Jukic, Anne Marie and Shruthi Mahalingaiah 2023

Anne Marie Jukic, Ph.D. and Shruthi Mahalingaiah, M.D., M.S. Oral History

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"Feasibility of leveraging menstrual cycle tracking apps for preconception research recruitment," Anne Marie Z. Jukic, Hannah R. Jahnke, Nathaniel MacNell, Danielle Bradley, Shannon M. Malloy, and Donna D. Baird, Front. Reprod. Health, 30 September 2022, Sec. Reproductive Epidemiology,
Volume 4 - 2022 https://www.frontiersin.org/articles/10.3389/frph.2022.981878/full

"Attempts to conceive and the COVID-19 pandemic: data from the Apple Women's Health Study," Victoria Fruh, Genevieve Lyons, Ariel L Scalise, Nicola J Gallagher, Anne-Marie Jukic, Donna D Baird, Uvika Chaturvedi, Sanaa Suharwardy, Jukka-Pekka Onnela, Michelle A Williams, RussHauser, Brent A Coull, Shruthi Mahalingaiah, Am J. Obstet Gynecol. 2022 Sep;227(3):484 https://pubmed.ncbi.nlm.nih.gov/35568191/

January 23, 2023

Behind the Mask

Anne Marie Jukic, Ph.D. and Shruthi Mahalingaiah, M.D., M.S.

Barr: Good afternoon. Today is January 23, 2023. My name is Gabrielle Barr, and I'm the archivist at the Office of NIH History and Stetten Museum. Today I have the pleasure of speaking with Dr. Anne Marie Jukic, an investigator in the Epidemiology Branch and Fertility and Reproductive Health Group at the National Institute of Environmental Health Sciences (NIEHS) as well as her collaborator, Dr. Shruthi Mahalingaiah, who is an Assistant Professor of Environmental, Reproductive, and Women's Health in the Department of Environmental Health at Harvard T. H. Chan School of Public Health. Dr. Mahalingaiah is also a physician in the Department of Obstetrics and Gynecology at Massachusetts General Hospital. Today, they are going to be speaking about some of their COVID-19 research. Thank you both for being with me.

Mahalingaiah: Thank you.

Jukic: Great to be here.

Barr: To begin, will you please briefly introduce the Apple Women's Health Study, including its objectives, how the study has been set up, and any information related to participant requirements and demographics?

Mahalingaiah: Thanks, Gabrielle. I'll take this question. I'll share a little bit about it and turn it over to Anne Marie for more input as well. The Apple Women's Health Study was initiated and launched in 2019. It is an observational longitudinal study to advance the understanding of menstrual cycle health and gynecologic conditions, including PCOS, infertility, and breast cancer. PCOS stands for polycystic ovary syndrome. A couple of important points: You don't have to be currently menstruating to participate. The requirements include having menstruated once in your life, being of consenting age which is usually at least 18 years old or older, live in the United States, be comfortable in speaking English, have the right digital technologies such as an iPhone, and be able to install the Apple Research app. Those are some of the main criteria.

Barr: It's ongoing, this study?

Mahalingaiah: It's ongoing. I can share that the participants who have contributed for the last three years range in age from 18 to 90. We are interested in looking at development of new disease as well as looking back in time to understand trends and patterns.

Barr: How did you both become involved in this study, and what have been your roles?

Jukic: I became involved with the study because I'm a part of a really amazing research team here at NIEHS. The people that have mentored and worked with me for most of my career have been researching menstrual cycles and fertility for upwards of 30 years. I was part of a really amazing team, and that team was invited to participate in the Apple study. We work together now—our NIEHS team, with the Harvard team, and with Apple—to conduct this research.

Mahalingaiah: I was similarly invited to participate in the leadership team of the Apple Women's Health Study at Harvard T.H. Chan School of Public Health when I became faculty, and ultimately, lead the team based on my background and expertise. This study conceptually merges my interest in digital public health, women's health, and menstrual cycle charting to optimize health. It is really exciting and unique that we have the collaborators at NIEHS—Anne Marie and the entire team there. That brings a historic expertise to menstrual cycle research, too.

Barr: Is this the first of its kind? Did you look at other menstrual cycle studies that have happened in the past in framing and designing this project?

Mahalingaiah: I do think it's the first of its kind. There have been some amazing studies that have established the field, like the Tremin study and the Tremin Trust, which helped us understand cycle length across the lifespan. I think the novelty and the aspect of this study that really sets it apart is that we are inclusive of geographic diversity across the United States, not just limited to one area in the Midwest. Due to the digital platform, we are able to recruit without an interface to a university or a clinic or a hospital. It really breaks down barriers to participation. What we see is that the other aspects of diversity are there too, such as socio-economic and race and ethnic background diversity.

Jukic: Yeah, this is definitely a unique study in that it is prospective, but as Shruthi said, the study enrolls people who have ever menstruated, so even people who are not currently menstruating can participate. It gives you this big window of opportunity to look at cycle characteristics across a huge population.

