Rh Sensitization in Pregnancy - Current Guidelines & Advances in Management

The presence or absence of the Rh antigen on human red blood cells determines if a person's blood type is "positive" or "negative." When an Rh-negative individual, who lacks this antigen, becomes pregnant and carries an Rh-positive fetus, the mother's immune system may recognize the fetus's Rh antigen as foreign and mount an immune response. This phenomenon, known as Rh sensitization, can lead to complications for the fetus.

Rh immunoglobulin (RhIg), derived from human blood, is commonly administered during bleeding events in pregnancy. While its benefits in the third trimester are well-established, evidence for its use in the first trimester is lacking. Overuse in high-resource countries, especially in early pregnancy without proven benefits, increases costs and limits availability in lower-resource settings. These concerns highlight the need to revisit guidelines and address knowledge gaps.

We are speaking with Dr. Courtney Schreiber from the University of Pennsylvania about the current treatment of Rh sensitization and her recent research, which could lead to updated pregnancy care guidelines and help bridge global health equity gaps.

Full Transcript:

Shweta Mishra: Hello, and welcome to Curetalks. I am Shweta Mishra, and today we are talking about the Current Guidelines & Advances in Management of Rh. Sensitization in Pregnancy. We have with us today Dr. Courtney Schreiber, who is Chief of the division of family planning in Obstetrics and Gynaecology, and Stuart and Emily Mudd, Professor of Human Behavior and Reproduction at the University of Pennsylvania. Joining us on the patient panel is patient advocate Davina Fankhauser, who leads strategic efforts to ensure infertility care benefits to underserved infertility patients through a nonprofit organization called Fertility Within Reach, and I have to mention this she is a proud contributor and co-author of a recent bill passed by Massachusetts on this July 29th that mandates insurance companies to cover fertility preservation for patients with medical and genetic conditions. So congratulations for that Davina and I welcome Dr. Schreiber, Davina, both of you, to this call today.

Davina Fankhauser: Thank you very much. Yes, it is a proud time to be connected with fertility healthcare. There's a lot of work to be done right now, and we're excited when good medical related legislation gets passed, and hopefully the rest of the country will follow, and I always say, I think it's research that can drive advocacy. So I'm really excited to be here with Dr. Schreiber and highlight the research that she has done.

Dr. Courtney Schreiber: What an exciting partnership to be able to be here with you. Congratulations on that huge achievement. Legislative change is so so difficult, it takes persistence often more than evidence. So congratulations.

Davina Fankhauser: Thank you.

Shweta Mishra: Thank you, doctor. Thank you, Davina, it's an honor to have you both here on the panel today and Dr. Schreiber, I will start with you. Your recent research is on Rh sensitization, and it has a

potential to remove barriers to early pregnancy, care and possibly change pregnancy guidelines. We will discuss all of that in a bit, doctor, but before that I request you to explain to our audience in very simple terms. What is Rh sensitization? Because it may be a bit of a confusing concept for a lot of folks.

Dr. Courtney Schreiber: Yeah, exactly. Thank you for the opportunity to try to clarify something that is confusing. So hold your hats because it can be tricky to describe and explain this. In fact, even in the clinical setting with the patient one on one sometimes this is hard to communicate. But probably most people in the audience are familiar with the concept of a negative or a positive blood type. So, for example, you may be A positive or B negative, and the Rh component is that negative or positive type. And what Rh sensitization is, is if a person has a negative blood type, for example, A negative, and they're exposed to blood with a positive blood type, for example, even A positive, the A negative person could mount an immune response to the Rh positive antigen. So what that means is an Rh negative person when they're exposed to the Rh positive Antigen can create a low level antibody response as a result of that. And that's what we call sensitized. And we say it's sensitized specifically in the setting of pregnancy, which is the most common time when this exposure occurs because in that particular first event rarely does anything damaging occur as a result of the immune response that's mounted. So we call it sensitized, because it's not until a subsequent pregnancy in an Rh negative person with a Rh positive pregnancy or fetus, that the immune response that's been mounted, or the sensitization that's occurred can actually potentially cause damage to the growing pregnancy or fetus, and that historically, before we had any way to manage or treat or prevent that would happen about 10% of the time among pregnant people who were Rh negative carrying an Rh positive fetus that the sensitization and poor outcome in the pregnancy could occur. The worst possible thing to happen from this is called hemolytic disease of the fetus and newborn, and that can require that the fetus have transfusions, or even have irreparable harm done that can lead to fetal or neonatal death, if the right treatment isn't given. Because of this risk most countries, including the United States, have worked very hard to prevent Rh sensitization with the delivery of what's called Rh immunoglobulin at the time of delivery. So when the baby is born, and in the 3rd trimester. And giving that immunoglobulin reduces the risk and the probability that any sensitization can occur and prevents complications in a future pregnancy.

