

Responses to Participants' Questions

This document provides responses* to questions raised by webinar participants related to the following presentations:

- **Presentation 1: *COVID-19 and Gynecologic Health***
Vanessa Jacoby, MD, MAS
- **Presentation 2: *Does COVID Have a Long-term Impact on Male Reproduction and Sexual Health?***
Jim Hotaling, MD, MS, FECSM
- **Presentation 3: *Sex Differences in the Placental Response to Maternal SARS-CoV-2 Infection: Implications for Fetal Development and Antibody-Mediated Protection***
Andrea Edlow, MD, MSc
- **Discussant: Torri Metz, MD, MS**

* Responses may have been edited for clarity.

All Presenters: Questions and Responses

Q1. How can medical scientists reach out and find patients like me more effectively, especially in rural areas, and especially as apps/reporting are decreasing in usage post Roe?

Responses:

Dr. Jacoby: I know that following the SCOTUS decision in Dobbs v. Jackson Mississippi Health a lot of women have been more reluctant to join studies where they would report pregnancy or menstrual function for concerns, particularly in states where abortion is restricted or prohibited. I just want to encourage people by letting them know that their RECOVER study falls under the National Institutes of Health certificate of confidentiality, where your information is completely confidential. We're highly attuned to these concerns and we think it's very important for everyone to feel welcomed into the study. If you have questions about that, please reach out to RECOVER. We really want you to feel comfortable enrolling in the RECOVER study.

Q2. Are there any early results from the pregnancy RECOVER sites?

Responses:

Dr. Metz: Dr. Jacoby and I are the two Principal Investigators of the pregnancy cohort for RECOVER and we don't yet have any initial data to share. However, we're aware that everybody's very interested in that and everybody wants to move that forward quickly. I don't know if that question is related more to pregnancy or really these

longer-term neurodevelopmental effects, which is one of the reasons we asked Dr. Edlow to come and speak today.

The focus of the pregnancy cohort in terms of Long COVID with offspring is really what happens when offspring are exposed to SARS-CoV-2 in utero. How does that have long-term implications? That's really what the pregnancy cohort is looking at in offspring. And does that exposure result in long-term neurodevelopmental dysfunction or cardio-metabolic dysfunction? I think what Dr Evans's data show us is that we're going to be very careful when we start thinking about that and make sure that we're accounting for sex differences.

These data won't be available for at least 1 to 2 years, as we'll have to wait for these children that were exposed to COVID in utero to have the capacity to do some of the more complex neurodevelopmental testing that's required to examine this question. Currently, we're starting to have children who are reaching the 24-month age range. We're in our initial testing and the RECOVER initiative is in that 24-month age range, so we hope to be able to share that in the future.

Dr. Edlow: We had done some in silico work (research conducted or produced by means of computer modeling or computer simulation) to create the electronic health records-based cohort for the reasons that you noted. It's challenging with this very short turnaround to have enough directly observed data to feel confident that a small number of individuals or observations in the sample can truly reflect something. Consequently, we looked across 8 hospitals in New England within our larger hospital system and looked at more than 7,700 deliveries, including 222 where the mother had SARS-CoV-2 in pregnancy, which was verified by the PCR test at the time. We're going to have to develop new methods now that rapid antigen testing is so prevalent.

But we were able to do it because we confined our search to the initial 6-month period of COVID, and what we saw was a signal toward significantly increased neurodevelopmental diagnoses at age one in these children who were exposed to maternal SARS-CoV-2 in utero. This was sort of an ICD-10 code bundle of ICD-10 codes and all the charts that were flagged where the infants had a neurodevelopmental diagnosis. We hand reviewed each one and found these to be real diagnoses that mostly related to delayed speech, babbles/word sounds, sitting up, grasping, and reaching. So delayed motor and speech were the main things impacted.

Now, our ICD-10 code bundle included more ICD-10 codes that we feel that we can carry forward to future cohorts so that we can follow this cohort over time as they get older and may develop more of these codes that are germane not just to age one but older ages. Obviously, we can't look at things like autism and other diagnoses that don't emerge until later in life than at one year of age, but we did see that early signal—and again, these are unpublished data—but we've also now re-queried the data for over 18,000 deliveries and more than 850 cases of maternal code and we've been able to replicate those results and are seeing again, unfortunately, an increased risk for neurodevelopmental diagnoses by 18 months of age.