Barr: During the course of this large longitudinal study, the SARS-CoV-2 pandemic erupted. How did you and others involved in this study amend it to encompass how women were affected by the new pathogen, and some of the circumstantial health related issues it triggered?

Mahalingaiah: One of the unique aspects of this study was that the emerging pandemic did not impact our ability to reach participants and recruit. That was kind of an amazing observation for many who were at home and may have even facilitated the participation. From my side of the collaboration, we were interested in understanding the impact of the COVID-19 infection and vaccine on reproductive health endpoints—from attempting conception to impact on fertility and menstrual cycle. A group of interested clinicians and researchers got together and threw together some questions.

Barr: Talk a little bit about the creation and deployment of the survey.

Mahalingaiah: Of course. We had some questions that were sourced from the clinic at Mass. General (Massachusetts General Hospital) as well as some of the epidemiologists at the Harvard T.H. Chan School of Public Health. We brainstormed on those questions with Anne Marie Jukic and Donna Baird. We also shared our interests with our sponsor, and this culminated in a survey that we are still using today. That was rolled out sometime in 2021 to understand vaccine usage as well as infections and side effects. Drs. Jukic and Baird commented a lot on questions they would want in the survey as well.

Barr: Can you talk a little bit about some of the questions you wanted to be in the survey?

Jukic: I'm a reproductive epidemiologist, and we're really interested in study design. One of the important aspects for us was timing and trying to get questions that could address that timing of things, especially as things changed throughout the pandemic. Trying to design a questionnaire that would help us understand the timing of when things happened—for me, that was really important.

Barr: Can you discuss how your group has gone about conducting analysis from this survey and some of the points that you looked at?

Mahalingaiah: That is a great question. One of the other unique aspects of this study is that we have data streams that come from surveys and data streams that come from menstrual health tracking applications that will help us understand when, as Anne Marie was saying, a menstrual period happened in relation to an exposure like the COVID-19 vaccine or an infection. After appropriate study design, we do look at what our exposures are and what our outcomes are. I'll highlight one analysis, looking at the vaccine as the exposure and the outcome as menstrual cycle length. Because of the size of the study and because of the technical expertise in terms of biostatistics and epidemiology, we were able to look at an individual's menstrual cycle length as their baseline and compare their own baseline to their menstrual cycle length and variation before and after the vaccine. This was a very unique approach to understanding change that is at the level of both the individual and the group, to show what the normal range of variation is and how far you go outside of that after an exposure—in this case, the vaccine—in order to really show that the change was present, but it was small and temporary and resolved over the next few months. To really reassure people interested in learning more about this that, in terms of the menstrual cycle characteristics, there is a sense of acceptability and safety for the vaccine.

Barr: Did you notice any differences amongst the different platforms?

Mahalingaiah: What do you mean by a platform?

Barr: The mRNA vaccine versus those that received the more traditional platform of Johnson and Johnson.

Mahalingaiah: We did look by the physiologic underpinnings of the vaccine, and we tried to even drill down further at timing of the vaccine and the follicular or luteal phases. At a high level, there were subtle changes, but not that I can report to you on now. Anne Marie and I have conversed a lot about interpreting those estimates, so I will turn it over to her, but that's a great question.

Jukic: Yeah, we're still [working] on some of it. I mean, we have the paper that was published to look at, but there are some complexities of the design that we're still kind of addressing and looking into. Overall, the message is important—that with the vaccine, while we saw changes in cycle length, they were temporary.

Barr: They were so small like a day or two.

Mahalingaiah: Yes.

Jukic: Yeah. From a statistical point of view, we can really focus on details and small things. That's what we do. Data scientists are really interested in that. But that's why I say the bigger message is that, while there might be changes and the people who have reported or observed these kinds of things happening to them should feel like they've been heard, we do see it in the data. It does happen, but it was temporary and returns to normal. That's reassuring for the vaccine.

Barr: Did you also look at the effects of vaccines that people report? You looked at the length, but did the people in your survey report they had more flow or more pain—or any other kind of symptoms that were different?

Mahalingaiah: Our survey didn't actually ask about the experience of flow. That is one drawback in that we couldn't comment about the flow experience. There are other studies emerging now that we'll likely see published in the next year that comment a little bit on that, but we couldn't get flow to the level that we wanted for this analysis. There are ways to kind of think about that, but in acknowledging that everyone uses their own period calendars differently, we didn't make any conclusions based on the number of days or flow patterns.

Barr: Did you take into account sociological situations that were happening at the time, in terms of a person's cycle? A lot of women are under a lot of stress during the pandemic for a variety of reasons.

Mahalingaiah: That is a great question. There were a few stress questions, and those were included in the adjusted models. That's why it's so important to understand one's own baseline. We did have baseline information from during the pandemic also when comparing before and after. But stress is a major factor in understanding one's own cycle.

