Miscarriages & the Immune System - All You Should Know with Dr. Jeffrey Braverman

A mothers immune system is altered during pregnancy so that the fetus is not rejected by her body and is allowed to grow. When this balance goes awry, the immune system may become the cause of a miscarriage or multiple miscarriages. We are talking to Dr. Jeffrey Braverman, a world leader in reproductive immunology, about the role of immune system in recurrent miscarriages. Dr. Braverman will talk about various immunity related conditions or issues that may be the cause of recurrent miscarriages, and also highlight the advances in the diagnosis and management of immune related pregnancy complications. Dr Braverman will be taking audience questions too. You may post your questions in the comments section below.

Full Transcript:

Shweta Mishra: Good afternoon and welcome to Cure Talks. I am your host, Shweta Mishra and this afternoon we are talking about the role of immune system and recurrent miscarriages. A mother's immune system is altered during pregnancy so that the fetus is not rejected by her body and is allowed to grow. When this balance goes awry, the immune system may become the cause of a miscarriage or multiple miscarriages. Dr. Jeffrey Braverman, a world leader in reproductive immunology, is here with us today to educate us how our own immune cells which are meant to protect us, maybe the reason behind these recurrent miscarriages. Dr. Braverman is the founder and medical director at Braverman IVF and Reproductive Immunology with offices in Long Island and Manhattan. He was honoured as the youngest graduate at New York University where he was accepted at the age of 14. He is one of the nation's leading authorities in reproductive immunology and consistently maintained highest success rates despite the complexity of the cases. A member of various procedures organizations in medicine, he has been featured on Discovery channel, local TV news stations and has hosted numerous radio shows on reproductive immunology and fertility. I welcome you to CureTalks Dr. Braverman and thanks for finding out time to be with us here. My co-host for today's show is Annie Kuo, Annie is a passionate infertility advocate and an ambassador for RESOLVE: The National Infertility Association. Annie advocates on the federal level for family building legislation and has been featured on various print and non-print media. She's on the Men's Health Campaign Council at UW Medicine and is also a founding member of Women for Men's Health.

On the panel, we have Davina Fankhauser, a member of the ASRM and New England Fertility Society. Davina is the foremost expert on policy related to benefits for fertility treatment and preservation. Davina and Fertility Within Reach's evidence based information are sought after at both patient and professional conferences. A former member and advocacy director of RESOLVE, she currently volunteers for the advisory board for Parents Via Egg Donation and serves on the BIDMC NICU Parent Advisory Council. We also have on the panel, Danae. Danae is an Episcopal priest and family therapist in Seattle area, and she uses this art, music, poetry and movement and counseling those struggling with infertility. Danae has also contributed to several books, plays and podcasts on fertility struggles. Before I jump onto the questions with Dr Braverman, I just wanted to let the audience know that we will be discussing questions in the last 10 minutes of the show so you can mail your questions to shweta@trialx.com

And if you want to ask a question live, please press one on your keypad and we'll bring you on air to ask them or you can also post your questions on curetalks.com website. So Dr Braverman, for over 25 years, you have treated patients who have suffered from multiple miscarriages and have been unable to carry a child to full term. It would really be great if you could explain in layman terms the basics of how may our own immune system which is supposed to protect us, affect our fertility and pregnancy. And what are some of the immune related diseases which make some women more prone to miscarriages?

Dr Jeffrey Braverman: Okay. It's a complex question, but I think the best thing to do is to go back a few million years and understand how the immune system even became involved in accepting pregnancies. So this all occurred between the transition from reptiles to mammals. So reptiles would lay eggs by the river and then they could leave, they were done. And it was pretty simple. The eggs were left on their own. The problem is that eggs were food and they tasted good and other animals ate them. So nature decided, it had to develop a mechanism where pregnancies would be carried inside of the mother until they could bear them near term. So in order to do this nature understood, it had to develop a mechanism whereby a placenta, which is the definition of a mammal, they develop a placenta with foreign genetics because the genetics on a placenta contain paternal genetics, which are foreign. That nature had to come up with a mechanism to begin to accept this, if mammals were going to thrive. So you can trace back all the way to this conversion where a new gene was developed called the CN1 promoter gene, and this gene is exclusively in mammals and this gene has one exclusive function which is to develop cells that have the primary responsibility of protecting this foreign genetic placenta from the maternal immune system. Because you're correct, the immune system is should attack and reject anything foreign because it does protect us. But in this situation, nature had to figure out a way to accept this foreign placenta. So this CN1 promoter gene developed a group of cells called T-regulator cells that were able to migrate to the uterine cavity and basically turn off the maternal immune response against the foreign genetics. So it's not that the immune system that normally is there to protect us suddenly has a problem, it's doing what it should do. It is going to mobilize and it is going to try and manage the response against the placenta. But these T-regulator cells basically turn off this response and protect the placenta and it turns out that nature figured out a way to assess when should they make these T-regulator cells and they do it when there are sperm in the vaginal canal that contain different genetics than the mother.

That's the signal to start making the volume protective to regulate ourselves and the more differences that the sperm had from the mother, the more volume of T-regulator cells that were made and when you reached a critical level of these T-regulator cells. Enough of them were generated to protect the embryo from the maternal immune system for all the paternal genetics and there are quite a few genetics on the invading embryo. So that's how the mechanism was developed. And now there are many, many things that can interrupt that cycle and among them and things that we will get into are inflammatory conditions. Because the key for the development of these T-regulator cells is the messenger cells of the immune system and these are called dendritic cells. They have to be able to not only pick up the paternal genetics and they scan them in the vaginal canal and they deliver them to the lymph nodes, but these dendritic cells have to be in a certain form, certain shape, and these are called immature cells or Tolerogenic cells. But any inflammatory condition, any autoimmune condition can prevent that conversion from happening. These dendritic cells can remain in their mature state or inflammatory state and then the whole mechanism becomes defective and now the immune response will be very strong and there are multiple ways that immune response can show itself and it can begin to reject the pregnancy leading to complete implantation, failure, early miscarriages, and even late pregnancy complications like Preeclampsia, preterm labor and God forbid, or even stillbirth.

