Responses to Participants' Questions

The overarching goal of the RECOVER Research Review (R3) Seminars is to catalyze a shared understanding of the research being conducted by the scientific stakeholder community within the RECOVER Consortium. The R3 Seminars and the Q&As typically feature highly scientific material intended for researchers and clinicians. For other audiences interested in these topics, a link to the National Library of Medicine's MedlinePlus medical dictionary is provided at the end of the Q&As as a resource to help in understanding the scientific terminology.

This document provides responses (edited for clarity) to questions raised by seminar participants related to the following presentations at the R3 Seminar *Long COVID After SARS-CoV-2 Infection During Pregnancy* held on June 10, 2025 (videos for this and previous seminars are available from the Seminar Series page on the RECOVER website):

- ***Overview of the Research***

  Valerie Flaherman, MD, MPH
- ***Post-Acute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) After Infection During Pregnancy***

  Torri Metz, MD, MS
- ***Long COVID After SARS-CoV-2 During Pregnancy***

  Chengxi Zang, PhD
- ***Discussant: Valerie Flaherman, MD, MPH***

All Presenters: Questions and Responses

Q. When you think about the development of Long COVID following SARS-CoV-2 infection during pregnancy, are there other conditions that either are more likely or less likely to develop during pregnancy that might provide parallels or insights to the process by which Long COVID is impacted by pregnancy?

Response:

Dr. Metz: We think a little bit more about what pregnancy does to existing conditions, rather than whether they are more or less likely to develop in pregnancy. It's not as much about newly emerging conditions typically in pregnancy, but certainly pregnancy does have an effect on people's existing medical conditions, and sometimes

those are diagnosed in pregnancy since patients may not have otherwise sought care for them outside of pregnancy.

The main things that we consider are immunologic disorders. So, we do see that with people who have conditions such as rheumatoid arthritis or inflammatory bowel disease or lupus, a lot of times their disease process is a little bit more quiescent or well controlled during pregnancy. We think that's because of the changes that happen to immune function in pregnancy, and that pregnant patients do have a little bit more immune tolerance during pregnancy because they have to tolerate this fetus that has DNA that's different from theirs.

These immune system changes also trickle down to changing immune function overall, which is why pregnant people tend to get sicker when they get viruses, but that does make it so that there's not so much inflammation happening that can affect some of those other disease processes. We certainly think about how pregnancy affects other systems as well. From a cardiac standpoint, we know that sometimes cardiac function can worsen during pregnancy, and that's because there's a lot more stress on the heart and cardiac system during pregnancy, as expansion of blood volume leads to more cardiac work. Certainly we do see pregnancy affecting other illnesses. We don't really know how pregnancy affects Long COVID and how Long COVID affects pregnancy, which we could talk about some more, but that's what a lot of this planned investigation concerns.

Q. How might Long COVID prevalence differ by trimester, and why we would be seeing differences?

Responses:

Dr. Zang: I have no answer to that yet from the clinical and mechanism interpretations here. However, from a data science perspective, and first of all, thanks to the data set, we just stratified the patients by infection during different trimesters, which enables more hypothesis generation. So, we will try to find how infection during different trimesters and its impact on Long COVID is different. From the electronic health record (EHR) cohort, we see they are different. However, why are they different? How to provide care to those infected during different trimesters requires follow-up studies. Right now there are a lot of big question marks, and this requires further investigations.

Dr. Metz: One explanation that we had for timing differences as we were looking at these data initially was that perhaps when we're looking at SARS-CoV-2 infection in the first and second trimester, and then evaluating subsequent Long COVID, that a lot of the participants who had SARS-CoV-2 in the first and second trimester were still pregnant or in the early postpartum period when we assessed for Long COVID.

And we know that a lot of the symptomatology overlaps between the pregnant or postpartum state and Long COVID. We see increased risk of arrhythmias in pregnancy, venous thromboembolism (VTE) in pregnancy, brain fog in pregnancy, all of these things. And we also see more interaction with the healthcare system in pregnancy. So,

patients are seen in the latter part of pregnancy every single week, and so it's a high intensity, high access time for healthcare. We wondered if we were seeing some masking of the differences in pregnancy, because we're seeing a lot of the symptoms we see with Long COVID when people are still pregnant, we're seeing them all the time, and then those sort of dissipate over time as we get further out. So, for the people who had a third-trimester infection then we're evaluating them 6 months later, we are evaluating them more remotely from pregnancy which may be a more accurate assessment of their Long COVID symptoms.

