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Why Hybrid Closed-Loop Insulin Therapy Should Be Offered to Pregnant T1D Patients

Dr. Buse:
Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse, and joining us to talk about her study focusing on hybrid closed-loop insulin therapy in pregnant women with type 1 diabetes is Dr. Helen Murphy. She's a Professor of Medicine in Diabetes and Antenatal Care at the University of East Anglia in the United Kingdom.

Helen, thanks so much for speaking with me today.

Dr. Murphy:
Thank you for the invitation. And, yes, I'm delighted to talk about our work in type 1 diabetes in pregnancy with you.

Dr. Buse:
To frame our discussions for today, Helen, could you tell us a bit about the problem of pregnancy complications caused in the setting of type 1 diabetes?

Dr. Murphy:
Sure. So, I mean, managing diabetes at any time of life is challenging, but, of course, it is so much more challenging during pregnancy, and there's a few reasons for that. The first one is that the pregnancy-specific glucose targets are so much tighter. So for people who don't work in pregnancy all the time, the usual glucose target outside of pregnancy is 3.9 to 10 in our UK unit, so that is 70 to 180 mg/dL in US units. For someone who's achieving 70 percent time in the target range outside of pregnancy, that is only 45 percent time in the target range during pregnancy, and that's because the glucose target in pregnancy is so much tighter, roughly 25 percent tighter. So that's one reason why it's difficult.

The other reason, of course, why it's really challenging for pregnant women is because of all of the physiological changes that happen during pregnancy. So typically in really early pregnancy, so from four to eight weeks gestation just when women find out they're pregnant, what we often hear them say is that their blood sugars are just skyrocketing. They're going high for no apparent reason. They're going low for no apparent reason. And often that's the first sign that a woman might be actually pregnant. After that in pregnancy, we get a period where there's a real risk of hypoglycemia, or low glucose levels, for the mom, and that tends to happen between about 8 and 16 weeks gestation. And then after that, women are no sooner through that phase when we start to see their rising insulin resistance and more frequent glucose levels above target. And if all of that wasn't hard enough, for all of those gestational changes and these tighter glucose targets, we also see that the absorption of insulin is very different during pregnancy. So insulin is absorbed much more slowly, meaning that women have to give bigger and bigger boluses and inject them earlier and earlier before eating.

Dr. Buse:
What do we need to know about the particular automated insulin delivery system that you used in your study to try and help women deal with all these complicated issues?

Dr. Murphy:
So, you know, the real crucial difference between the automated insulin delivery system that we used and some of the other commercially available systems is that our system has been customized specifically to work during pregnancy, so that together with Roman Walker, who's a bioengineer, we've worked really over the last 10 to 15 years to understand much more about these physiological changes in pregnancy to understand the differences in insulin pharmacokinetics during pregnancy and to have an

algorithm that we know can very safely push the mean glucose level lower without putting the mother at increased risk of hypoglycemia. So it's crucial because, as I mentioned, those pregnancy targets are so much tighter than at any other time in lifestyle, so a closed-loop system that is tuned to deliver good glycemia for the standard range of 70 to 180 mg/dL won't necessarily perform as well for 63 to 140 mg, the tight pregnancy targets. So we had maybe 10 or 15 years of background of testing out our system initially in inpatient hospital studies, then in home studies, before proceeding really to the pivotal trial in real-world clinics with pregnant women.

Dr. Buse:
Do tell us about the design features of the trial. How did you set things up to answer a study question?

Dr. Murphy:
So we set the trial up as a randomized controlled trial. So that means that half of the women in the trial were allocated to the hybrid closed-loop system; the other half of women were randomly allocated to their usual insulin delivery, so that could be insulin pump or it could be insulin pen. And then, crucially, women in both arms of the trial had the same high spec continuous glucose monitoring sensor. So for this trial, we used the Dexcom G6 because of its accuracy in the lower glucose range.

So we made everything as identical as possible between the study arms; the only difference being that women in the hybrid closed-loop arm were having what we call automated insulin delivery, really meaning that the basal or the background insulin was being delivered in a manner that we describe as glucose responsive, so the algorithm, which sits usually on a smartphone, is taking the data from the continuous glucose monitor, it's calculating the insulin dose, and then it's adjusting the dose in small, precise, personalized amounts every 8 to 10 minutes. And obviously, that's something that neither you nor I can do. In our normal clinics, we adjust insulin with patients based on their glucose levels and insulin doses over the preceding one or two weeks or one or two months, but what we have with automated insulin delivery is a system that adjusts the insulin according to the real-time glucose levels, and it's doing that in the background 24/7, day and night, so it's much better able to keep up with these physiological changes during pregnancy.

