the protein chemist. And the three of them together came up with this not only theoretical approach but practical approach to preventing sensitization to Rh. I would like to just emphasize that this is not a treatment. So if a woman is already sensitized, it's at that point, it was too late to prevent future pregnancies from having Rh disease. And one would have to treat them with intrauterine transfusions or, or other approaches for them to deliver live and healthy children.

Tony Casina: Thank you. OK. Can you briefly describe how and when Rh immunoglobulin treatment is provided to Rh negative women in pregnancy?

Dr Spitalnik: Yes. So, there's actually an interesting historical aspect to this which is when Gorman, Freda and Pollock started this approach. They thought it would be unethical to give Rh immune globulin during pregnancy because they would actually be giving the mother the pathogenic problem, the antibody that could then cross the placenta and cause the disease. So they insisted on only giving Rh immune globulin postpartum typically within the first three days after birth, that turned out eventually, when this was approved for clinical use and put into practice, that approach turned out to be about 90% effective in preventing alloimmunization, but what about those other 10%? So the Canadian group, a Canadian group discovered that, that actually fetal maternal hemorrhage using the Kleihauer-Betke test, which we still use today. But this was in the 1950s. Alvin Zaborsky discovered that fetal red cells can cross into the maternal circulation particularly in the second and third trimesters. And so the Canadian group thought that if you waited until delivery, the mother may have already become allo immunized from fetal maternal hemorrhage earlier in pregnancy. So they came up with the approach. Remember that the Columbia group thought was unethical of giving Rh immunoglobulin around 28 to 32 weeks. And when they did this, they discovered that this approach would then become 99% effective. And interestingly that the fetus and the neonate were unaffected even by having antenatal Rh D. And the mother would have circulating anti D actually, when I knew Tony and when I was a resident, I actually remember reading this paper and thought that what was the evidence that the fetus was unaffected? And so we did a study where we found that yes, the antibody actually crossed the placenta got into the fetal circulation was present when the neonate was born. And, and sometimes the neonate would actually have a positive direct anti-globulin test. But interestingly, they never had hyperbilirubinemia. And so, the general thought was that the antibody titers circulating and the fetus were low enough that it wouldn't cause disease. But the circulating antibody in the mother was high enough titer that it would prevent alloimmunization. So I certainly understand where Colombian Ortho groups were concerned about harming the fetus. But in because of the Canadians, if you will bravery and trying this approach and the bravery of the women that were under their care turned out that they came up with a more effective approach that was actually safe for the fetus. So the current standard of care is to give Rh immunoglobulin typically in the 28 or 32nd week and then also give it postpartum. And then if the woman has had an intervention like chorionic villus sampling or some potential trauma to the fetus, then we may give another dose to protect against fetal-maternal hemorrhage in that case. But the typical standard of care now is two doses, one before partition and, one after.

Tony Casina: Thank you. Are there other situations in which Rh immune globulin is used to prevent Rh antibody development?

Dr Spitalnik: Yes, there are. So, I've already described to you multiple settings in the context of pregnancy, both the common and the uncommon indications during pregnancy. But there are other settings which are somewhat controversial. And so if an Rh-negative premenopausal woman or a man happens to be exposed to Rh-positive or platelets from an Rh-positive donor. Even though there are very few red cells present in modern platelet units, many people will give RH immunoglobulin to protect against sensitization in that setting, both for a man so that, that they're safe in the future. If in an emergency, they need to receive Rh-positive products. And certainly for a premenopausal woman to try to prevent allo immunization and, and pregnancy problems. And so, that's pretty commonly used although a little controversial as to whether it's necessary or not, what is coming up as, as more controversial. And I certainly don't know the answer yet and I don't know that the field knows the answer is in out-of-hospital or pre-hospital transfusions in emergency situations. So if someone has a gunshot wound or is in a car accident and they're in an ambulance on the way to the emergency room. Should we be transfusing blood in the ambulance before the patient hits the hospital? And if so what blood should be used? And, many of the proponents of this approach, which arose out of experience in the military. Many of the proponents of this approach, advocate for the use of low titer whole blood in the ambulance. And at the moment, virtually all if not all of those units are coming from O Rh-positive individuals. And this is before you even know the blood type of the trauma patient. And so some of those are going to be women, some of those are going to be premenopausal women and they will get transfused. And, and so what do you do in this context? If the woman has received an entire unit of O-positive whole blood and in some cases after the patient is in the emergency room or in the OR, the surgeon may want to continue with that blood type and not change the blood type. And so what happens if the patient gets one or more units of O-positive red cells? Do you use RH immune globulin in that context, if you do, is it effective? Is that a good use of, of this drug which currently has a worldwide shortage. These are at least in my opinion, unanswered questions that are still subject to discussion and argument. I'll leave it at that.

