DM in Pregnancy and AI

Gladys (Sandy) A. Ramos: [MUSIC] Thank you, Drs. Alperin and Su for the invitation to speak today. I'm Sandy Ramos. I am a clinical professor in the Department of Obstetrics, Gynecology and Reproductive Sciences, and I'm also the Director of the Diabetes and Pregnancy Program. Just one disclosure that I do receive research from Dexcom in the form of CGM devices.

Let me start off by just framing the question. Why is insulin management so difficult during pregnancies complicated by diabetes? Well, it's super important to have optimal glycemic control, which is much tighter than outside of pregnancy. And this is important because we know that hyperglycemia is associated with adverse maternal and fetal complications. However, it's very difficult to manage during pregnancy because there's a continuum that we see with rapid changes to insulin resistance, which is mediated a lot through placental hormones. But in the first trimester, for example, there could be a risk of hypoglycemia which can really adversely affect the mother. Then in the second and third trimester, rising insulin resistance, which usually peaks in such a way that for Type 1 diabetes patients, they can be on 300% higher doses of insulin than pre-pregnancy.

So, traditionally, the way we optimize care was through self monitoring of blood glucose. But this entailed finger sticks up to 4-7 times a day, which was painful and burdensome and limited with regards to the data. You can see on this figure, we have a patient who's monitoring her glucose, and it looks like the red circles are within the desired range. However, there's some missed opportunities to check the glucose, as you can see with the open white circles. However, wouldn't it be wonderful if we were able to see a 24 hour continual set of data where you can find opportunities for treatment with missed hyperglycemia and also some missed hypoglycemia, probably linked to overtreatment with insulin.

This is where continuous glucose monitors come into play, and this has really changed the way we manage diabetes. As you know, it measures institutional glucose continuously every 1-5 minutes, and it's attached to the skin with a sensor, and then we usually use a phone nowadays for receiving that information. Really, this tool became useful in the cohort of patients with Type 1 diabetes. This was the seminal article about CGM use in pregnancy in those with Type 1 diabetes, where they found that CGM alone improved neonatal outcomes with lower rates of large for gestational age infants, hypoglycemia, and NICU stay. Not many women needed to be wearing CGM in order to see these effects.

The American Diabetes Association has come up with glycemic control targets utilizing CGM. You can see here this is a Type 1 diabetes and pregnancy management algorithm. However, for GDM and for Type 2 diabetes, they say it's actually based on expert opinion and not evidence based. Honestly, this is where we need more research. The American Diabetes Association does not recommend the use of CGM for Type 2 and gestational diabetes in pregnancy until we have this data, although people are using it clinically, as you know. We have more than 11 actively recruiting trials currently, and we're lucky enough to be one of those centers that is doing a clinical trial on the use of CGM in Type 2 diabetes in pregnancy, and we're currently enrolling. We also have some trials underway for gestational diabetes here in California, including the CAPO trial, and some studies are actually using CGM for postpartum screening for Type 2 diabetes after gestational diabetes, which is the POSTPOD trial.

But there's possible uses outside of diabetes care with this technology, which is super exciting. Investigators have been able to actually define what is normal glycemia in pregnancy. Believe it or not, we had some old insulin clamp data that suggested this is what we should be doing. This was studied retrospectively to look at neonatal and maternal outcomes. But now we have some really good pull data that tells us what is normal in pregnancy. Now, even going further, some of you clinicians in the room have asked me, can I use CGM to diagnose GDM? Not yet. But GO MOMs is a very exciting study that is looking at CGM wear starting in the first trimester and

looking at maternal characteristics like age, BMI, family history, and two hour GTT clinical results to identify women who are at risk for GDM and how to utilize CGM for the diagnosis.

But here at UCSD, we've also taken a step further, and we've looked at characterization of glucose in normal labor. Because again, this is an area where we're really lacking evidence as to what we should be telling our patients who are pregnant with diabetes and where should they be targeting the glucose? We found out that about 25% of people going through normal labor without diabetes have glucose higher than what we recommend typically for those with diabetes. Then lastly, we're looking at this data, also CGM use and comparing it to capillary blood glucose. We found an excellent correlation between CGM in women with Type 1 diabetes who had it on during labor and comparing it to capillary glucose, which really has promise for managing labor in these people without having to do painful one hour capillary glucose. It also has the potential to decrease nursing burden. I'm very excited about this data, which will be published hopefully shortly. This was a study led by one of our medical students.