Dr. Buse:
For those just tuning in, you're listening to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse, and today I'm speaking with Dr. Helen Murphy about her study on hybrid closed-loop insulin therapy in pregnant women with type 1 diabetes.

So, Helen, if we focus on the results, can you tell us about the findings of the trial?

Dr. Murphy:
So the first thing to say about the trial is that the patient characteristics, the women that came into this trial—124 of them—the background characteristics were very reflective of our background maternity population. So by that I mean the baseline glucose levels were very similar to a standard population of women with type 1 diabetes, so about one-third of women had HbA1c's less than 7 percent, one-third between 7 and 8 percent, and one-third of above 8 percent. Half of the women in our trial had used an insulin pump prior to pregnancy, but half of them used multiple daily injections, and this was really important to us to have a population that was technology-naive as well as those who were experienced pump users.

What we found was that regardless of the mother's baseline glucose levels, regardless of whether she had experience with using technology or not, those that used the hybrid closed-loop system had an extra 10.5 percent time spent in the pregnancy-specific target range, so that's 63 to 140 mg/dL, and that equates to about 2 1/2 additional hours per day in the tight pregnancy zone. The closed-loop users also had less time spent with glucose levels above range. They had a lower HbA1c level. They had no more frequent problems with hypoglycemia. And, actually, one of the results that mattered most to women and the participants in our trial was the fact that they achieved these beneficial effects in maternal glucose as well as less gestational weight gain, so the women who used the automated insulin delivery system actually gained 3.7 kilos. I think that's like just over 8 pounds, 8 1/2 pounds less weight during pregnancy. So the closed-loop was able to give women a higher percentage time in the pregnancy target range, less hyperglycemia, which we know is problematic for babies, and also less gestational weight gain. So that's something that's hugely important to women in the management of their diabetes both during pregnancy and after it.

Dr. Buse:
Were there any adverse findings reported that were of concern to you?

Dr. Murphy:
No. This study was done during the COVID pandemic, so many of the trial appointments were virtual at a time when we were trying to keep the face-to-face contacts to a minimum, but women in both arms of the trial still managed to attend about 95 percent of their appointments. The use of CGM and of hybrid closed-loop was really high, so more than 95 percent in both arms. As you would expect in a type 1 diabetes pregnancy, there were some women in both arms with episodes of severe hypoglycemia, but I have to say the hypoglycemia rates were the lowest we'd ever seen in this sort of patient population. And there was one episode of DKA in each arm in

the trial, so absolutely nothing of concern.

Dr. Buse:
The conclusions you provide in the articles are quite strong, but I do think reasonable, and so I'd like to quote them. Quote: "Hybrid closed-loop therapy should be offered to all pregnant persons with type 1 diabetes," closed quotes. Is there anything else you'd like to share before we close for the day?

Dr. Murphy:
So I'd like to say that this is the pregnancy-specific hybrid closed-loop, so it is a system that uniquely targets those pregnancy glucose levels. And just the other thing to mention is that the hybrid closed-loop system was started early during pregnancy, so it was started in the first trimester, and the benefits were really rapid. So on average, we started women around 11 weeks gestation, and even by the 12 weeks we already had five percentage point increase in the time spent, so we could start closed-loop very safely during the first trimester both in pump users and an injection users. And we know this is crucially important for pregnant women to have the safety and for clinicians who are looking after them. So I would say the earlier you start hybrid closed-loop, the better, preferably before pregnancy, but if started during pregnancy, then sooner is better than later.

Dr. Buse:
That's very well said. This has been a really interesting conversation. I'd like to thank my guest, Dr. Helen Murphy, for being here and for sharing her findings on hybrid closed-loop insulin therapy in pregnant women with type 1 diabetes.

Helen, it was great speaking with you today.

Dr. Murphy:
Thank you very much, and I'm more than happy to be contacted by anyone who has questions about this study.

Dr. Buse:
For ReachMD, I'm Dr. John Buse. To access this and other episodes from our series, visit *Diabetes Discourse* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.