PEDIAPOD MARCH 2022 TRANSCRIPT

Geoff Marsh
Hello and welcome back to Pediapod for March 2022. This month we're investigating the fetal immune response to maternal SARS-CoV-2 infection.

Thousands of women have been infected with SARS-CoV-2 during the COVID-19 pandemic. Whilst very few of these infections have been shown to transmit vertically from mother to offspring, it remains unclear what effect a mother's SARS-CoV-2 infection has on fetal development. This is a concern because maternal immune activation can have long term consequences for their newborns, including abnormal brain and immune development, as is seen with other types of infections. In this episode, we meet Brian Kalish from the University of Toronto and the Hospital for Sick Children. He set up a study, along with his colleagues, to assess the potential impact of SARS-CoV-2 infection during pregnancy on the fetus by characterizing the composition and cell type-specific translational landscape of umbilical cord blood mononuclear cells. Here's Brian…

Brian Kalish
I'm originally from Chicago, Illinois. I attended college at Johns Hopkins University, followed by medical school at Harvard Medical School in Boston. I completed my pediatrics training as well as my training in neonatal-perinatal medicine at Boston Children's Hospital and in the Harvard program in neonatology. And then I was on faculty there at Boston Children's Hospital in neonatology, prior to being recruited here to the Hospital for Sick Children, as a staff neonatologist and as a neuroscientist. So my scientific training is in neuroscience and I have extensive experience with single-cell genomics, which is pertinent to this particular research study. But one of my scientific interests is in trying to understand how early-life experience, particularly stressors during pregnancy, can affect fetal brain development

Geoff Marsh
Have there been robust links documented between maternal infections and poor outcomes?

Brian Kalish
I wouldn't want to make large claims about what the impact of a COVID-19 infection during pregnancy has on offspring because we just simply haven't had enough time to follow those cohorts of children long-term and ascertain what, if any, effects there might be. But I think importantly, when you look historically at either prior pandemics or significant waves of infection that have occurred, including influenza pandemics, it's been noted that severe infection during pregnancy has been associated with neuropsychiatric disease in the offspring long-term. And that's been found with a variety of different infections- viral, bacterial, parasitic. So I think there's reason to believe that risk could exist with COVID-19. But again, the evidence just isn't there to know definitively.

Geoff Marsh

Pregnancy itself is already a very tight immunological balance to be had when a mother's immune system is thrown out of whack by something like COVID-19? What's the worry?

Brian Kalish
Yeah, so you're exactly right, Geoff, that pregnancy is this beautiful, delicate immune balance and there are shifts in the immune system, both systemically and at a local placental level that occur throughout pregnancy in order to maintain both maternal and fetal well being. Certainly other investigators have described widely the impact of COVID-19 infection on pregnant women, showing that there's an increased risk of severe disease and complications in pregnant women in particular, who may not have other risk factors for severe illness. And others have also suggested that there may be increased risk of preterm birth associated with severe COVID-19 infection. I think the data on that has been a bit conflicting but certainly we have observed, anecdotally, that especially in women who have had severe infections and are hospitalized in the ICU, sometimes the consequence is the need to deliver the child quite early. But really, the motivation behind this study was thinking potentially more about the long term- is there the potential to program fetal development long-term? Obviously, we didn't have the ability to look at that in this particular study. But I think our study provides a hint that there are changes in the fetal immune system that can occur when the mother is infected with COVID-19.

Geoff Marsh
For anyone who hasn't seen this sort of study before, how do you get at questions about fetal immune development?

Brian Kalish
So in this study, we looked at pregnancies that were complicated by COVID-19 infection versus those that were not. We collected umbilical cord blood from those pregnancies and we isolated mononuclear cells from the umbilical cord blood and then subjected them to single-cell genomics. And in doing so, we were able to discern the cell type-specific immune response. So, pinpointing how gene expression in different cell types in the immune system may be changing in response to COVID-19 infection.

Geoff Marsh
So you compared the gene expression between different sets of immune cells from your controls and those of children from mothers who had had an infection. What were the standout cells that had clear differences in their gene expression?