Then lastly, CGM supports positive behavior change. In a cohort of people with diabetes, they saw that about 87% of people changed their food choices, 43% were more active, and 90% reported healthier lifestyle with the use of CGM. This is the feature. This is where we're going. But we're also collecting this amazing wealth of data with clinical factors and how can we leverage this to improve the care? This is where Ben's lab is going to be stepping into.

But before we transition to Ben, I wanted to just thank the UCSD Diabetes and Pregnancy Program, all of my diabetic educators, our nutritionists, our fellows, our social workers who work so hard to provide the care of our patients and to lead us in the future with the use of this technology. Thank you. [Applause]

Benjamin Smarr: Then I'll take over from that. Thank you for having me here. It's a real privilege. I wasn't able to attend last year, and I was sad about that. I really appreciate being invited back. I'm Ben Smarr. I'm a professor in bioengineering and data science, and my training was in squishy stuff. I spent 15 years doing things with mice and rats and learning about neuron endocrinology. Then garage banded my way into data science, largely out of frustration about the kinds of things that a lot of these talks have shown us.

There's a figure from an old R1. But, we look at animal models and we say, well, I understand there's these hormonal feedback systems. The SCN is doing circadian regulation and sleep, which we heard about earlier today. Pituitary, HPA, HPG. All these things are doing pulsatile, circadal within the day, ultradian pulses. The time of day, the time of hormonal pulse, of course, is being modulated by things like estrus rhythms in rodents, menstrual rhythms in humans. Yet, we use these animal models because that was the only place we could get data on these things. If I want to go figure out how do these hormones change over time, like I was doing in my PhD a long time ago, I would get blood samples every hour from some rat. It's incredibly labor intensive. The joke was always, we were really studying me, circadian disrupting myself to be able to get these data.

The other problem with that is then people get very concerned about all the variance, the differences between rats and mice and humans, which are substantial. We try to constrain sources of variance by doing things like mostly only studying particular breeds of rodents, particular strains of mice, mostly males. We end up with a great deal of depth, but real trouble translating, which we've heard over and over again today. I'm still a huge fan of all of this research. It's the necessary way to understand mechanism.

But we live in an age of radical transformation about where data are available. This is now even a few years old. I stole it from Wired. These days, people are generating more data than clinics are, and they're doing it for their own reasons. It's not the case that if we want to get data on humans, we have to get an RO1 with enough of a budget to buy a device for every single participant. People just do this. In fact, getting to follow Peter is a perfect example. People are

happy to do this for their own reasons on which then research can be built. It gives us this opportunity to start to really see in depth with temporal resolution that captures these different timescales of change, what do people actually look like? How are we different from each other, and how does that then leverage different treatment outcomes, different treatment choices?

I want to highlight just a little bit of work that Lauren Bruce over there did when she was a PhD student and now a postdoc between myself and Dr. Perry. Just some basic phenomenology, saying, if we get people to donate their wearable device data, in this case, oral rings back in 2020, 2021, so during a bunch of COVID studies, we can start to see here the X ticks are days. Each pixel basically is one day across cycles in pregnancy. You can see at the beginning on the left, DKP is date known pregnant. You can see there's this big cycle of temperature, that's menstrual cycles. Then you can see pregnancy onset.

You see there's a drift in temperature over time in blue, but daytime temperature is different. It's coming up instead of going down. Activity, heart rate, heart rate variability, respiration. They all have a shape in time. None of this has ever been seen before. We didn't have resolution like this on humans before, even though it's fairly, I would say basic, fairly phenological. But it allows us to make comparisons not to something like, what's your average temperature, but what's the change over time, and is your change over time, look like a wiggly boat or look like smooth sailing?