Shweta: Wow. Thanks for that very comprehensive explanation and the pathway that you just described. I'm sure for many of the audience out there it would be something new that they learned today. So how common is this problem? Is it a really common problem that people get recurrent miscarriages due to immune system problems?

Dr Jeffrey Braverman: It's very common and the problem is that it's not recognized. So, there are many, many reasons when we tell people they should begin to seek our advice. And there are about 15 reasons I list them on our website. I won't run through all of them now, but the most common are: a miscarriage that was proven to be genetically normal. Somebody with failure of PGS tested embryos, probably two of the most common things that we see, a miscarriage after detection of the fetal heartbeat when no genetic analysis was able to be performed. And the biggest mistake that the regular community makes Ob-Gyn or their fertility community is that they live by this guideline that you have to have at least three miscarriages, some say five before you need a workup. And the problem is that all of these papers, and probably the biggest one, it was written back in 1999. That was a study that I've written about that was very effective because they didn't do genetic analysis. They knew nothing about immunology, but unfortunately they've

kept that going in the Ob-Gyn. And there are REs who quote this and tell women, no matter when they've had the miscarriage, no matter whether or not it was genetically normal, it's normal until they've had three or five and that's just completely wrong. And we discuss that very clearly on the website. One last thing I'll say is when you have a recurrent pregnancy loss and it's associated with previous pregnancies, with late pregnancy complications like Preeclampsia, intrauterine growth retardation, even autism, these also show this is very likely a strong immune component and these need to be worked out.

Shweta: Sure. Thank you for that answer. Dr. could you talk a bit about the battery of tests that a woman or a couple of must go through if they experienced recurrent miscarriages?

Dr Jeffrey Braverman: Well, again, there's always an initial scan that's done by the General Ob Gyn or the reproductive endocrinologist. And the initial testing is pretty simple. You look for uterine deformities, uterine anomalies. You look for the inability for the uterine lining to appropriately thick in, you look for genetic abnormalities in the mother or the father do they carry what's called a translocation. That's easy to check by doing a karyotype or genetic analysis on both parents and that's really where the workup should start. If those are completely normal and there's still no explanation, these patients typically get moved into an incorrect diagnosis of unexplained infertility. It's not. It's just at this point, it could it be beyond the scope or the regular Ob Gyn or an RE and at that point they should then move into the immunology workup.

Shweta: Sure. Thanks for your answers Dr Braverman. At this point, I'll now hand over to Annie is our co-host for today. Annie you are on air.

Annie Kuo: Hi everyone. This is Annie from Seattle. I'm actually want to two panelists on the call from Seattle. Danae and I are are friends. We met through the fertility support space and I actually also know Davina on the other end there. We've advocated for family building legislation in Washington DC together and I heard much about Dr. Braverman's work. So thank you. I feel very privileged to be among the company today. We have several questions. We're going to rotate throughout the panel, and I'm actually going to hand it over to Danae who has a handful of questions first, she's going to have to have to leave us first. So Danae welcome to the panel. Would you like to address Dr Braverman with your first question?

Danae Ashley: Thank you, Annie. Hello, this is the Reverend Danae Ashley. Thank you Dr. Braverman for your time today. Can everyone hear me? Great. So I am representing many, many different facets of reproductive challenge across the United States, especially with clergy women. And here's some of their questions. The first question that folks wanted to know was what kind of treatment does an immunologist do compared to an MFM or an RE?

Dr Jeffrey Braverman: So completely different. You have to remember that MFMs and REs don't have a single day of training, in their training or fellowships in immunology, so they really don't understand how to use immunology treatments. And I think in order to prescribe these types of treatments, you have to have a full knowledge, not just in the field of fertility, but you have to know every field of immunology from autoimmune disease immunology, cancer immunology, transplant immunology, allergy immunology. I mean it's a very complex field. And the immunology work has moved into the personalized medicine field. And what I mean is that when we do the workup of some patients, we not only look at their entire immunology profile, which is extensive. It's on my website. People can go look it up, but we also look at all the HLA genetics. So I know all of the autoimmune issues they are predisposed to. And the predispositions helped me to identify what the possible underlying, preexisting autoimmune conditions can be. And in fact we many times can identify these even before the patients actually get the syndromes. So when you asked me about the medications, they're as diverse as they are a number of autoimmune diseases that are out there, some are autoimmune diseases some are inflammatory conditions, but it's not just a garden variety of immune therapies. It's really specifically tailored to what we find on each individual patient.

Danae: That makes sense. And so when you mentioned this a little bit, you touched on it previously, but when a person who is having repeated pregnancy loss and has their tests come back normal, but their doctors won't refer them to an immunologist who specialize in miscarriages, how do they get to you? Can

they get to you privately or do you need a referral?

