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Why Are the Fetus and Placenta Not Rejected by the Mother? New Insights Into Maternal Anti-Fetal Rejection

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Why Are the Fetus and Placenta Not Rejected by the Mother? New Insights Into Maternal Anti-Fetal Rejection” is provided by Omnia Education.

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Dr. Shulman:
The founder of the field of reproductive immunology, Sir Peter Medawar, posed the essential question: How does the pregnant mother contrive to nourish within itself, for many weeks or months, a fetus that is antigenically foreign body? In other words, why are the fetus and placenta not rejected?

This is CME on ReachMD, and I'm Dr. Lee Shulman. I am delighted to be joined today by the renowned international expert Dr. Roberto Romero, who will break down how this concept of maternal anti-fetal rejection is the mainstay of how a pregnancy is maintained. Dr. Romero, welcome to the program.

Dr. Romero:
Thank you, Lee. I am Chief of the Perinatology Research Branch, or NICHD/NIH, and I have worked in the field of maternal anti-fetal rejection for some time.

Dr. Shulman:
Let's get right to it. Let's start, Dr. Romero, with our first question. Could you remind us of what alloimmunization is and what pregnancy complications are due to alloimmunization?

Dr. Romero:
Dr. Shulman, alloimmunization is an immune response to non-self antigens, over a genetically distinct organism of the same species, which may lead to tissue injury. In the case of Rh disease, an Rh-negative pregnant mother is exposed to non-self antigens, which are Rh-positive red blood cells of her fetus. She generates an immune response in the form of circulating antibodies, which cross the placenta and cause destruction of the red blood cells, causing anemia.

In this podcast series, we have discussed alloimmunization causing red blood cell or hemolytic disease of the newborn, alloimmune thrombocytopenia, and alloimmune neutropenia. However, it is now clear that there are some cases of newborn renal failure and liver failure that can be due to maternal alloimmunization. The reason why we included this subject in this series is because I believe that maternal anti-fetal rejection is a mechanism of disease for many pregnancy complications.

Dr. Shulman:
So in that regard, the concept of alloimmunization, can we say that the fetus and placenta are considered to be transplants?

Dr. Romero:
Yes, the fetus and placenta are transplants. So the fetus is a semi-allograft, the placenta is a fetal organ, and therefore, both are a special type of transplant or semi-allograft.

Dr. Shulman:
So in that concept, obviously you've stated this in a more forthright manner, why are the fetus and placenta not rejected in most cases of pregnancy?

Dr. Romero:
So the mother does not reject the placenta and fetus under normal circumstances because [of] immunological tolerance, a term that is defined as a durable state of antigen-specific unresponsiveness.

Now, the mechanisms that are responsible for maternal fetal tolerance are complex, and I'm just going to highlight 3. First is a separation of the maternal and the fetal circulation. When we transplant an organ, let's say a kidney, a heart, a lung, the transplanted organ is connected to the circulation of the donor. This does not happen in the case of the placenta. There is hemochorial placentation, but the fetal and the maternal circulation are separate.

The second innovation that allows or promotes tolerance is modification of the antigens expressed by trophoblasts at the surface of the placenta. Please remember that [in] the intervillous space, maternal blood is in direct contact with the villous tree.

The third adaptation is a modification of the maternal immune response during pregnancy. And this is accomplished largely through 2 mechanisms. First, the action of T regulatory cells that are called immunosuppressor cells, which are key in achieving tolerance to paternal antigens. The other mechanism that is responsible for tolerance in terms of the maternal immune response is production of some cytokines that suppress an immune response. An example of these is IL-10.

Dr. Shulman:
Dr. Romero, given that elegant description, why do you think that maternal anti-fetal rejection is thus a mechanism of disease in pregnancy?

Dr. Romero:
In contrast to other disciplines in medicine, for example, genetics, in which there are thousands of conditions, the main complications of pregnancy are really 5: preterm labor, premature rupture of membranes, fetal growth restriction, preeclampsia, and fetal death. For example, premature labor is often caused by infection. But there are many cases of premature labor that are not due to infection.

What are the other mechanisms of disease involved in preterm labor, preeclampsia, fetal deaths, etc.? We have found that a subset of patients with these diagnoses have chronic inflammatory lesions of the placenta. And the term chronic inflammatory lesion of the placenta is employed to describe that parts of the placenta are infiltrated by maternal lymphocytes or macrophages. Now, these are the same lesions that are observed during the rejection of transplanted organs. In pregnancy, we have the largest human biopsy, the placenta. And we have circumstances in which, in the placenta, we find these inflammatory lesions, chronic inflammatory lesions, and then some degree [of] organ dysfunction, such as rupture of membranes, fetal growth restriction, and in extreme cases, fetal death.

Dr. Shulman:
Given those mechanisms, what's the pathophysiology of antibody-mediated maternal anti-fetal rejection?

Dr. Romero:
Transplant immunologists classify rejection into 2 broad categories. Cellular rejection, in which there is infiltration of lymphocytes or macrophages in the transplanted organ, or antibody-mediated rejection. And this antibody-mediated rejection is very important.