As an example of that, what she was able to do, this was a voluntary dataset. There was zero budget attached. Within about a week, 1,000 people had asked, can I give my data to your study? As we heard from Peter, lots of people want to participate. We looked at just this first little bit and fetal loss that had occurred retrospectively natural experiments in some participants. What we saw was that you could really easily see when fetal loss was occurring from this deviation of the temperature trend, which you see as these dotted lines falling off the blue curve. That's just an example. It's again, basic phenomenology. But it shows us, with zero budget with one very talented student, we can surface these things quickly. We can surface them with the ecological relevance. We can do it by working with communities that previously have felt understudied. It's a huge opportunity to change the way we think about where truth comes from. Again, not to criticize anything else, but just to augment with these human observations.

I'm going to pivot and just talk about how this isn't just pregnancy, though. It's really all of a woman's lifetime that we haven't studied very well that we can now start to fill in some blanks. When we think about transitions into perimenopause and menopause, when we think about menarche and cycling and cycling stability, and how does that change over time with pregnancy, with other health conditions. Lauren was helping to manage, then a whole team of students doing women's health research in my lab. This is an example from Sa Yun, who just got her honors master's degree in bioengineering. This is a surface of several thousand women, and we've statistically extracted what looked like menstrual cycles from their temperature data. Then in the colors over on the left, we're comparing the place these people sort out to when we compare them against each other. We get these nice smooth gradients.

We're looking at the age that those people were. What you might notice is that it goes purple at the extremes and then red, yellow, green on the inside. That's 20s 30s, 40s, so it's this progression of age. You can see there's a diagonal trend, which means cycles are getting faster on average as these women are getting older. This is known on average in the literature, but not at the point where you could give to an individual and say, do you fit the trend or not? As you deviate from that trend, what does that mean about the kinds of menopausal symptoms you might expect? That's now on the table. Again, people generate these data with or without me. But I think there's a huge opportunity that probably we're not as tapped into of building those community collaborations to help people surface that data and learn about when is that information there, even if it isn't a random and controlled trial, even if it's not something that we have specific funding to investigate.

When we featurize these data, we break out a bunch of statistical features of these wearable data. We can cluster women in what we call high dimensional spaces, which is just to say, we compare a bunch of stuff together. Here's these same women. The most simple version of this is a principal component analysis. A linear projection through a bunch of dimensions into two dimensional space. The green over there is younger women. The blue is older women on the top. You see this triangle. On the bottom, what we're seeing, modalities. That's when we look at temperature, when we look at heart rate, when we look at respiration, THNR there, do we see clear menstrual cyclicity or not? It's not, is this woman cycling? It's by which modalities is it obvious that she's cycling. Different modalities are obvious for different people.

That's Thing 1. Thing 2, we start in green over there, and we grade through red, orange into blue. That's the loss of modalities. That is to say it's less and less clear in their physiology that they're stably cycling. It doesn't mean it's a binary on off. But we're able to watch that progression as it becomes less and less clear, as it gets lost. The really interesting thing to me is as they get into that blue, not cycling space, they actually are showing a great deal more diversity. The physiological space is expanding. That means when we think about aging trajectories, menopausal trajectories, there's a ton of diversity in what that means. We really don't have functional definitions because it's been hard to get data like this. It's now no longer rate limiting.

As Peter alluded to, it's not even really limiting to do the analysis because we have very talented students. We also have a lot of agentic support. We can get very complex, very fast. The thing that used to really slow us down is not a barrier anymore fundamentally. There are barriers like equity of access, but we can start to understand the ways in which people differ much more granularity than just perimenopause, yes or no, menopause, yes or no. That's really exciting to me. I think that's a huge opportunity.

The vision that we have, I would absolutely love to talk with anyone interested. How do we, in a clinically translational way, go from, well, your average value is within the Gaussian, so I guess we're fine or we don't know, or let's retest you in a month, which has been the standard because that's what we can do. Now, all of a sudden, we can do this much more interesting personal journey thing where we go, my data is wandering into that red zone if I'm those yellow dots. Maybe I should talk to my doctor about that. Maybe we can see who else was on a trajectory like that maybe in the Amazon way of, people like you who bought these hiking boots, bought these tents. Maybe we can build those exact same recommender systems and say, people like you really responded well to hormone replacement therapy or really responded well to diabetes control, this thing. Again, the engineering is no longer actually rate limiting at all.