Brian Kalish
So broadly speaking, we noticed a profound interferon-stimulated gene response across several different immune cell types. And interferon is an important cytokine for viral-related immunity and the response to viral infection. So I think that, in and of itself, is quite interesting. Because obviously, in a perfect world, the fetus would be completely protected from these maternal perturbations, but clearly, even when there's not direct infection of the fetus, the fetus is able to seize, ‘quote unquote’, this inflammatory response and viral infection in the mother, and is mounting this interferon-stimulated gene response. This was particularly notable in a particular type of immune cell called the monocytes, so across several different types of monocytes we noted this interferon-stimulated gene response. So I

think that was the most profound change that was noted. But we noticed other immune changes in a variety of other cell types, including T cells, and B cells.

Geoff Marsh
Before we move on to the changes in T cells and B cells, do you have an understanding of how that interferon action would have come about? Are those cytokines coming from the mother or are they coming from the fetus in response to other circulating compounds?

Brian Kalish
That's a great question, Geoff. And that's something that still needs to be resolved. The most likely answer is that in the setting of COVID-19 infection, there is some weakening of the placental barrier function meaning that the placenta can become a bit leaky in the context of this inflammatory response. And when it becomes leaky, molecules in the mom's blood may leak into the fetal circulation at an increased rate. So I think it's most likely that there's some sort of microscopic leakiness, so to speak, of the placental barrier, leading to some fetal exposure to this maternal infection and inflammation. The alternative is, as you said, that there's some passage of cytokines directly from the mother to the fetus, for instance, interferon or other inflammatory cytokines like IL-6, but I think that hasn't been shown definitively and the human studies on that context are a bit conflicting. And the reason I think all this is important is that I've studied this phenomenon in mice quite extensively- looking at maternal infection and inflammation and its impact on the fetus and particularly the fetal brain. There are specific cytokines that are associated with an impact on the fetal brain and many of those cytokines are also dysregulated in COVID-19 infection. So I think there's some biologic plausibility there about how infection during pregnancy could theoretically affect fetal neurodevelopment.

Geoff Marsh
You mentioned there are also differences in B cells and T cells.

Brian Kalish
Sure. One of the other things that we did as part of this study, in addition to sequencing the RNA of each individual cell, we also to sequence the T cell receptor which is an important component of the adaptive immune response. And we saw that in those fetuses born to mothers that had COVID-19 during pregnancy, there was an expansion in their T cell receptor repertoire. That phenomenon has also been observed in adults with COVID-19 infection, again suggesting that this response in the fetus parallels what might be seen in an adult or an individual who might have a primary infection.

Geoff Marsh
You described this study as an exploratory- you had small numbers of patients- even so, do you think that the differences in the immune responses between the two groups tells you anything about the impact that these changes were having on those newborns?

Brian Kalish
I think even with the small cohort there was a clear distinction between the cases and controls and quite a robust and profound change in gene expression across multiple different immune cell types.

And all of the women in the study who had COVID-19 had mild to moderate COVID-19 infection. So this was not even severe infection to the level where women are intubated and receiving mechanical ventilation in the ICU. Moreover, all of the infants after they were born, tested negative for COVID-19 and were otherwise well. So I would say that, if anything, the cohort that was described here is a relatively mild, moderate cohort with very little morbidity or consequences in the short-term for the infants, thankfully. But I think what's become apparent in subsequent waves of COVID-19 is that there are much more extreme situations where the mothers are critically ill and in some circumstances where the neonates or the infants are also infected with COVID-19 and can become quite ill. So we didn't study those situations but I think our description of the immune response was probably just the tip of the iceberg and that if we looked in some of these more extreme cases that have since arisen, I'd imagine the immune changes to be even more profound. The individual who is the first author on this study, Dr. Juan Matute is a neonatologist at Massachusetts General Hospital in Boston, they have collected a large cohort of biospecimens from pregnant women and offspring who have been exposed to COVID-19. So there's many ongoing studies using a larger cohort of samples to further tease out the trajectory of these immune changes and to try to look at the association with subsequent outcomes. My work also as a laboratory based neuroscientist is modeling this phenomenon in mice and other model organisms to try and get at the molecular mechanisms and potential treatments or interventions to try to protect the fetal brain in these situations.