Dr Jeffrey Braverman: No, they can get to me privately. The way that it works now is patients can go directly to my website and it says patient consultation. They click on it and it's funny having gone in there myself recently, but my web team designed or this, it seems to be working, but when they click on it, they'll get a calendar in front of them and they can just pick a date and the first opening I get they'll be put into that opening. They put a little, a few sentences about their case. And then I call them and I call all the patients directly. We discuss their case. It's a free call, no matter where they live. And I do these all over the world. It doesn't matter where the patient lives and we have a quick discussion. By speaking with them, I can usually tell very quickly, do they need my help. Some people I say, look, you don't stay with what you're doing, but if they do need my help, then we figure out a way for them to get my help. There's not much you can do if an RE is not open to understanding what we do. And again, remember, a lot of this is beyond their scope. They haven't learned about this and I think they still feel they're doing the best for their patients and I never have an issue with that. You can't blame somebody for what they don't know what they don't understand. But I think, patients have the option to change REs, we work with our REs in so many states that we can usually find somebody that they can go to that will collaborate with us. And I let a lot of the patients that are out of state stay with them, we just direct them how to handle the immunology workup, the analysis, and immunology treatments while they do whatever therapies they're going to do, whether it's IVF or IUI and we can guide them. So generally it works and we don't have a problem.

Danae: Thank you. And do you know what current studies in the US are actually impacting how REs and MFMs are managing miscarriages in partnership with an immunologist in the way that you are doing it. Or have you done more studies recently? Are other people doing studies? What is the latest?

Dr Jeffrey Braverman: Here's the problem when it comes to studies. Most of the REs are going to quote studies that were done many years ago where they randomly took patients. So a few of the studies that were done many years ago where they looked at random immune therapies such as IVIG or intralipids or Prednisone. These were done in women that had RPL but had no immunology workup. So the studies themselves were not at all valid and yet a lot of the REs will follow those studies when they say, these therapies don't work and we're not going to use them. Not of course understanding how complex the workups are to try and determine who needs therapy and it's not dissimilar to somebody going to a doctor with a cough and everybody getting tuberculosis medication. It's not going to work. If you do the workup and you find the etiology of the cause, it's going to work much better and we've been doing this for years. It's really hard to do well designed and controlled studies in this field. The reasons I stated from the outset, and this is what nobody really understands. There are so many factors that play into each patient's problem, that each patient is almost unique to themselves. So you can't get a study done with a) you're going to get a control population. Certainly people calling me, none of them want to be a control. None of them, they want to come here and they want to have their baby so you can't get a large enough control population and then the control populations have to be very similar and it's very difficult to do because each case is so dramatically different.

So if you understand all the mechanisms that I briefly went into in the beginning and you understand how transplant immunology works and how similar by the way the immune system's reaction to a donated organ is to an embryo. I use it to extrapolate a lot of these therapies. When you understand all the immune mechanisms that are at play, it's not hard to develop the therapies. But to prove them in the fertility field is very difficult for the reasons I told you. So all you can do is what we've done is we say, well, if somebody comes to me with RPL and immune issues, what's likely that we're going to get them a baby and then compare that to what's been done prior. And that's what we've done. So we put that data up on our website and we have different age groups, but roughly 70-80% of the patients who come to us with five or more miscarriages are going to have the baby with us, which was much higher than anything I've ever reported. So we know the therapies work, but in order to single out and you have to enroll someone, you publish the study, nobody wants to look at multiple therapies, which almost all our patients are on. They only do one study, one drug, does Neupogen work. Well, when they did the multicenter trial on Neupogen about five years ago and it failed and they called me and they asked me my advice on doing. I said, you will fail if

you try and use one single therapy for these patients and after $20,000,000 spent, it failed. Yeah. We use Neupogen all the time. It's extremely successful because it has to be combined with so many other things. Some people need surgery, some people need Prednisone or Lovenox. We have to treat their autoimmune disease. I mean these are very complex. So to put together a study that you could publish in one of the fertility journals is near impossible because you can't get the controls, but the data on how successful a patient is when they come to our centers, based on five more miscarriages, based on my way which we can get to later based in endometriosis are all much higher than anything I've ever reported and that's our proof that this works. Besides the fact that about 70 IVF centers now refer their patients to us because we've had great success for them.

Danae: Wow. Thank you. One more follow-up question from some of the things that you've already mentioned. So if someone is having or has had five or more miscarriages, but they have gotten the tissue tested and it came back as chromosomally abnormal, would that also be an indicator of an immunology problem or is that, is that a whole other issue?

Dr Jeffrey Braverman: No, that's a very good question. I'm glad you brought that up because it's another strong area of misconception. Number one, it depends on the age of the patient. Well, let's take a patient who's 35, and they have multiple losses and they tested a few of them. They come back as aneuploid and most of the doctors and the REs will say, well, that's the reason for your loss. Let's just move on and try again. But what we've learned, and I write about this on my website and I've named it and we call it correctable, which is a keyword, recurrent aneuploid conversion syndrome. And what this means is that due to immune issues or inflammatory issues, the eggs during their development, because by the way, it's not normal for a 35 year old woman who has normal karyotyping tab recurrent aneuploid losses. So what we've learned is that due to these inflammatory or immune issues, the egg during its development, and this has been proven that there is a large amount of a product called reactive oxygen species in the developing egg. And this is a product of local inflammation, local immune responses. And it damages the mitochondria of those eggs. So now when the eggs are fertilized and they begin to develop, if you all remember your high school biology, the mitochondria organelles that supply the power for a symmetrical nuclear division. So when these eggs are damaged, and by the way, endometriosis is one of the big reasons why, and we actually figured this out from our endometriosis patients. When you transfer these embryos in or if the patient gets pregnant naturally, the power necessary to continue to symmetrically divide the nucleus is lost and at some point that embryo converts to aneuploid. That's why it's called aneuploid conversion syndrome.

And we see this in a lot of our patients with immune conditions with endometriosis and it's correctable because if you correct the conditions that are causing damage to the mitochondria, you can lower the chances that this patient is going to have another aneuploid pregnancy. Even if by the way that pregnancy was tested as PGS normal because those don't test the mitochondria. You take a PGS normal embryo with damaged mitochondria and you transfer it. The majority of them won't take, the ones that do, a lot of them convert to aneuploid. So a lot of them fail to get to see me. Nobody understands that a young woman having multiple aneuploid losses, it's another sign that there's something going on that can be treated and corrected.