Figuring out how to get people involved and how to make this something that we can lean on, even if it isn't a 10 year clinical trial arc as things used to be, to me, those are the big challenges. I'm, you can tell, I think, super passionate about this. Love to connect with anyone and everyone interested in figuring out how do we do this better faster.

With that, I'll just say thank you to funders, my wonderful lab. If anybody's looking for an off scale researcher or an admin, Lauren's amazing. I'm not trying to get rid of her, I'm just saying. I think we have time for questions. Thank you. [Applause]

Speaker 1: Thank you so much, guys. Fascinating. I have a question. I think it's a little bit more toward Ben. I talked to a lot of people who have those rings. They tell me that sometimes when they wake up and they feel very rested and the ring tells them that they didn't and vice versa. I guess my bigger picture question is, while we're having all this data, clinically, we have very crude phenotypes. We absolutely want to collaborate with people like yourself so we can have a better phenotype, so we can have more personalized care, not just in oncology. But you're still educating these models on the data that you're getting from these devices or from whatever. What if it's wrong, and how do you know?

Benjamin Smarr: No, that's a key point. First of all, without wanting to cast shade on anybody, I

would never believe the interpretation of any company or for that matter, any doctor a priori. I have some intuition about whether I think that makes sense or not, and I like to argue. The thing that I think most of these companies have not taken advantage of sufficiently, and it's why I was so impressed by Peter's thing about education and engagement with participants is exactly what you said. A lot of these companies, going back to Apple and Fitbit in 2014, when this really started taking off, said explicitly, we don't need to involve the users. That's going to give them a lack of trust in our brand. We'll just somehow mine out those patterns and tell them. Exactly what you said happens. We go, you slept well, and you go, I don't feel like I slept well. All it does is erode trust.

It's a missed opportunity. Doing the research collaboratively in a participant engaged way lets us build those better models. Exactly, again, what Peter said, lets us much more accurately project horizons of certainty. Here's what we think we can say confidently. Tell us if we're wrong. Here's where we don't know. You might be the first person experiencing this, generating data about it. We should make that a collaborative discovery process and not a source of shame that we don't have certainty about what we've never seen before.

Speaker 2: I had a question. I guess maybe for those in the audience, and I'm not that familiar with wearables either, can you talk about the type of data that is currently able to be gathered and think of it in terms of women's health applications, and then also what is coming down the pipeline? What do you think we will be able to measure soon?

Benjamin Smarr: The things we measure are still, I would argue, super interesting proxies. Things like heart rate, temperature activity, glucose, certainly. The things we want to measure are really the abstractions from that. Things like sleep stability, propensity for depression. Those are more complex physiological constructs. The question is, how well can we define these things that even right now are really fuzzy. But if we say depression, it's not like there's really an operational definition for that. Or that it's a thing at all. We need to try to, I think, go both directions. Do the data help us understand when there's a real object and when maybe what we've called depression is several objects? Are they concrete? Are they fuzzy?

Then, how does that construct stability differ if it's a different sensor? Do I really need temperature? Would your phone activity get me there? Sometimes we do things just with apps, just with Internet activity. To me, it's about seeing the patterns of change in time. It's not about, do I have a higher resolution snapshot? I'd like to see the movie.

Gladys (Sandy) A. Ramos: Then for us in this space, we've actually had patient driven innovation. There are patients that have actually taken CGM data from people with Type 1 diabetes and created algorithms to then be able to use within pregnancy, especially for Type 1 diabetes, because people have been wearing it for so long, and there are no pregnancy specific insulin pumps. Consumers have pushed forward and said, we're going to develop some really smart engineers who have Type 1 diabetes, and their, family members, etc., have created this now algorithm to be able to apply to any pump since the pharmaceutical companies are not pushing for a pregnancy specific pump, and they've come up with an algorithm, which I think is really cool.

Benjamin Smarr: I want to expand on that for a second, if you don't mind. I'm so happy you brought that up because I encourage everyone to look up Open Humans. The Type 1 diabetes group was really what got me into this work. It's really their fault that I'm bothering you guys. They're so good. There was this nucleus, Open Humans, where they said, I've got a insulin pump, I've got a glucose monitor. They don't talk to each other. The insulin pump is basically a square wave all the time. Just a level all the time, even though clearly my body's doing this. They would crack these things open and hack into them, again, back in the teens, 10 years ago, and they weren't supposed to. They were violating all the user agreements. They were violating all kinds of things. Suspiciously, these companies never went after them. I thought that was brilliant.