First, the fetus and the mother have an incompatible genotype for major histocompatibility antigens, in this case, HLA [human leukocyte antigens]. Second, the mother is exposed to the incompatible fetal antigens, either in a prior pregnancy or in the current pregnancy. And this can happen because fetal white blood cells are known to cross the placenta to the mother, even in the course of normal pregnancy. Third, the mother becomes sensitized to fetal antigens and develops antibodies, which, if they are IgG [immunoglobulin G], can cross the placenta. Fourth, antibodies against paternal HLA antigens cause tissue damage often through the activation of complement, and then these can be detected by observing placental lesions which are chronic inflammation, which I will discuss in a moment.

Dr. Shulman:
So what are the placental lesions that occur in such cases that are in fact suggestive of maternal anti-fetal rejection?

Dr. Romero:
The placental lesions observed in cases of maternal anti-fetal rejection are located in the anatomical sites of interaction between the

mother and the fetus. And fundamentally, there are 3 sites.

First is the intervillous space, which is the large surface of interaction between the mother and the fetus. The second interface is the one provided by the chorioamniotic membranes and the decidua. The decidua is secretory endometrium that contains maternal immune cells; the chorion and the amnion are fetal tissues—part of the graft. And the third is the basal plate of the placenta. That, when one delivers the placenta, is what covers what is visible in the maternal surface.

In a previous video podcast, Dr. Benachi and Dr. Zuber discussed intervillositis, and there is another lesion called perivillous fibrin deposition that affects the villous tree. But the 3 main categories of lesions are the ones that I just cited.

Dr. Shulman:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Lee Shulman, and here with me today is Dr. Roberto Romero. We're just about to delve deeper into maternal anti-fetal rejection, and what the community clinician needs to know about the latest advances in the pathophysiology, diagnosis, and treatment of alloimmunization disorders.

What laboratory tests can we as clinicians use to diagnose maternal anti-fetal rejection?

Dr. Romero:
So the tests that can be performed to diagnose maternal anti-fetal rejection are really readily available because they are used in clinical transplantation every day.

The first test is to detect whether the mother is sensitized with HLA antigens, in other words, whether the mother has circulating antibodies against HLA. And there is a test that is used in clinical transplantation that we call HLA PRA. The PRA stands for panel-reactive antibodies.

The second step, just like we do with red blood cells, is if the Coombs is positive for red blood cells, there are some antigens that cause hemolytic disease and others which do not. So, we need to know what is the type of antigen. Remember, Rh causes alloimmunization and fetal anemia, but Lewis [antigen] doesn't. So we need to go through the same exercise. So the second step is identification of the specific antibody that has resulted in an HLA PRA positivity. The third step, once we know the identity [of the] antibody, is genotyping the fetus to determine whether the fetus in the index pregnancy carries the antibody. The fourth step is to look at the placenta and see if there are lesions of maternal antibody. If you have done that, then the next step is to detect [if] there is complement activation. But once these criteria are met, we say that there is evidence of maternal anti-fetal rejection.

Dr. Shulman:
Recently, there has been advancements in the noninvasive prenatal testing or screening arena that has potentially allowed for the detection of fetal genotype with a maternal blood draw. And while there is still the need for better validation studies, this may in fact be able to provide important information for managing pregnancies at risk for these alloimmunization problems without the need for a diagnostic test, an invasive test, that could in fact lead to adverse outcomes in and of themselves.

Dr. Romero, now that you've elegantly described the pathophysiology, the diagnosis, let's speak briefly about the management. Once you've made a diagnosis of this, what therapeutic options are there for the maternal-fetal specialist or even the community-based obstetrician?

Dr. Romero:
Dr. Shulman, this is a new area in maternal-fetal medicine. At present, there are not well-established means of treating maternal anti-fetal rejection. One of the options to consider is the administration of high-dose immunoglobulin because this has been used as a strategy in autoimmune diseases, including in alloimmune diseases during pregnancy [for] the patient who is highly sensitized and has recurrent pregnancy losses.

Now, in the horizon, one of the frontiers is the administration of monoclonal antibodies that can block the FC receptor that is responsible for the transfer of immunoglobulin from the mother to the fetus. So antibody-mediated maternal anti-fetal rejection has a hope that if these antibodies become clinically available and effective, then there may be an opportunity to treat maternal anti-fetal rejection for the first time.

Currently, the focus of these monoclonal antibodies is Rh disease or hemolytic disease in the newborn. But please consider that this is a rare disease compared to maternal anti-fetal rejection that is an etiologic factor in fetal growth restriction, premature labor, preeclampsia, and fetal death. So when we think of this therapeutic strategy, the field is conducting trials to prevent or ameliorate sensitization in patients at risk for hemolytic disease of the newborn. But an exciting prospect is that this approach, if successful and safe, can help the patient with maternal anti-fetal rejection. So I envision in the future, that just as we screen for red blood cell maternal alloimmunization, we will be able to screen at the beginning of pregnancy or during pregnancy for the presence of antibodies against

HLA and then monitor the person who may be at risk for maternal anti-fetal rejection and offer therapy.

Dr. Shulman:
Unfortunately, that's all the time we have today. So I want to thank our audience for listening in. And thank you, Dr. Romero, for joining me and sharing all of your valuable insights. This was an incredibly special time for myself and for our audience. It was great speaking with you today, and I thank you so much for joining us today on this podcast.

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