Danae: Wow. I wish I would've known you long before this. Thank you.

Dr Jeffrey Braverman: If you look at my website, that's probably the most common statement I hear, except my wife. I hope she is not listening, I'll be in trouble.

Annie: You're helping a lot of people. Yeah. Building families. It makes the world go round.

Dr Jeffrey Braverman: I always tell people that, I don't remember the people that I did get pregnant. I just remember the ones I don't. And those are the ones, I worked. I think every case is solvable. That's always the way I believe.

Annie: Reverend Danae Ashley, here in Seattle. I also wanted to mention that she's one of the contributors

of the book, Still a Mother: Journeys through Perinatal Bereavement, which came out in February 2016 by Judson Press and is available on Amazon. Thank you Danae so much for joining us today on the panel and for your question. We're going to move on to Davina Fankhauser who's over here from the east coast on the same side of the country as Dr Braverman. Davina, thanks for joining us today and I'm excited to be on this podcast with you. Would you like to address Dr Braverman with two or three questions?

Davina Fankhauser: I would. First I would just like to thank you Dr Braverman for hosting this important topic. This is why I have these questions that I wanted to ask and as I'm listening to your responses to the other questions, I'm just coming up with additional new ones, but I won't go there. I'm passionate about this topic. And one of the questions though, because personally I experienced this, but professionally I experienced this as well, so I'm hoping the information you gave me, I know what helped other patients that are out there, both men and women who as they're trying to conceive, experienced miscarriage, but also professionally I'm trying to pick your brain. I heard you that well designed design studies are challenging to create and it makes sense. I am curious, there's a 2016 study on the role of infection in miscarriage and quote it was published in human reproduction update. It asserts that potentially preventable infections may be responsible for up to 15% of early miscarriages and 66% of late miscarriages. What I'm wondering is, two little questions combined. Have these statistics shifted since 2016 and have the percentages either increased or decreased over the past decade?

Dr Jeffrey Braverman: Okay. Well you have to be very careful in the way you just quoted that study because this is a big problem in this field. So you quoted a study that said that there was these infections may be responsible for miscarriage. So the question is what do they mean by that? And how did they draw that conclusion? Because there's a difference between an association, meaning that anywhere from, you gave me numbers of 15-60% of and I know it's mycoplasma ureaplasma may be associated with infertility. But in order to decide if it's an association or a cause, what you need to do is treat the infection in that population and then say, did that improve the overall pregnancy rate. So that's how you differentiate it from a cause versus an association. And that was never done. Now it's quite possible that there was an association, and we know this by the way, just about every organism has been associated with infertility, including, certain viruses, other bacteria besides the mycoplasma. And so the question is, does the immune or inflammatory environment predispose to the growth of these organisms? And that they're not really the cause. Now we tested for mycoplasma, ureaplasma from years ago. I didn't see any benefit from exclusively looking at that. It's clearly not a major cause, cause not association, but a major cause of miscarriages. But I will tell you that in many of our patients when we do let's say an IVF transfer, I pretreat them with antibiotics because I want to make sure that if there is any indication or infection or endometriosis may be playing a role, I want to treat it. But looking for specific organisms didn't seem to be a value because we know there's a high association, but the key question is did treating it significantly decrease and treating it alone maybe with no other therapies and we didn't see that and the studies don't look at that. They didn't look at the obstetrical outcomes in these patients. They just did, whether it was a retrospective study. And so yes, there's a high association but it's never been proven causative. And that was the big issue.

Davina: Right. And I am a big believer in proof and I also love your mindset of every case is solvable and I can hear that you continue to consider everything you know from your experience, but you're also able to think out of the box and that, that brings me to one question.

Dr Jeffrey Braverman: By the way, I want to make a correction. I don't think out of the box, I think in a much larger box within it.

Davina: Okay. Alright, that makes sense. Well, I'm going to go out of the box. I'm going to go out in the box and say we've seen in and read and heard in media that immunotherapy can be used to treat cancer and allergies. Is there some form of immunotherapy that could be used as a treatment for people who experienced miscarriage due to immunity issues?

Dr Jeffrey Braverman: Oh, absolutely. I mean that's what we do, but as I explained earlier in the program that there are multiple immune causes. And remember the key here, going back to what I originally said, is

that these immune issues, when we discover them, they typically interfere with that normal mechanism of T regulatory cell development, immature messenger cell, dendritic cell development, and that's the end point. There are many triggers that affect that and then different autoimmune diseases present themselves differently. Some autoimmune diseases of antibiotic media, things like Lupus, they require different treatment. Some autoimmune diseases are cellular mediated, they require different treatment. And then the amount and you have to remember, and what we also ended up dealing with here is that the initial insult to the maternal immune system may lead to a secondary problem. Once the mother loses tolerance to the paternal genetics, then there's a whole secondary set of problems that we now have to treat. This is why these things are so complex, so it's hard to say, one specific treatment for immune disorders, but the answer is yes, and in fact, a lot of the treatments we use to correct the triggers are the same treatments that these women would use in their own autoimmune disease. People who come to us with rheumatoid arthritis may end up on Humera, some of with Lupus may end up on IVIG. So there are a lot of very specific treatments to treat the triggers that cause that end result of losing tolerance for the embryo.

Davina: That's great. Thank you. That's helpful information. So I have a two part question for you because I'd like to do that. The collective quote unquote, we are told the way to increase your immune system is to reduce stress, get enough sleep, eat a healthy diet.