Tony Casina: Thank you, Dr. Spitalnik. Next question I have is has Rh disease been eradicated by the availability of hH immune globulin or are there still challenges with preventing it?

Dr Spitalnik: The answer to this question is near and dear to my heart and is actually the stimulus for a group of us organizing wire the worldwide initiative for Rh disease eradication, which is um at the moment, there's not enough Rh immunoglobulin available in the world nor is it distributed everywhere it's needed. And so we've done a study where we estimate that about half the women in the world who need Rh immunoglobulin just for pregnancy and just for postpartum use of Rh immunoglobulin don't have, it don't have access to our human globulin. Part of this is due to the amount of or human globulin that exists in the world. It's a product that's currently made from human donor plasma. And so there needs to be enough human donor plasma of high enough titer to be able to manufacture Rh immune globulin. Part of it is cost, one can't drive the cost to zero or close to zero because it has to be made from human plasma that needs to be obtained from donors. Part of it is availability in some countries, one can't even import it into those countries. And part of it is due to awareness and education of patients, physicians, midwives, nurses, healthcare workers of all sorts. The most dramatic such example is in China at the moment which when it had a one-child-only policy was not really an issue because as I described women typically become all allo immunized during the first pregnancy, but the first child is ok, but now

that the one child only policy no longer exists, women in China are having more Children. And even though Rh negativity is rare in China, there's only about half a percent of individuals are Rh-negative, there are over a billion people in China, and half of them are women so there are many Rh-negative women in China who almost always will the father will be Rh positive. China has a policy that if they don't make a drug like Rh immune globulin in their country, they will not import it, it's illegal to import it. And so as China has become less open to the world, shall we say? And because they have no way of manufacturing it in China, none of those women receive Rh immunoglobulin, even though the economy of China is more of a high income country now and things like that. So, this is an issue and the solutions to this issue globally are not necessarily obvious or easy to scale. And that is a reason for our group's interest to see how and if we can help.

Tony Casina: OK, thank you, Dr. Spitalnik. You've answered my next question about your mission and what WIRhE's mission is to the world. One other question before we move on is where can we find more information about WIRhE?

Dr Spitalnik: Sure. Maybe I can say one or two additional words about WIRhE and then I'll tell you where to find us. So, WIRhE is an interesting organization. I think it, it's certainly interesting to me because it combines contributors to, to what we're doing including patients who have Rh disease or hemolytic disease of the fetus. And newborn mothers are involved. It involves obstetricians, pediatricians, neonatologists, midwives, transfusion medicine physicians like me who's a pathologist. It's an interesting organization that basically attracts and includes anyone with an interest in this illness and ways of preventing it. The best way to find us is we have a website www.wirhe.org where we have information that is relevant to patients, to physicians, to technologists and other health care workers. And we welcome you to look there, talk to us, you can email, there's an email address there, you can email us questions or comments and we are also putting together additional educational information for individuals. And we also are working with various groups of individuals to help them do studies particularly in lower- and middle-income countries to raise awareness and use this approach more.

And we are also working with investigators to see if there are other ways of increasing the stock if you will of Rh immune globulin, including our monoclonal antibody approach is useful. And if they're useful, how does one prove that? And how does one get in particular companies interested in producing and providing effective monoclonal antibodies?

Tony Casina: Ok. Well, thank you very much, Dr. Spitalnik. I really want to thank you for taking the time with us today and giving us your experiences and insights on the need to eradicate Rh disease. It has been truly an honor to talk with you about the importance of recognizing the worldwide need to prevent Rh disease and the challenges that exist.

Dr Spitalnik: Thank you very much for this opportunity. I really appreciate doing it. I appreciate that you're doing it to advocate and publicize this information and given our long history together, Tony. It's really a pleasure to do this with you. Thank you very much.

Tony Casina: It very much so was the same for me. Thank you, Dr. Spitalnik. OK. I hope you all have enjoyed this podcast episode. Make sure to review the sections within the podcast description for any reading materials that we've suggested. Based on today's podcast, I'll leave you with our pop quiz. What challenges exist today to eradicate Rh disease? You can always go back and listen again. Thank you for listening and please subscribe to QuidelOrtho Science Bytes brought to you by QuidelOrtho Corporation

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