They said, these people are reporting how much better it makes their life. They were allowed to be guinea pigs, as far as I can tell. But they were really good, and they kept finding these dynamic feedback systems, exactly what you described, which were still, much better than commercial standard. I love that. I love the idea that if we can activate these communities, they can be part of this process. They don't have to wait for some doctor to happen to care about them. There's a ton of energy and capability in everybody, in all these populations. How do we enable that faster is a big challenge.

Speaker 3: The question I have is along those lines. First of all, great talks, and, we think about wearables so much right now. Living in San Diego where Dexcom exists, and for the first time I hear a patient who told me her Dexcom didn't go along with her glucose screen, and I thought, I really missed something. You're a diabetic, and of course, she was not. I guess the question is, should we reframe the way we're thinking about this to say, wear whatever device you have and let us get the data because her control data is so helpful, but we haven't thought about that.

We said, this CGM is for this person, sorry, you can't wear it, but now we want their data. Think about what's an IRB driven way to responsibly collect this data and then use it to inform what we do. Because the data are the data. They're not right or wrong, they're just the data, and then how can we inform what we do based off of that?

Benjamin Smarr: I don't know if you want to jump in, I have thoughts.

Gladys (Sandy) A. Ramos: I think it's hard. You're right. We can actually pull data from clarity reports in Dexcom. If we did have an open IRB, I would be able to pull that information because I have it at our fingertips. It's actually really easy to capture CGM data. Now, the same thing, I think with over the counter Stelo, which is probably what your patient was using. It would have to be a matter of just, getting consent. But you're right. I think honestly that Dexcom probably has all of that information ready to be mined.

Speaker 3: Thank you.

Benjamin Smarr: Well, Gladys, I think you said, there's these populations where they're not able to wear a CGM because it's not recommended. The concept of an IRB is to protect people from unethical experimentation. In my mind, there's a new countervailing force, which is that it's unethical to deny people information they could be generating. That doesn't have policy around it yet. I was told by our tech transfer office years ago, whatever you do, don't get into a fight with Apple about whether they're violating your patents because their legal business is larger than the entire UC budget. We'll just throw you to the wolves.

But what that says is that, some of these early adopters aren't thinking about policy probably the way that we are. I don't know what the IRB solution is. I don't know what the ethical solution is. I do think we have not dealt with this change appropriately yet. We're just beginning to grapple with it. There has to be some ethical framework within which people that want to discover things about themselves are encouraged instead of discouraged. That's very hard in the current framework, which is partly why I like to stir the pot and suggest maybe we need to change that framework a certain amount.

Speaker 4: Regarding the CGMs but also pumps, Dr. Ramos, can you talk a little bit about insurance coverage for those and both in California and if you know other places in the United States and how that might impact equity with these devices?

Gladys (Sandy) A. Ramos: Absolutely. Right now in California, we're able to get CGM devices if you're on insulin. If you happen to have gestational diabetes and aren't treated with insulin, it's very hard for us to get a CGM, although we can go through a huge rigmarole of getting PAs and all these things. It's really difficult from that perspective. However, in our clinic, we are able to use it for folks that speak a different language, that are immigrants, that are unable to follow the

directions. I mentioned fingerstick is the gold standard, and doing it 4-7 times a day plus dosing insulin. It's a lot. Folks that are working two jobs, for example, that don't have the time to monitor their glucose values. Using CGM in this way, I think, in those with insulin has been able to help me at least be able to address some of those health disparity gaps.

We still have a long way to go because, again, the American Diabetes Association doesn't outright recommend it. They say it may be useful. Actually now, I think at the new ADA meeting, they said that potentially for Type 2 diabetes outside of pregnancy, they would recommend CGM. I think insurance companies will get on board and start to accept it. But we're hoping to get our study done before that happens so that we can actually have evidence based guidelines for managing diabetes in pregnancy.

Speaker 5: Great. We're going to go ahead and wrap up this. Let's thank our speakers again. That was a wonderful talk. [Applause] [Music]