Dr Jeffrey Braverman: Let me just correct something. I don't know what that means to increase the immune system. Remember, the immune system has multiple directions it can go in the body. It can become tolerant, it can become aggressive, inflammatory. So older people, they tend to lose that ability to be aggressive. And so there are things that we do to try and boost their immune system. Women that I see have the opposite problem. Their immune system is overactive. We're looking for things to do to reduce that.

Davina: Well, you see. You're answering my questions before I even got there.

Dr Jeffrey Braverman: That's my job. That's what I'm doing this for 25 years. So I know.

Davina: So I was going to say, those with a history of miscarriage, they may have a different prescription for strengthening their immune system to support the reproductive system. So I was going to ask you, does a patient need care? And I know from your responses, I already know this answer now, do they need a care that specifically targets the reproductive system or is it other issues that are impacting the reproductive system?

Dr Jeffrey Braverman: Well, here's the problem. This is where the mistake is made. The reproductive system involves the immune system. It's one that's what people don't understand. It's one system. Now, depending on what the defect the patients have or the treatments are multiple, I'll give you another example. What's become very popular is this Th1/Th2 ratio. People talk about that in the late field when I read things on facebook, people feel it's better to not be in a Th1 state, better to be in a Th2 state, one of them is basically anti-inflammatory, one is inflammatory, but both of them into fear with those normal maternal immune mechanism, they both require different treatments. So it's really hard until you work a patient up to know what you have to do with their immune system. It's very complex.

Davina: Well, that is actually my last question for you. I'm wondering what guides your treatment for multiple miscarriage? Do you rely on research experience, other factors, everything under the umbrella. I'm just wondering how do you work your magic?

Dr Jeffrey Braverman: So let me tell you the process. So we do our full immunology profile, which as I said, it's very complex. When we get all of the data back, we tabulate everything. I've been keeping track of these results now for almost 15 years and we put every single result into a percentile, so now how this patient is compared to the last patient. We get that clinical history. Very important. We get the family history, very important, and then we actually have a meeting for each case with our research department. At that point when we see unusual things in the history like anybody else, we do our literature search on it to see if in any way impacts the findings and our treatments. Each case that we do, case is about two or three hours

to put together. It's not a quick cook book. It really takes a lot of time and many times we discovered things we didn't know when we started going through it. But that's what we have to look at each of these cases and sometimes we'll see result and seeing this kind of strange, we haven't seen that elevated before and we have to go back and look at literature and seeing what that's associated with this sort of human disease. We know how to treat that disease and it'll change our therapy. So the research phase of it, yes. There's not a research in what I do because we've basically pioneered this field. But the research in other autoimmune diseases, there's a lot of it out there. And obviously we search all of that before we put our reports together.

Annie: Thank you Davina, you have some great questions. I get to ask a few now Dr. Braverman and now you're ready for me.

Dr Jeffrey Braverman: Right ahead.

Annie: Okay. Actually would love to lead with a question on men's role, if any in miscarriage. As Shweta mentioned at the intro, I am on a men's health counsel for the University of Washington medicine. I'm interested if you could comment on the role, if any, that men might play in miscarriage.

Dr Jeffrey Braverman: Yeah, good question. We need a lot more work on this. It's appearing to us that immune issues may actually play a part in sperm development and may play a part an abnormal morphology, DNA fragmentation, and we've ourselves just began to look into this. When the men get tested and they have completely normal semen parameters and they have normal DNA fragmentation and they typically don't really play a part. Because fortunately, once they make a good sperm, they are pretty much done. Now, I spoke originally about the need for, differences, on a certain group of HLA genes called class one that must occur between the man and the woman for the production of this high volume of protective T-regulator cells. So yes, if the man doesn't have enough of those differences, that can play a part outside of the sperm parameters. But when we see abnormal semen parameters, and I've written about this on the website, we've seen that when the men have abnormal inflammatory profiles, we now look at their omega 6 omega 3 ratios. We measure those, we correct those, that has shown improvement. We've seen men with the MTHFR defects, when they take their, methylated folate that improves parameters. We know that, again, I'm speaking specifically about men with abnormal semen parameters.

We know that undiagnosed prostatitis can cause that. When we see we put men on the antibiotics for a couple of weeks to treat. We know that just like when there are high levels of this product called reactive oxygen species in the egg, the damage to the mitochondria, the men can have high levels of reactive oxygen species on the head of the sperm, that damage the sperm. We actually contest with those levels when we do our sperm parameters, but they are you treat with antioxidants. So there were a lot of therapies that we're now giving to the men that have abnormal semen parameters, but if the semen parameters are normal, that doesn't appear to be much, that the man will be contributing to the recurrent pregnancy loss panel. And again, you look at the HLA genetics which are very important for immunologic incompatibility, but outside of that is really not much more than men would contribute with perfect semen analysis.

Annie: And interestingly enough, thank you. I know that there's apparently a sperm crisis in the western world as some of the news headlines have attested to. I think like earlier this year, Newsweek had a cover story on how there's a sperm crisis in America. So in the best of all worlds, men are not contributing when they have normal semen parameters, but it sounds like increasingly there are some issues.

Dr Jeffrey Braverman: Let me say one last thing that I forgot to bring up, I apologise. We haven't looked at this yet. We're setting broadly up to look at this, but I spoke about it way back at the beginning of the call, the development of the CN1 promoter gene that mammals have, that produces T-regulator cells and it seems one of the things that triggers that gene to be activated, is TGF Beta, which is a cytokine that is in the seminal fluid and we know that the TGF Beta binds to the CN1 promoter gene, that also helps to increase the production to regulate ourselves. It's possible that some men may be deficient not only in TGF 1 Beta, but also prostaglandin E2. Both of these may be important helping to generate tolerance. We're just now

beginning to look at this. I was going to take us some time to put it together, but it's quite possible even with normal semen parameters, if men are deficient in either one of these, it could also lead to failure to generate tolerance that could contribute also to recurrent pregnancy loss.