But we don't know. As Dr. Zang said, these are all just hypotheses that I think are going to require more work to delve further into, but that was, as clinicians, what we thought about when we saw those results.

Q. Is there any data on postpartum outcomes and experiences after Long COVID during pregnancy? So, when Long COVID occurs in pregnancy, how might that affect the postpartum course?

Responses:

Dr. Metz: We're actually looking at that right now in both the EHR cohort and the observational cohort. I think this is a question that's of really high interest to the Long COVID community. I've had a lot of people ask me about this and I've seen patients who come to see me to ask me about this. "If I have a diagnosis of Long COVID, how is that going to affect my pregnancy outcomes and what do we expect in terms of pregnancy outcomes?" We just really need information on this. We don't have it now.

And I think that what has really motivated the investigators in RECOVER to examine this question is really the patient representatives and Long COVID community coming to us and asking for this information. And so, we are moving forward with an examination of this research question in the observational cohort, and we're also collaborating with the EHR cohort and trying to look at pregnancy outcomes among the patients who have a diagnostic code for Long COVID prior to the pregnancy. We are hoping to be able to provide information really soon related to that question.

Dr. Zang: To add one more comment, this seminar is more focused on how pregnancy impacts Long COVID, right? Just as mentioned by Dr. Metz, and our ongoing efforts to study vice versa, how Long COVID impacts the pregnancy outcome, is this leading to healthy deliveries or not? So, we are working on that.

Q. Have there been pathology findings in placentas that correlate to Long COVID, and is there any correlation between maternal vascular malperfusion and the development of Long COVID?

Response:

Dr. Metz: That's a great question. We know that there are placental findings with SARS-CoV-2, and this really came up mostly with the Delta variant. The Delta variant of SARS-CoV-2 was particularly damaging to placentas, and basically created a pattern of placental insufficiency and we saw much higher risks of stillbirth during that particular time period with that variant.

We don't know why that particular variant had those effects, but definitely that was demonstrated across several cohorts and demonstrated that there was placental damage that resulted in placental insufficiency. To my knowledge, nobody has looked at that in terms of the development of Long COVID and whether that propensity for placental damage would also result in propensity for other vascular damage that could lead to sequelae and Long COVID.

I have not seen anybody examine that. Unfortunately in RECOVER we do not have placental pathology data. It is something that investigators have definitely talked about. There's an interest in it, there's a potential that some existing specimens could still be assessed related to the placenta, but right now that's not part of the RECOVER protocol.

Q. We've received a few questions from the audience about vaccination status and if this is protective against Long COVID for pregnant individuals. Dr. Zang, you mentioned data was a bit limited to have any confident conclusions, and Dr. Metz, you found results that were not statistically significant. Could you comment on your reaction to that, if that is at all surprising, or if it differs at all with what we would expect for nonpregnant populations?

Response:

Dr. Metz: That's certainly a hot topic currently. I think that in our data we did show that the direction was towards protection, meaning that among people who had been vaccinated before, the direction was towards having some protection against the development of Long COVID. We just didn't have a large enough sample size to be able to say that definitively, and our relatively small sample size resulted in wide enough confidence intervals around that estimate that it crossed 1, which says that we can't say that the result was statistically significant. But I wouldn't say our results are in opposition to other results. I think probably we just had not a large enough sample size to really look at that robustly.

In the pregnant population, we know that vaccination is safe and effective. It's a strategy that we've been using, honestly, for decades, both for protection of the mother as well as antibody transfer to the neonate, at a time when neonates are particularly vulnerable, prior to the time that they can receive any vaccinations themselves. It really offers them protection in those first couple of months of life, even up to 6 months some of the studies would demonstrate.

So, I think that broadly the American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine certainly support vaccination against COVID-19 in pregnancy, and the rationale for that is reduction in disease severity in a population that's known to be at increased risk for severe disease and death, as well as some neonatal protection.