Shweta Mishra: Thank you for untangling that for us in a very comprehensible way. You touched upon the current guidelines a little bit, could you provide some context on how these immunoglobulin treatment guidelines were set?

Dr. Courtney Schreiber: Sure. So, as I briefly mentioned before, prior to the discovery and use of RH immunoglobulin to prevent poor outcomes among Rh negative women or people in pregnancy, about 10% of Rh negative people could become sensitized with a full-term pregnancy they delivered who was Rh positive. With the advent of giving Rh immunoglobulin, which is trade named RHOGAM, some people may have heard of that brand name. At the time of delivery, and in the 3rd trimester maternal Rh sensitization rates decreased from that 10% to 1%. So, a huge drop from giving that medication at the time of delivery, or in the 3rd trimester. But you asked me about guidelines, and I will say that it is really globally recognized that there is value, and it is really important to give Rh immunoglobulin later in pregnancy, 3rd trimester, and at delivery to prevent complications in a future pregnancy. But where the guidelines have been in conflict, and the conflict in the guidelines globally is due to a lack of evidence is what to do in the early stages of pregnancy for example, the 1st trimester. And you can all imagine when we're talking about a 1st trimester pregnancy, we have a teeny little pregnancy with a very low blood volume. Perhaps no blood volume on which to produce this antigen that could affect the sensitization, and then a problem in a future pregnancy. And is it necessary to give Rh immunoglobulin for an earlier bleeding episode. For example, a miscarriage, right? So, when a person has a miscarriage and loses their pregnancy in the 1st trimester that is accompanied by bleeding. Or if they have an abortion and end their pregnancy, and have a procedure or use medications to end their pregnancy, that's accompanied by bleeding. So, across the world, depending on where we live, some countries recommended giving Rh immunoglobulin for any bleeding episode at any stage of pregnancy to prevent these rare outcomes in a future pregnancy, and some countries recommended not giving it in early stages of pregnancy and some guidelines would say, give it for abortion, but not for miscarriage, and some would say, give it for miscarriage, but not abortion or what if you have a bleeding episode. But the pregnancy continues, and you wind up delivering a baby. All of these things have been extremely confusing,

and we haven't had good evidence to guide how to manage a bleeding episode in an Rh negative person in the 1st trimester, and whether or not Rh immunoglobulin is necessary in early pregnancy. And why does that matter? Well, this potentially causes barriers to care and difficulty accessing care for abortion and miscarriage patients, and those with a bleeding episode in pregnancy. Is it very important to get your blood type tested so that you know whether or not you need this therapy or not. Do you have to wait online or in the emergency room in order to get that blood type tested, and in order to get the therapy early in pregnancy, or is that not necessary? So, this is the reason why this became an important clinical question to address because we didn't really have robust evidence to guide the need for testing and treatment or really prophylaxis meaning prevention of a future problem among people in early pregnancy with a bleeding episode, and the guidelines across the world have really been in conflict with each other. So, depending on where you live. You may or may not get treated.

Shweta Mishra: Thank you. Thank you. And you answered another question as well, which was about your research that you just talked about. You are trying to answer this question, whether or not to administer the immunoglobulin in the 1st trimester bleeding cases or abortion cases, right? That's your research question.

Dr. Courtney Schreiber: Yeah, that was our question. I mean, we and others really question the need for testing which you know, everyone has to get tested in order to potentially treat or prophylaxis, small proportion of people. So, that's a lot of cost to society and its time and stress for individual. So, do we need its testing for everybody or urgently early in pregnancy in this setting of a bleeding episode or not and just by being a physician or being a scientist and putting that to a side, just putting that aside just biologic when you think about just a small gestational sac, the likelihood of that actually producing enough antigen to create an immune response, just biologic, seemed a little bit low. And again, there wasn't really robust evidence to guide us about that. But in the United States, it really became very habitual that any person with a bleeding episode in pregnancy, it was like, oh my goodness, we immediately need to have them tested to know their Rh status and to decide whether or not they need the Rh immunoglobulins which is, by the way, human blood product, right? So, we're giving potentially human blood products to individuals who may not need it and exposure, they may not need. And this is a limited resource. So, if in fact we were giving this uh, treatment to individuals for whom it wasn't providing benefit that means that people who really need it and do get benefit may have limited access to that resource. And we're seeing that actually now in the United States, even there is a shortage of this therapy Rh immunoglobulins.