Annie: Thank you. I just love your comprehensive answers. I feel like this is jam packed with so much helpful information. My second question turns to the woman, risk of miscarriage increases with a woman's age. I've heard it's 25% risk at ages 35-39, 51% at ages 40 to 44 and then goes up to 93% at over 45. Are there any lifestyle diet or supplement choices that a women over 40 can do to reduce the risk or is this just an inevitable biological declined based on egg quality?

Dr Jeffrey Braverman: Nobody's family answer that question. I mean, clearly you should see what you just quoted because as you get older there are two key factors that probably dictates failure. And by the way, these studies don't separate out those with immune condition. So, they're all thrown together, which is another problem when you quote studies like that. But the two key issues is when we get older is aging the mitochondria. We've already spoken about that, being an issue and shortening of the telomeres, the little caps on the DNA, they're promoting this on tv now. Find out your real telomere age and they show people riding a bike and being healthy and then they get the report that the telomere age shows 63 and they stopped riding a bike because they're afraid they're gonna hurt themselves. But, I don't get the reason for that. But anyway, so the question is, can you correct both of these factors now? I posted this recently, our success in my practice with women over 40 is higher than any reported anywhere. And we were kind of surprised about that, that even in the age group, 43- 44, 30% of the patients who came to me had a baby with us and the numbers are now reaching statistical significance. I didn't really talk a lot about it because I used to say, well the numbers are too low, but now the numbers aren't too low. So here's what I believe. I believe a lot of the therapies that we're using to treat immune issues. A lot of the therapies that are preventing mitochondrial damage are probably overlapping in some of these age related issues.

And we also know that a lot of these antioxidants may actually help prevent telomeres for shortening. So I would say that everything that you would typically do to treat the munitions probably overlap with these age related issues as well. Antioxidants being very important, anti inflammatory diets being very important. And I think that's, and I still need more evidence, but that's where I'm heading. Although I don't think we can make a significant dent. I think we have. And I think that's how, as you get older, you can try and help yourself.

Annie: Right, right. Thank you. Just keeping an eye on the time. It looks like we planned for 10 minutes of audience questions, but I have three more hopefully short questions. I'll just kind of brief briefly a highlight what the topics are. The first question is about the threshold for testing and evaluation the threshold of the number of miscarriages. The next question, would be about unexplained recurrent pregnancy loss. And the third question is about, this comes from a place I'm involved in Resolve support groups about practical and emotional support work best for people who suffer from RPL. So the first of those three questions addresses, the ASRM threshold for testing and evaluation after clinical miscarriage and 2013, that threshold went down from three or more to 2, I understand from some of our layman's woman's research that, our study, quoting that many providers in your birth still not testing after two miscarriages, waiting for three to happen. Can you tell us how there might be a sea change in the global industry so that people can get an earlier diagnosis and that providers are not only better educated about this need but activated to provide better and earlier care?

Dr Jeffrey Braverman: Well, here's the answer again. You can't just give a blanket. You have to have two more losses. And as I said, you have to define the losses. The minute anybody has a genetically normal loss they need to work up. But you understand that, even the ASRM, there's nobody writing these protocols in a immunology, they don't understand the mechanism. The second was rejection of a genetically normal embryo or pregnancy. So it shouldn't be that road. Every case is different. I have a miscarriage in somebody who has a history of Preeclampsia. I know it's immune. They need to workup, it's going to be beyond the expertise a simple RE, but like I said, I put up on my website, the 15 or more reasons when you should get the immune workup, I won't go over well with them now. I probably can't scoop them off the top of my head, but that's what people should be following, and you can't take a recommendation from a group that doesn't

understand the reasons for miscarriages and that's the problem. So how do you get everybody to do it? Well, they got to do their homework. They've got to go out there and they've got to open up a book. Look, when I did this 25 years ago, I wasn't any different. I knew something was up. I opened up the books. I knew I didn't understand my field completely. I knew the immune system was involved in this. I had to go and learn immunology, I think that's the responsibility rather than leave it up to a committee to tell you this works, this doesn't work, pick up a book because I'm telling when you read about it, but certainly when the people speak to me and I explain it, they get it and they say, this makes perfect sense. So I don't believe in any of these wrote recommendations, wait for three, wait for 2; each case has to be identified on its own. Like for an egg donor for instance. If you got an egg donor miscarriage, the likelihood is that was genetically normal. You got to do a work up. You can't just do it again. God knows how many times I see that.

Annie: Yeah. Oh Man, I've seen it too. Advocating for my sister to get to workup by her regular Ob with what I knew about infertility and going home and wanting to show that that will actually show me the doctor.

Dr Jeffrey Braverman: Patients should never have to be their own advocates. No patient should have to be the one to go out and look up on the internet. That's the job of the doctor, and if he knows that his scope in his field goes beyond simple making eggs, but the immune system's involved rather than wait for a committee opinion, tell them what to do. You're a doctor. Open up the books and learn. So when I did this and I tell people it's not easy. They just can't pick up a book tomorrow and know everything about it, it takes years. I've experienced the learning curve is huge, but you gotta start somewhere.

Annie: Right. I love that we have an advocate here inside the medical community among peers. Before moving onto the next question. I'm assuming this may also lead to your opinion, what you've just shared with us on the direction ASRM I might take in approaching biochemical miscarriages as well as the clinical.

