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Parallels Between Kidney Transplantation and Maternal Anti-Fetal Rejection

Announcer:
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Dr. Shulman:
What do kidney transplantation and maternal anti-fetal rejection have in common? On the surface, these may look like 2 very different issues, but in this podcast, 2 experts will shed light on why it's beneficial to see the parallels between these seemingly disparate complications.

This is CME on ReachMD, and I'm Dr. Lee Shulman. I'm delighted today to be joined by 2 esteemed colleagues, Dr. Alexandra Benachi and Dr. Julien Zuber, who will help explore these connections.

Dr. Benachi:
Hello. I'm Alexandra Benachi. I am a professor of obstetrics and gynecology at Paris-Saclay University. I'm a maternal-fetal medicine specialist with a specific interest in fetal medicine and rare maternal diseases.

Dr. Zuber:
Hi. I'm Julien Zuber. I'm a transplant nephrologist and professor of clinical immunology at Paris Cité University.

Dr. Shulman:
Well, I want to welcome you both to today's podcast. So let's just get started. Dr. Benachi, let's get into it, or as you would say, allons-y. Please tell us about your views on these matters that have started to shift.

Dr. Benachi:
So, actually, it all started because we were sitting next to each other with Julien in a nephrology meeting. I received a text message from a patient asking whether I had received the results of her pathological examination of the placenta from her last pregnancy, which unfortunately ended with a fetal demise. So I looked at Julien, and asked him if, as an immunologist, he has ever heard of chronic histiocytic intervillositis, and it all started from there. This cross-disciplinary discussion prompted us to address the hypothesis that chronic histiocytic intervillositis – which I will call CHI for the rest of the talk, if you don't mind – could be the manifestation of antibody-mediated rejection of the placenta.

So, CHI is a rare condition and is defined by marked intervillous CD68+ histiocyte infiltration and fibrin deposition. CHI is associated with severe obstetrical complication, including fetal growth restriction, intrauterine fetal demise, or recurrent miscarriages. The recurrent rate is reported to be really high, ranging from nearly 70% to 100%. The cause is actually unknown, and there seems to be a correlation between the placental infiltration by the monocytes and the severity of the disease, ie, intrauterine fetal death or intrauterine growth restriction for the less severe cases, and there is absolutely no efficient treatment available published today.

Notably, recurrent CHI most frequently occurs after a normal, end-term pregnancy, so we propose that the first pregnancy serves as a sensitization event, when the mother acquired the antibodies against paternally inherited antigens.

Dr. Zuber:
I think we should, however, acknowledge that the parallel between transplant and pregnancy immunology has been a long-standing controversy. Two main arguments were put forward against these comparisons. First, the placental surface – and I should say, at least in its physiological condition – does not express polymorphic HLA antigens, which are the main drivers of the rejection process in transplantation. And so when the immune cells involved in antigen-specific recognition, that means the T and B cells are either excluded from the placental interface or tolerized during normal pregnancy. Hence, to convince the community, we really aim to provide a robust demonstration, and to this end, we applied the 3 diagnostic criteria of antibody-mediated rejections, used in the international Banff Classification for allograft pathology, to pregnancy settings.

And this encompasses 3 main features: the presence of high-level, fetus-specific anti-HLA antibody, evidence for antibody-induced complement activation at the surface of the fetal trophoblasts, and recruitment of inflammatory cells, primarily CD68+ microphages. But at last but not least, we showed that in inflammatory settings, the villous trophoblasts express the polymorphic HLA antigens, which are precisely targeted by fetal-specific antibodies.

Dr. Shulman:
Well, I must say that this is an incredibly fascinating concept, because on the surface, as you mentioned these are 2 completely separate, different cellular processes, but because of the effect of inflammation, we, in fact, do see a considerable similarity in the pathophysiology between the fetal newborn alloimmune disorders and organ rejection.

Alexandra, let's explore this further. Why is it beneficial to look at these topics in this new way?

Dr. Benachi:
We are talking about women, couples who have gone through very traumatic and devastating experiences of fetal losses, sometimes repeatedly. So there is often a feeling of guilt, a sense of injustice, and always a profound distress fueled by the lack of understanding and the uncertainty of the future for those women.

So I'm really convinced that providing them mechanistic insights and explanation will help them cope with the trauma. Naming the problem is always a relief, even before any discussion about the therapeutic option will follow – we hope.

However, we do realize that touching on immune compatibility within a couple is a very sensitive topic that we must address carefully and tactfully. So far, the women with recurrent CHI are offered a combination of various drugs, including immunotherapy such as anti-TNF alpha, which are not devoid of side effects. Bottom line, empirical therapies have not changed the outcome of CHI significantly, and they remain very poor. We anticipate that these new insights will lay the groundwork for highly targeted therapies.

We also believe that the role of harmful alloimmune responses goes beyond the scope of CHI, and there are numbers of other chronic inflammatory placental conditions for which clues accumulate to support the role of dysregulated alloimmune responses.