Shweta Mishra: Thank you. Thank you, Doctor. I know Davina has more in-depth questions to you about your research but before you go ahead with your questions Davina, would you like to share briefly about yourself and your connection to this topic?

Davina Fankhauser: Thank you. Thank you, yes. So, I'm very interested in this topic. It impacts my life personally, I was an RH factor baby and I remember of course, this was a little more than a half a century ago. They actually recommended to my mother that she terminate the pregnancy and she chose not to. And now I have a child that is Rh negative and I know that this can impact potentially her future, and her ability to build a family. So, I'm very connected to this topic and I love that it can merge with my interest and fertility health care policy. So, I'm wondering how does your research suggest changes in the existing policy and practices related to RH immunoglobulin treatment?

Dr. Courtney Schreiber: Thanks so much for that question. It might surprise you that there are actually States that legislate that any patient who needs an induced abortion, which could be for any reason it could be for foetal anomaly, it could be for health indications for that person. It could be just because this is not the right time to become a parent. You know, there's so many reasons why people need to access abortion care. Many states, including the state in which I practice, Pennsylvania require by law that any person before they have an abortion, get Rh tested. And if they are Rh negative, be treated with Rh immunoglobulin, even though there's been no evidence to support that. So, this is a really great example of health care, legal policy and regulations, influencing how we deliver care and not in line with the scientific evidence. So, our study was really to look at the medical necessity of this treatment so that people like your daughter can hopefully have access to this therapy if and when they ever need it at the time that she hopefully has the

perfect pregnancy ending in a beautiful baby and needing to access Rh immunoglobulin in order to prevent any complications in future pregnancies. We want everyone to get evidence-based care that they need with inequity lines, right. That means not overutilizing resources and time as when it may not be necessary. And, honestly could cause harm since this is exposure to human blood products. When it may not provide any benefit to that woman or to her future fertility and her future babies. So that was our research question, is it necessary to give our age immunoglobulin in a first trimester bleeding episode? And in order to answer that question, we did a very sophisticated, prospective cohort study of over 500 patients, where we tested their blood using high throughput flow cytometry and actually counted the number of fetal red blood cells in the circulating woman's blood volume before and after she had an abortion and those were both medication abortions, which very closely mimics a natural miscarriage and also induced abortions with a procedure. So, we had a combination of those types that really gave us a very robust ability to look at like the different types of bleeding episodes in the different ways that the pregnancy comes out of the uterus in the first trimester with the bleeding. And we measured whether or not there was a change in the amount of fetal circulating, hemoglobin and the woman's blood, because you need to have those blood cells there in order to amount the immune response that we've been talking about, the can be harmful to a future pregnancy. And we found there was no change from before the abortion whether it was medication abortion or procedural abortion to afterwards and we also found that the amount of these circulating fetal red blood cells did not cross a threshold which had been previously published by us in pilot data and also other scientists as being the critical amount necessary to mount an immune response. So, this was done again, as I said in over 500 patients, we actually were able to conduct the study during the pandemic which was nothing short of a miracle that we were able to recruit those people. We had such an amazing study team. I really want to shout out to my collaborators. The other scientists that help to carry out this complex work, and produce a really important finding so that clinicians and scientists, policy makers to your point Davina, medical organizations can really revisit how they're helping clinicians and patients to make decisions in pregnancy and utilizing resources.

Davina Fankhauser: So, well that leads me to my second question because I was going to ask what ways do you believe your research or your study will change the approach to Rh sensitization prevention in the clinical practice? Do you have any recommendations that you suggest?