Dr Jeffrey Braverman: Same thing. You have to look at the case. So, I get calls sometimes, from a young woman, let's just use 35 because the middle age. They had a they look, I've had a biochemical, what do I do? And I look at their history, if they've got immune disease, I'm going to work them up, you just don't wait, if they have nothing else in the history, they've had a biochemical. I say, look, try again, it could have been a random loss, but when I see a young woman starting to have more than one biochemical, it's not normal. So each case is so individually different. You just can't make these rote recommendations to try and get everybody to follow a cookbook pattern when to work them out. It doesn't work that way. So complex each case alone. That's the reason I do this because I speak to them. I can quickly know they do it, don't need it.

Annie: Great. Could you comment on unexplained recurrent pregnancy loss and the best solutions to consider for that?

Dr Jeffrey Braverman: Well, that's the same topic. I mean, I told you there's no such thing as unexplained. Unexplained means the Doctor is seeing the patient does not know how to explain it. There are explanations and typically when they get to that point where they've been given the label of unexplained, almost certainly immune, at that point just go get the workup because there's no such thing as unexplained, there is nothing.

Annie: Okay. Okay. Great. And then the last one is a little bit soft and fuzzy. What types of practical, what kind of practical and emotional support have you found work best for people who suffer from recurrent pregnancy loss? We found in the Resolve community here in Washington state that when they meet with a general infertility support group, a lot of folks are having trouble getting pregnant at all and so there's a little fine line. We can also offer mutual support to one another, but we're wondering is there, what have you found work best for your patients who are suffering emotionally and after a certain point, do you think there's a psychological mind body link involved with recurrent pregnancy loss?

Dr Jeffrey Braverman: Okay. That's a really good question. I want to be very careful how I answer that question. Let me just start by saying that if stress was a major cause of recurrent pregnancy loss, none of my patients would get pregnant. Because everybody comes in here and they're very stressed. But with that

said, locally, I work with psychologists and psychiatrists that specialize in this area. I know them well and locally, I refer my patients out when I feel they need help. I wish I was more familiar with, doctors all around the country. I don't have them. I did post a book up on our website and I worked with a great author in Australia who wrote a book on how to deal with the emotional issues and recurrent pregnancy loss. It's something, I personally don't handle it in my practice. I refer them out locally and again, if ever Resolve group, I do send them to the support centers there. I don't really have any other way of helping them deal with this except that when I identify it, I do refer them out. And there was a couple of studies that were done showing that have the psychological stress does increase inflammatory cytokines that we know are associated with the RPS. By the way,

I'll just tell you a story very quickly, a very complicated case we had and we were trying every therapy, nothing was working. The husband came to me and said, look, we're from the Greek Orthodox church and we're going to go on a retreat. We heard this works great. And they went on the retreat, came back the next month they were pregnant. And the second time around, they had similar issues. He said, I'm going to go back on this retreat. He went, got pregnant again. So, you see this, you see women who sometimes adopt and then suddenly they got pregnant on their own. I see this. So I don't think it's a large percentage of the patients, but there are people where there is a psychological component and sometimes it can make things a bit more difficult.

Annie: Right, right. Thank you for addressing that question. I just see that a lot, in offering support to people here and hear about it through the network of Resolve volunteers, so really appreciate your addressing that kind of emotional, psychological aspect. I'm actually done with my questions. So with that, I want to thank you Dr. Braverman. So hand it over to our principal host, Shweta to take it away.

Shweta: Thank you Annie. Thanks for your questions. Dr Braverman, I have a couple of my own questions and then I'll move on to the audience questions. We have a list of questions from the audience coming in. One of the studies published recently in May showed association between this preconception, vitamin D deficiency and miscarriages. I'm wondering, could you talk a bit about that study and if the Vitamin D supplementation may help in preventing miscarriages and how is vitamin D is related to our immune health?

Dr Jeffrey Braverman: Sure. So let me say a couple things. If you go to my website, I wrote an entire blog on that study. I broke down the study and I went through every single aspect of it and how I think it affects fertility. Anybody interested can go to my website under my literature blog. If you scroll down, there's a study Vitamin D and Miscarriage new study, so everything I'm going to tell you is there, but let me just make it simple. That we know that vitamin D deficiency can lead to multiple inflammatory disorders. We see very commonly in our patients, very common that this vitamin D deficiency, whether it's our endometriosis patients or recurrent pregnancy loss patients, vitamin D deficiencies is extremely common and basically vitamin D is like a hormone and it helps to do multiple things. In fact, if you look at what I wrote about on our website and you look at the issues for recurrent pregnancy loss, we know that in vitamin D deficiency, there's much higher prevalence of antiphospholipid antibodies and vitamin D deficiencies, there's a much higher prevalence of anti-nuclear antibodies, almost triple in the group have low vitamin D levels. There is a very high prevalence of double stranded DNA. Almost 3.5 times higher in the vitamin D deficient group, higher levels of thyroid antibody, higher levels of NK cytotoxic activity. So I can go down the list, but ultimately it seems that when vitamin D is low, the body allows itself to go into an inflammatory state and that shows up multiple ways. So almost all of our patients are taking vitamin D, it seems to be critical for the treatment of recurrent pregnancy loss.

Shweta: Okay, sure. Thank you for that answer. The other question that I have is one on preimplantation genetic testing. So how accurate is that in getting to know the chances of miscarriages?

Dr Jeffrey Braverman: Well, the people who know me, know my view on this, I'm not a fan. As you know, I published the first study showing that abnormal PGS embryos could still make normal babies and this kind of opened up to the PGS companies finally admitting there's a major flaw in pgs that, abnormal embryos. Almost 41% of the time it's led to normal pregnancies. The other problem is, in our immune population, just

remember this is a subgroup, we spoke about this correctable recurrent aneuploid conversion syndrome, and I told you even PGS normal embryos have been mitochondria damaged, don't lead to successful pregnancies, almost always. So it doesn't appear PGS is helping in one way or the other and that the goal should be to focus on mitochondrial function and not worry so much about PGS. And the fact is that women who do PGS, the take home baby rate is significantly lower and that's the only statistic that matters to me and it's a lot of money to spend. I'd rather spend that on the therapies they need.