It remains to be seen what this means long term—and it also needs to be replicated in prospective studies, like the ones that you folks are doing—but I do think that looking at sex differences is going to be very important. The

other thing I think will be important is this “two hit” idea: it could be there’s an in utero vulnerability from maternal fetal interface immune signaling and so on that’s different between males and females, but also if male infants somehow have increased vulnerability to themselves being infected with COVID in infancy, what does COVID do as a second hit if the child is infected with COVID. It will be important to look at whether there are sex differences in your RECOVER cohorts in the infant rate of getting COVID, and how does that modify the neurodevelopmental outcome in some way if the mother just had COVID and the child did or didn’t get COVID, because some data suggest that males might be more vulnerable to also getting COVID.

Q3. The information presented seems to focus on the effect of the vaccines or COVID infection on menses and/or fertility, but not necessarily reproductive health. What has been the impact of the vaccines or acute infection on uterine fibroids, cysts, cancer, or other reproductive diseases? Is there any information about that now or planned to be studied?

Response:

Dr. Jacoby: Thank you, I really appreciate people bringing up these very common and critical issues in gynecology. One of my main areas of research is trying to improve care for people with fibroids, which affect up to 70% of all females by the time they reach menopause. I can tell you that my review of the literature shows almost no data about COVID and fibroids. The only thing I’ve seen is the one large survey study that I showed you about menstrual health after vaccination in 39,000 people.¹ They did do a small subgroup look at people who had fibroids, endometriosis, adenomyosis, or other common gynecologic conditions and found that these people were more likely to have menstrual irregularities, particularly heavy bleeding. But again, there are a lot of limitations in that study, as I pointed out, including who answers those online questionnaires and not having pre-COVID vaccine data. And again, with these vaccine studies, we’re not talking about just COVID infection.

I think the take-home message is that these issues have been off the radar for understanding COVID and we need to put them back and to be central to all COVID studies going forward, including the RECOVER study.

And as for people having concerns about their own reproductive health, if you’ve had COVID and want more information, I would say this is a pitch to consider joining the RECOVER study. We’re enrolling people who have COVID now or who have had it in the past 3 years. If reproductive health issues are of importance to you, we need you, so please join us and we hope to be able to answer some of these questions.

Q4. I think it would be good for someone to clarify the relationship of these talks to the RECOVER Initiative. The work discussed today seems to focus primarily on acute COVID and not on post-acute COVID.

Response:

Dr. Metz: We have very little data about Long COVID and the reproductive system. We don’t have slides that we can put up here to say what’s happening long term because it’s just not out there yet and that’s one of the things

that the RECOVER Initiative is really trying to answer. Dr Jacoby's shared some shorter-term data saying, "yes, we see maybe these disruptions in the very short term, but over a couple months we see return to normal function." So, we'll look to expand the data that are available over time to see what's happening as years pass. We can say the same thing about the male fertility aspect with Dr. Hotaling's data: these changes are very temporary with acute COVID infection, but the initial data seem to suggest that these changes then subsequently resolve and potentially there isn't a long-term impact on male fertility and male sexual function.

Q5. Are any studies looking at how sex hormones may be contributing to PASC symptoms, to account for the gender disparity in the PASC population?

Response:

Dr. Jacoby: We showed some studies that have found that women are much more likely to have PASC than men. We in RECOVER are collecting samples where we can run hormonal assays. We're not running those right now as part of the first wave, but we have stored samples, and I really hope it's something we can do in the future.

To Learn More

- **Information about RECOVER research and to volunteer for studies:** <https://recovercovid.org/research>
- **Frequently Asked Questions about RECOVER and PASC:** <https://recovercovid.org/faqs>
- **CDC information: Information for the general public and for healthcare providers about post-COVID conditions:** <https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/>

References

1. Lee KMN, Junkins EJ, Luo C, Fatima UA, Cox ML, Clancy KBH. Investigating trends in those who experience menstrual bleeding changes after SARS-CoV-2 vaccination. *Science Advances*. 2022;8(28). <https://doi.org/10.1126/sciadv.abm7201>