Dr. Courtney Schreiber: Yeah, thanks for asking that. So, our study shows that RH testing and provision of Rh immunoglobulin should not be used for bleeding episodes, less than 10 weeks of pregnancy. Sorry less than 12 weeks of gestation or the length of 12 weeks of pregnancy since the last menstrual period. And you know as often true in science our results actually surprised us ourselves to see that there was no change from before to after the abortion in in our study. So, the recommendation here is that guidelines should change to be in accordance with this to decrease burden on patients who experience miscarriage, abortion bleeding episodes in early pregnancy and in order to keep resources available to those who need it in the third trimester and at delivery across the globe. This is ultimately truly an inequity issue, right. I mean, first of all, Rh negativity doesn't affect all populations in the same, this is genetically determined Rh negativity is very low prevalence in some areas of the world and in some populations and higher prevalence in other areas of the world and, in other populations. And we've sort of been treating it as one size, fits all, but as it turns out, in addition to population, differences stage of pregnancy matters also. And so, if we can conserve the resources for the people who need it and not provide an unnecessary treatment to those who don't, that's better for health economics, and that's better for people's outcomes. So I hope that guidelines will change and to the extent that regulations interfere with medical care that will also change. But I also know that change is extremely slow and this as you know yourself, I'm sure Davina. This is a long arc towards justice and we just need to keep reminding people of what the most recent scientific evidence is. Allow people to acclimate to what's actually quite tricky to de-implement is actually even harder than implementing and it can take as long as 10 years for clinicians to adopt a new practice. Hopefully opportunities like this to get the message out help to accelerate that, but it's going to be a slow change for sure.

Davina Fankhauser: I think you touched upon my question about closing the health equity barriers. So, if unless you have anything more to add to that, please feel free. But I also have another question related to the field that I'm working in which is to help access fertility treatment there's in vitro fertilization, you can do

genetic testing on embryos and wondering if we know a female patient who is going to be carrying the embryo is RH negative, do we want to look at whether the embryo being transferred is also Rh negative or RH positive that way through the pregnancy they can monitor closely or what are your thoughts on that?

Dr. Courtney Schreiber: Yeah, it's a little tricky because of when the RH antigen starts to be produced in the developing embryo, so that may be at a later stage than before, the embryos are placed back into the person who's hoping for the pregnancy. But there are other kind of prenatal testing that can be done that can potentially look at this. Some of them are coming to scale. So, some companies are trying to bring More technology around early testing. And I think that's fine I don't have a problem with that. I do wonder about costs, right? So, those can be very expensive and may not be accessible to everybody. And while in vitro fertilization we do wanted to be accessible to everyone who needs to use that therapy to complete their family size. Of course, a large proportion of the population does not use IVF to build their family and so wouldn't necessarily have that opportunity anyway, and may not have access to emerging technologies for this testing. I do think that we may get to a point in the future when we don't need to give Rh immunogloblin to every patient at delivery if we're able to know their fetal blood type. And in fact, there's another good way of knowing that which is whether or not the father, what their blood type is because if they're also Rh negative and if they will be Rh negative and we don't need to worry about this. So, there are ways to tailor care already to the specific pregnancy, but when we're thinking about kind of public health and population health, our biggest win is to really work on focusing the needed interventions for the needed, need the populations who need it and being more discerning and thoughtful about giving interventions when there is no evidence that it is needed in that setting. And in fact, when there's evidence to demonstrate that, it's not needed in that setting. So that's kind of like just the individualized way of managing care versus thinking that it's reasonable to make decisions on population in public health levels for the better of global health.

Davina Fankhauser: Oh my gosh, thank you so much for doing this. And taking this on. I can only imagine, actually, I can't imagine how much time and work you put into this, especially during the pandemic to get this, to come to —. I'm very hopeful about the future of these patients. So, thank you for this.

Shweta Mishra: Absolutely thank you Davina, great questions. And I totally agree with Davina, Dr. Schreiber, your research is really thoughtful and we will keep in touch for sure with the developments on this front. So, both of you thank you so much for your time today. It's time to wrap up the talk now, and we will put the show up on curetalks.com in sometime and we also like to thank the University of Pennsylvania for their help.

Dr. Courtney Schreiber: Thanks, I do just want if I can quickly conclude with thanking you and also thanking my co-scientists and co-investigators and all of the patients who participated in this. So, Dr. Sarah Horvath who really brought a lot of this science to our lab and really seeded the idea and Dr. Luning Prak was an incredible collaborator on this study and these individuals who contributed their time, those participants we are so grateful. So, thank you.

Thank you.