I think our data would suggest that it's probably not different in pregnant populations from other populations in terms of vaccines being protective against Long COVID, but our population was a little bit limited and I think it's hard in the EHR cohort, because not all the vaccination data would necessarily been captured there. Specifically, it's tricky to capture patients who were vaccinated in other places outside of their centers with the EHR data.

Q. Did the analysis for the trimester effect take into account the patients who have reinfections?

Response:

Dr. Zang: That's a great question, and so in all our primary analysis, we just check their first-ever documented infection during pregnancy. And our colleagues, as far as I know, they find reinfection will increase the incidence of Long COVID in general populations, but if this is true for pregnant females and this specific population, we don't know. So, it's a great question and I think we can answer this through further investigations on this.

However, for this study, we didn't investigate this. We just checked their first-ever infection.

Q. Has the influence of multiple gestation on the risk of developing Long COVID been explored at all, or are there plans to explore this in the future?

Response:

Dr. Metz: We have not explored that at this point. Definitely twin pregnancies are at increased risk for pregnancy complications, but they also have all the physiologic changes of pregnancy magnified times two, and so it's this balance of are we going to see increased risk because of the increased risk of the pregnancy itself with the twin gestation? Or do we end up seeing even more protection, because you have an even larger physiologic response to the pregnancy?

I think that's all to be sorted out. I think that it's going to be helpful to have the results from the observational cohort data comparing pregnant to nonpregnant RECOVER participants. We do ask about multiple gestations, but honestly, typically in obstetric research, for better or worse, unless we're specifically focused on a multiple gestation population, we end up excluding them from a lot of analyses, just because they are such a different population and really do focus on the singletons.

I think we have a pretty low proportion of multiple gestations in the RECOVER cohort. We didn't exclude them, but it's only 2% to 3% of the population, so it just ends up being a small part of any cohort, unless you're really focusing on multiples. But there's not anybody who has actually looked at that specifically to my knowledge. It would be an interesting population in terms of looking at mechanism.

Q. It can be common for mothers to develop conditions that are implicated or similar to Long COVID, things such as postural orthostatic tachycardia syndrome (POTS). Do we know the reasons since from your research it sounds like pregnancy is slightly protective against Long COVID?

Response:

Dr. Metz: This gets a little bit into that question of why did we see the difference by trimester? It makes me wonder if some of these conditions that emerge are more affected during pregnancy. Potentially we're seeing that overlap still when we're looking at patients who are in late pregnancy and postpartum and then they get better, once they get out of that pregnancy and postpartum period. Whereas the people who acquired it in third trimester and then we're looking at it further out from pregnancy, that's why we hypothesize that we're narrowing that gap.

There are so many physiologic changes during pregnancy. POTS specifically tends to get worse in the 16- to 24-week period when we have patients with the lowest blood pressures that we're going to see, because of the pregnancy effects, the progesterone effects, and the dilation of the peripheral vasculature at that point. And so, we may still be seeing some more of those symptomatic patients in the pregnancy period, so then it looks like maybe it's not as protective, and then that pregnancy effect goes away and then maybe it looks a little more protective for other reasons, because there's not as much inflammatory response, or there's other things that are modulating that differentiation.

But this is all clinical knowledge and hypothesizing that is happening here. This is an area that definitely needs more work and it's great that RECOVER has invested in really focusing on this pregnancy population.

Q. Is it possible that the threshold to diagnose these conditions, including the nonspecific Long COVID, may be higher for pregnant individuals compared to nonpregnant individuals? And are there any biomarkers that could be used to help in this comparison?

Response:

Dr. Metz: I think that is definitely possible. I do think that patients who potentially have symptoms of Long COVID could be dismissed in pregnancy for sure. For example, if a patient said, "I feel tired all the time." Many clinicians

may say, "Yeah, you're pregnant." So, I can definitely see those types of symptoms requiring potentially a higher threshold for the diagnosis.