Dr. Shulman:
Julien, next, can you delve a little deeper into how the similar pathophysiology may influence the way we think about these 2 seemingly disparate conditions in terms of management? How can this outlook help us as we approach diagnosis, counseling patients, and current or even future treatment strategies?

Dr. Zuber:
Okay. Your question covers different topics. I think that first, in terms of predictive tools, the ability to quantify donor-specific antibody levels with Luminex technology has been a major stride forward to stratify the risk of rejection before transplantation. Thus, I feel it is reasonable to assume that the quantitative assessment of fetus-specific antibodies before pregnancy will similarly help individualize the risk of obstetrical complication and guide the therapeutic decision. Now, talking about treatments, increasingly powerful desensitization regimens that are meant to decrease the levels of anti-HLA antibodies, are currently optimizing transplantation. They combine plasma cells and B cells, targeted therapies, along with immunoadsorption or plasmapheresis. I doubt, however, that these strategies, with a potential iatrogenic risk, will be used in healthy women with CHI. Yet, I feel that the experience gained in transplantation could help to improve the therapeutics, including immunotherapies to mitigate the harmful effect of alloantibodies. And these include anti-inflammatory therapies, polyclonal immunoglobulins, complement blockade, and FcRn blocker, which will not only reduce antibody levels, but also prevent the transfer across the placenta.

Dr. Shulman:
You know, I must admit, I would have never believed that some of the well-known clinical assays used to assess transplantation

rejection would at any time be potentially useful in the assessment of fetal and neonatal autoimmune conditions. But both of you have presented just incredibly interesting and new information that I think we all need to take heed and get a better understanding of because we clearly have at hand a new approach to autoimmune disorders in the pregnant woman.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Lee Shulman, and here with me today are Dr. Julien Zuber and Dr. Alexandra Benachi. We are just about to transition our discussion to what the community obstetrician needs to know about how kidney transplantation can inform maternal anti-fetal rejection.

Well, Dr. Benachi, let's get back to basics and break this down further for our audience. How do you think this novel perspective will impact the community obstetrician's clinical practice?

Dr. Benachi:
Well, I definitely think that the alloimmune hypothesis could reshape our understanding of a significant number of obstetrical complications that are otherwise poorly understood and associated with fetal growth restriction and fetal demises, especially in the setting of sterile chronic inflammation of the placenta. So screening for fetal-specific antibodies should be performed from the mother's serum once HLA typing has been obtained from both parents and from the offspring. However, it is worth keeping in mind that child-specific anti-HLA antibodies frequently occur following pregnancies, but at a lower level than the one we found in the patient with CHI.

Dr. Zuber:
In this respect, there is a tremendous interest in understanding why, following a healthy pregnancy, a small subset of women develop high-level, child-specific, anti-HLA antibodies that could jeopardize subsequent pregnancies. It might result from a breach in the placental barrier during the first or the sensitizing pregnancy and with the release of fetal blood cells into maternal circulation.

Alternatively, but not exclusively, there might be high HLA disparities between the mother and the father or even maternal predisposition to mount an excessive antibody response. So all these leads need to be investigated in further studies.

Dr. Shulman:
I think it's important for our audience to understand that this breakthrough in our understanding of the pathophysiology of these autoimmune conditions, while at least at the present time will have implications for only a small number of women, our better understanding of this process is going to likely lead to better outcomes for an even larger number of women who not only suffer from unexplained conditions leading to adverse outcomes, but even those women who are going through routine pregnancies and having ostensibly good outcomes, our better understanding is going to potentially improve the outcomes of pregnancies across the board of all risk groups.

So finally, what do each of you want to be sure our audience remembers from our discussions today?

Dr. Benachi:
I would say that in case of recurrent pregnancy loss, pathological examination of the placenta is paramount. Looking for those infiltration of CD68+ cells, and when there is a feature of CHI, when they are highly suggestive on antibody-mediated rejection and should lead to screening for fetal-specific anti-HLA antibodies, because these new insights definitely pave the way for new therapeutic avenues.

Dr. Zuber:
Bottom line, bidirectional dialogue between the obstetrical and transplant communities will help unravel and delineate the scope of alloimmune-driven obstetrical disease.

Dr. Shulman:
A better understanding of the cellular mechanisms that lead to recurrent pregnancy loss or immunological conditions clearly will not only improve outcomes for that small subset of women who suffer through recurrent pregnancy loss, but ultimately will lead to advancements in diagnostics and therapeutics that are going to benefit all women who are seeking to become pregnant and expecting good outcomes from their pregnancies.

Unfortunately, that's all the time we have today, so I want to first thank our audience for listening in and thank you, Dr. Alexandra Benachi and Dr. Julien Zuber, for joining me and sharing all of your valuable insights. It was great speaking with both of you today.

Dr. Benachi:
Thank you very much. Good-bye.

Dr. Zuber:
Thank you very much for this opportunity to share our work and for the stimulating discussion.

Announcer:

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