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Concentrating on the MOMPOD Trial for Metformin Plus Insulin

Dr. Buse:
Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse, and joining us to talk about the MOMPOD trial that focused on metformin plus insulin for preexisting diabetes or gestational diabetes in early pregnancy is Dr. Kim Boggess. She's a Professor of Maternal Fetal Medicine at the University of North Carolina at Chapel Hill.

Kim, thanks for speaking with me today.

Dr. Boggess:
I'm delighted to be here. Thank you, John.

Dr. Buse:
To give us some background, can you remind the audience why gestational diabetes is important and about the top-line screening recommendations?

Dr. Boggess:
Well, John, as you know, gestational diabetes, which is glucose intolerance identified during pregnancy, is the most common form of diabetes that we encounter in our pregnant patients. Added to that is preexisting type 2 diabetes, which is the most common form of preexisting diabetes in pregnancy. These conditions are associated with numerous adverse maternal, fetal, and neonatal outcomes. And we know from decades of experience and research that the key to optimizing health outcomes for both the mother and her offspring is to optimize maternal glucose control.

Dr. Buse:
I take it that there's been some controversy regarding the treatment of gestational diabetes and preexisting diabetes in pregnancy. What have been the standard treatment recommendations of late?

Dr. Boggess:
There's been a lot of interest in optimizing glycemic control and the best pharmacologic agents to do so, and the gold standard to which everything is compared to is insulin. Insulin is the agent that is used to treat preexisting type 1 diabetes and for many, many years was the first-line therapy for treatment of gestational diabetes and type 2 diabetes in pregnancy. There was some data published in the early 2000s that showed that oral hypoglycemic agents were an acceptable alternative to insulin for the treatment of gestational diabetes, and that early data was very promising, particularly in the use of the sulfonylureas and metformin. However, later data showed that those agents were not comparable to insulin in terms of maternal and infant outcomes, and so the pendulum went from "insulin only" to "oral agents are acceptable and comparable," to "wait a second, maybe the oral agents aren't as good." And our current recommendations from our national guidelines are "insulin is the treatment of choice for gestational diabetes and for preexisting type 2 diabetes."

Dr. Buse:
Great. That really sets things up perfectly. So let's talk about your MOMPOD trial. By the way, best trial name ever. Can you tell us about the study design?

Dr. Boggess:
So the MOMPOD trial is a randomized clinical trial of adjuvant metformin versus placebo added to insulin for the treatment of gestational diabetes identified early in pregnancy defined as less than 23 weeks or patients with preexisting type 2 diabetes. All of the participants received insulin, and half of them received either oral metformin or placebo for treatment of their diabetes and for management of their glycemic control.

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. Kim Boggess about her study on metformin plus insulin for preexisting diabetes or gestational diabetes in early pregnancy.

So, Kim, with all that background in mind, what were the key findings to the MOMPOD trial?

Dr. Boggess:
Well, our primary outcome was the composite adverse neonatal outcome that encompassed the common adverse outcomes seen in infants born of mothers with gestational or preexisting type 2 diabetes, and we hypothesized that metformin would improve maternal glycemic control, and thus result in improved neonatal outcomes. However, we found that the addition of metformin did not improve our overall composite adverse neonatal outcome. However, we did find that the participants that were randomized to metformin were significantly less likely to deliver a large for gestational age infant, and they were significantly less likely to have an infant with macrosomia.

Dr. Buse:
So it's interesting in the clinical trials of metformin plus insulin versus metformin alone in just type 2 diabetes in adults, metformin doesn't really improve glycemic control in that setting either. It does result in a slightly lower insulin dose and less weight gain. Did you have changes in weight that were important?

Dr. Boggess:
So we did not. Surprisingly, John, we did not find that patients who were randomized to metformin used less insulin or had less weight gain, and those findings are actually in contradistinction to the findings of another randomized clinical trial of metformin plus insulin versus placebo in pregnant patients with type 2 diabetes. The Canadian trial called the MiTy trial also found no difference in composite adverse neonatal outcome, but they did find maternal benefits in that there was less weight gain and less insulin dosing used.

Dr. Buse:
I took a look at this paper, and in the second table, just about everything important for the baby trended in the right direction. As you mentioned, there weren't major statistically significant findings. The one thing that trended in the wrong direction, which I can't wrap my head around at all was there were numerically a few more small for gestational age or low birth weight infants. Was there any thinking about that, or is that just the play of chance? I mean, was this statistically significant?

Dr. Boggess:
I'm really glad you brought that up, John, because, as I mentioned, the MiTy trial in the previous response, they actually found a significant increase in small for gestational age infants, and so we were very interested in SGA as a secondary outcome in our population. And as you noted, while there was a trend towards an increase that it was not significant. What's interesting about our findings is that we had a much lower prevalence of the occurrence of SGA, or small for gestational age infant, in our population compared to the population of the MiTy trial, and so we clearly weren't powered to see any difference. However, it's also a very different population of patients because the rate of SGA was so much lower in our study than it was in the other trial.

Dr. Buse:
Great. And with all that said, does your study or the MiTy trial have implications for where the guidelines need to go?

Dr. Boggess:
Well, right now I think it's fair to say that metformin, at least in a US population, cannot be recommended solely for the improvement of a composite neonatal outcome, and it shouldn't be recommended for improvement in the maternal outcomes, at least weight gain and insulin dosing. What was reassuring about our trial is that we had over 800 participants, and so we were able to look at safety data and adverse events in a more detailed way than other studies of metformin in pregnancy because of the number of patients that we enrolled. And I can at least reassure providers that there at least does not appear to be any short-term harm or short-term adverse effects of metformin use. I don't think we're at the place where we can change our recommendations to say you absolutely should or should not include metformin as part of the treatment algorithm for pregestational type 2 or early gestational diabetes in pregnancy.

Dr. Buse:
And as I understand it, your team will be following up on the offspring of participants from the study. What are you looking for?

Dr. Boggess:
That's a wonderful segue to the thought that there weren't any adverse short-term outcomes because we know that metformin has the potential for reprogramming through epigenetic mechanisms, and there is animal data to suggest that in utero metformin exposure may, in fact, lower birth weight, which it did also in the human trials, but sets those offspring up for obesity later on in life, so our follow-up study will focus on the primary outcome of childhood overweight and obesity. We also know that there are potential effects of metformin

on cardiovascular health and renal outcomes, and we will be looking at those as well. We'd love to look at the development of type 2 diabetes in our children, but our study cohort will only be about age seven to 10, so we won't have enough children to look at that outcome.

Dr. Buse:
Well, maybe our children as future healthcare professionals can continue to follow that cohort and give us some more answers 50 years from now. Before we close, Kim, are there any final thoughts you'd like to share with our audience today?

Dr. Boggess:
I think that it's important for the audience to recognize that diabetes-complicating pregnancy is a very common disorder that has significant implications for both maternal and infant health, and thinking about how to optimize outcomes by improving glycemic control should occur as early as possible in the pregnancy to give that dyad the best chance of a healthy outcome.

Dr. Buse:
Well, Kim, thank you so much for your leadership in this field and for today providing us this really interesting conversation. Thank you for sharing your insights on your study focusing on metformin plus insulin for preexisting diabetes or gestational diabetes in early pregnancy. Kim, it was great speaking with you today.

Dr. Boggess:
Thank you very much, John.

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.