Barr: What are some of the next steps for this study in general, and also in terms of understanding how COVID-19 has affected women's cycles?

Mahalingaiah: I'll start, but Dr. Jukic has a lot of great ideas as well for where we can go. We're really excited to look at if there are groups of people that already have some sort of gynecologic condition who may be even more impacted, let's say, by the vaccine or the illness. Really bringing light to those kinds of at-risk groups is something that greatly interests me. Then from really collaborative work with NIEHS and the scientists, understanding our appreciation of menstrual cycle lengths and bias is another thing we're going to think about scientifically, to get the most precise estimates of effect.

Jukic: That was a great summary, actually. We definitely have a lot of opportunity for developing methods and examining our statistical methods for looking at menstrual cycles because we have a large study. Thinking about all the different kinds of cycles that we can look at within our analysis is important. That's an important advantage of the study. Methods is definitely a future direction for our study, but I think there are other aspects. One of the nice things about having this in-progress study—a study that's always live, that people can join and contribute to—is that we can respond. We can respond to things we don't even right now know are coming. Like treatments or other vaccinations. As we move forward, we may have more or different kinds of vaccines or boosters. Having a place where we can be responsive to what's happening is really exciting as a menstrual cycle researcher, because that's not something that's existed in the past.

Barr: Did you look at how COVID-19 affected fertility in your survey? Did you look at whether it incited menopause?

Mahalingaiah: Those are great future studies. We haven't looked at the impact of the infection on those reproductive endpoints. That's one of the strengths of this study. I feel like we are developing a foundational data set that we can actually ask so many important questions of, and because of its size we will likely be able to identify an analytic sample and hopefully identify the potential sources of bias that could impact it. We do look forward to really drilling down on two factors that may impact time to conception. This is one of Dr. Jukic's focuses and is something interesting to me as well for my fertility clinic population. Also, populations at risk—for those with preexisting irregular periods, how that irregularity works and how we study the patterns of irregularity before and after an exposure is something of interest. In terms of menopause, this is a huge question of understanding the environmental lifestyle and demographic factors that can either accelerate or ameliorate the symptoms that are experienced. Half the population will experience this at some point and understanding who may have more propensity to what symptoms and at what severity can help us inform individuals and maybe even lead to some prevention or treatment.

Barr: Did you experience any challenges conducting any aspects of your study during the pandemic? What do you feel that you've learned so far?

Jukic: Who didn't experience challenges in research during the pandemic? There were lots of different kinds of challenges in terms of concrete access and also people having less time or more stress—and how that affects people's ability to participate or even consider participating in research. I'm sure our study is influenced, but it's really a large event in everybody's experience—personally, professionally, all of it.

Mahalingaiah: Because it was digital, it really was a unique opportunity to be able to continue to collect data and respond to pandemic-related acute issues and situations like the vaccine and menstrual cycles. We did look at the decision to attempt conception during the pandemic, which is a little different than fertility impacts. We were able to see trends in how our participants were thinking about attempting or not. From my perspective, I feel like getting at those early decisions around whether or not to attempt may actually help us understand live birth rates nine or ten months down the road. We did see some parallels in what was shown in terms of the birth trends also, but it was really interesting to see that.

Barr: What did some of those show?

Mahalingaiah: What we looked at was what the self-reported trends were in attempting conception during different periods during the pandemic. We looked at it from the beginning, so I would say early 2020, to right when the pandemic was declared as a comparison to a few different time windows. There was definitely a decline in the summer of 2020 with a slight recovery by the fall of 2020, except in those with self-reported low socio-economic status. There was a kind of dip and then attenuation back up for that year.

Barr: In addition to being scientists and physicians, you're also people who have been living through the COVID 19 pandemic. How has the pandemic affected you personally? What are some ways that you have coped with it?

Jukic: For me, I work well with keeping a schedule and keeping the same patterns. Even with our participants who were in the study, people had job changes or lost jobs, lost health insurance—all these things affect life. For me, it was really important to keep a regular schedule of some kind, whatever it was, even though my kids were not in school. I have kids and it was all digital virtual school. Trying to keep everybody's schedule maintained for some normalcy was the biggest effect for us. I mean, there was obviously isolation. Everybody had isolation at various time points. We felt isolated from our family and from our friends. That was hard too, especially for kids growing up.

Mahalingaiah: I agree. It was a very unique time for me personally, as a mother of three daughters. One experienced an earlier than average first period or menarche. The difference in how we interacted with our support systems, like family members and distant extended family, definitely allowed for a reflection on the fabric of what keeps us together. I feel like it was a unique time. Then as a clinician, being on call on some of the first weekends of the pandemic for the fertility unit was just really unique, thinking about "building back with fertility" when this pandemic was rolling out. It was just so many things all at the same time. I'm curious to see how all of those threads continue to weave together in the years of our recovery from this.

Barr: Thank you both for all your work and I look forward to more results from the study!

Mahalingaiah: Thank you so much.

Jukic: Thank you.