I think that one of the reasons that we wanted to publish this prevalence and risk factors paper was really to raise awareness of the fact that people could have Long COVID in pregnancy, and maybe it's that and not just normal pregnancy symptoms. It's always hard to sort that out. Pregnant people have nausea, they have gastrointestinal upset, they have reflux, they have fatigue, they have brain fog. I think it's a little bit hard to sort out whether these are normal pregnancy symptoms or something more, so it is possible that Long COVID was coded differentially less for them.

I think that is an excellent point and it is definitely something we've thought through. I think, on the flip side, they could end up with the diagnosis more, because they're in the healthcare system a lot more than people who potentially are at home not accessing the healthcare system. All of these data have these flaws and things to think about, and I appreciate you bringing that point up. Because it's definitely something to consider.

In terms of biomarkers, RECOVER has tried to look at standard laboratory values at least to see if there's a particular lab value phenotype, for lack of a better word, that would suggest that somebody had Long COVID. RECOVER investigators have examined what changes we see in more typical labs that we get in patients in the clinical setting for those with Long COVID, and is there something that would indicate perhaps that it's more likely that particular person has a diagnosis of Long COVID? And unfortunately, there wasn't really anything that panned out that could tell us this is the gold standard. We can't draw blood and say, "Yes, this is Long COVID." We don't have a tool like that now. I think as we continue to get more information about Long COVID and do some more detailed laboratory analyses and really look at omics and different kind of modeling, I'm hopeful that maybe we can get there so we can give people better characterization, but we don't have that capacity right now.

Q. How can we better protect pregnant people from COVID and other infections? Should healthcare settings adopt any stronger protections, and how can we help communicate the importance of these measures?

Response:

Dr. Metz: I think that's a clinical question so I will answer it. Vaccination definitely is what we talk about with our patients in pregnancy, as a very effective measure to prevent not only COVID-19, but flu, which is the other big one during respiratory virus season that we worry about in pregnant people. I tell my patients to exercise additional caution, certainly during that cold and flu season. I think we all used to be around a lot more people that were sick and we didn't worry about that, but now we recommend really trying to avoid that, and if you're in that setting, use masks to try to prevent the transmission of that infection.

Certainly really good hand hygiene, just going back to general infection prevention measures. Encouraging patients to wash their hands, especially if they've been out in a public place and touching a lot of surfaces, that's just important regardless of the virus. None of us enjoy being sick, but especially when you're at higher risk for complications of these viruses as you are in pregnancy. I think these measures to reduce the risk of infection are really important.

Q. Expecting moms might not be aware of their underlying conditions, as most young people don't see a doctor regularly. This may make them ineligible for COVID vaccination, which can limit their access to this important layer of protection against infection, therefore increasing their chances of developing Long COVID. For that reason, shouldn't we have vaccination recommendation for all pregnant people? What is your recommendation for pregnant people in preventing Long COVID?

Response:

Dr. Metz: The recommendation has been that pregnant people be vaccinated against COVID-19 and a number of other infections. Vaccination is safe and effective in pregnancy. Vaccination has been shown to reduce the risk of SARS-CoV-2 infection and the risk of adverse pregnancy outcomes—likely because it reduces the progression to severe disease. Recommendations for the upcoming fall virus season and vaccinations are developing. The Society for Maternal-Fetal Medicine and American College of Obstetricians and Gynecologists recommend COVID-19 vaccination during pregnancy.

Q. Did the study have data on the duration of persistent symptoms after pregnancy?

Response:

Dr. Metz: We have examined this in the adult cohort broadly but have not examined this separately in the pregnancy cohort. Pregnant participants are included in the adult analysis.

Q. Are there any findings about the neonates born to the women who had COVID-19/Long COVID?

Response:

Dr. Metz: We are studying the offspring of participants who had SARS-CoV-2 during pregnancy. This is another big and important part of the RECOVER pregnancy study. We will be submitting a manuscript examining neurodevelopmental outcomes in these children at 12 and 18 months of age soon.

Q. Have the father's genetic makeup and human leukocyte antigen (HLA) or past history of autoimmune disorders or similar been examined as potential risk factors for developing Long COVID in pregnancy?

Response:

Dr. Metz: This has not been examined. The fathers of the offspring enrolled in RECOVER are not enrolled as participants, so we do not have information on the paternal contributions.

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