Shweta: Sure. Thanks for your input on that. And I'll move on to the audience question now. So the first question that just came up on our website says, how do you feel MTHFR and Prothrombin relate to first tri RPL (recurrent pregnancy loss) and MTHFR for our audience is methylenetetrahydrofolate reductase gene.

Dr Jeffrey Braverman: Well, it's a complex question again, and here's the problem. You don't look for a single issues to define a patient's reason for recurrent pregnancy loss and MTHFR deep exit, very common in the population. If they were a significant issue, we'd see much higher rates of recurrent pregnancy loss. I think you should test for it, it's part of our panel. If you see it, you treat it. But I never say to somebody, well, you having recurrent pregnancy loss, let's take your MTHFR. You do the entire workup. You look for the full diagnosis remember. There are usually multiple etiologies for recurrent pregnancy loss. So MTHFR, prothrombin genes and all these thrombophilia, they probably don't play a major role in recurrent pregnancy loss. The issue here is, a lot of these people get treated besides the methylated folate, which is very important.

They get treated with blood thinners like Lovenox. But what we know is not the blood thinning capabilities of Lovenox which is seen to be the most important, but many other properties of Lovenox has meaning. A lot of these women get the right treatment for the wrong reason. So I get these emails all the time, should I check my MTHFR, the answer is yes, but along with everything else. So don't just look at two things because it's unlikely that it's the only single contributor, it is all you look at. You're likely not going to be successful unless, like I said, you get the right treatment for the wrong reason, which does happen. A lot of patients that you end up taking Lovenox for prothrombin gene, but they really had antibodies for something else unusual, it was being treated. You need to get the full workup.

Shweta: Sure. The other one says, what advice would you have for a patient with a history of chemical pregnancy losses. Two of which were with genetically normal embryos.

Dr Jeffrey Braverman: Right. And that's my same issue. You want to rule out this correctable recurrent aneuploid conversion syndrome, because there's two reasons why there would be a loss that the embryo converted to abnormal or they were immune issues that rejected the embryo. Remember, the immune issues make cause both problems. The immune issues may cause damage to the egg leading to what we call cracks, or the immune issues may have led to loss of tolerance for what could have been a perfectly normal embryo. So the same immunity causes both problems. So you don't know what somebody just calls me up and says, I get this of course, all the time, I'm failing transfer PGS normal embryos. I'm getting chemical pregnancies. I have to work them up and many times the issues of both their embryo quality and immune issues. So you have to treat the munitions and hopefully you then correct both at the same time.

Shweta: Okay. I have just a couple more. I'm taking a couple more minutes of your time to end in the hour. The person who has written the question, I'm diagnosed infertile due to salpingitis isthima nodosa. Can I conceive baby naturally after treated infection and my right Fallopian tube is open she says.

Dr Jeffrey Braverman: Okay. That's a very difficult question because again, when she says she's infertile, I need to know why, there's a lot of the history needs to be known. But let's just take the infection process. It's not just the tube being open, that's the issue, but if the tube itself gets damaged, it can be open and it may not be functioning properly. The cilia that are here like projections that move the egg down the tube may not be functioning properly and so there's not enough information there to answer the question because I have to know the whole history. Again are there any other factors for infertility here, but just dealing with tubal infection, just the tubing opened doesn't guarantee the tube is going to work properly.

Shweta: Okay. The next question is, I have severe allergies, endometriosis, ovarian cysts, TMJ and Hashimoto's thyroid and I'm also anaemic. My immune system is in hyper mode. Is there any day I can carry a baby full term?

Dr Jeffrey Braverman: Yeah, absolutely. I don't know what they mean by immune system in a hyper mode. That sounded like a layman's terms. So that kind of a scary herself probably. It's very common in women with endometriosis to have allergies, we know that endometriosis has higher activation of mast cells that make IgE. I look at these levels in all my endometriosis patients and we commonly see this so that doesn't surprise me. Hashimoto's, has a very strong genetic link, endometriosis I see Hashimoto's in endometriosis linked all the time. Hashimoto's by itself may not be the major issue, just it's the linkage to the inflammatory disorder and we didn't talk a lot about endometriosis, and my thinking that the answer relates to fertility, but it's likely that thyroid disease is a trigger to inflammation in the peritoneal cavity and is that inflammation is susceptible women that triggers the endometriosis, but it may be the trigger of the inflammation and these usually due to activation of macrophages that may be the primary problem in infertility and not necessarily the endometriosis that's a result of that. So, that's a very big question. She has a lot of issues. Some are like that. Needs a complete workup and needs to be managed meticulously. I don't think anybody outside of my center is going to manage that perfectly.

Shweta: Sure. Well, thank you so much for all the answers you've given us today Dr Braverman and thank you so much for finding out time on your busy schedule to be with us today. It was really a very informative session. Of all the statements that you said, this one statement that every case is solvable, this is going to give a great deal of hope to all the people who are suffering from miscarriages. So thank you so much for that thing. And Annie, Davina, Danae thank you so much. Thanks so much for accepting my invitation to join this panel and thank you so much for your insightful questions. Audience, I thank you for your support and we look forward to having you all join us on our upcoming Cure Talks docs and you can check our lineup of our talks on curetalks.com and the link for today's talk will be sent in via email to all the participants. So until the next show. Thank you everyone and have a great day.