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Guiding Principles of Treating Gestational Diabetes

Dr. Buse:
Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse, and joining us for a discussion of the treatment of gestational diabetes is Dr. David Simmons, who's a Distinguished Professor of Medicine at the Western Sydney University Macarthur Clinical School in Australia.

Dr. Simmons, thanks for speaking with me today.

Dr. Simmons:
Thank you very much, John. Thank you for giving me the opportunity.

Dr. Buse:
So, David, guidelines around gestational diabetes have been in flux for a number of years as we struggle to develop the evidence base on how intensively we should be managing women during pregnancy in an effort to normalize outcomes in the setting of gestational diabetes. Can you give us the background on why we keep pushing in gestational diabetes for more stringent efforts?

Dr. Simmons:
Yes, certainly, John. Essentially, gestational diabetes is a glucose that's just slightly raised, less than overt diabetes in pregnancy, but not at the background rate. And for many years, it's been thought that the increase has been starting at 24 to 28 weeks, but there's been a growing recognition that in fact, the glucose may actually be high when women come into pregnancy. And the reason that this is important is that there are many obstetric and neonatal complications that come with gestational diabetes. Many of those are because of the increased size of the baby. It's a fatter baby, and therefore can get stuck, so therefore more shoulder dystocia and more birth trauma, and also the risk of stillbirth if the obstetric care cannot identify that that is a risk.

Gestational hypertension is also more common in preeclampsia, and there's more chance of the baby ending up in the neonatal intensive care unit, needing to be born earlier, and also for the mother to be longer in the wards, and also more chance of cesarean section, of course, to have that early intervention, which makes counting the harms that happened a little bit more complex because that happens to prevent stillbirth and prevent those fractures, so those are often underestimates of what would have happened had there not been intervention. And we have good randomized trials at 24 to 28 weeks showing that intervention can prevent many of these complications.

Now one of the reasons this is particularly important compared with type 1 and type 2 diabetes in pregnancy is because of the large numbers of women that are involved. If you think how many women have impaired glucose tolerance, impaired fasting glucose in the population, then you can see that this could actually be a very large number of babies ending up in the neonatal intensive care unit, for example.

Dr. Buse:
That's a great background. Can you tell us about the design of your particular study?

Dr. Simmons:
So we recruited women with risk factors for gestational diabetes and diabetes, including ethnicity, which included increased body mass index, age, and the usual suspects, prior gestational diabetes and so forth. And then at the beginning of pregnancy, before 19 plus six weeks, we undertook a glucose tolerance test, and we randomized those with early gestational diabetes as defined by the World Health Organization, or IADPSG, or one of the American Diabetes Association criteria so—and I apologize that this is in European—millimoles per liter but a 5.1, 10, or 8.5 millimoles per liter thresholds. There was no prior glucose challenge test, so risk factors, then straight into

that glucose tolerance test. And if elevated, then they were randomized to either early treatment or no treatment until the results of the glucose tolerance test at 24 to 28 weeks gestation. And some of those women did not have gestational diabetes on that repeat test, which is important. So we had 802 in the randomized trial who were well-balanced, but we also have the rest of the cohort for further studies, which I think you'll find is important downstream as we try to place the results of this randomized trial into what should we do with a wider population.

Dr. Buse:
So basically, that works out to a test of whether screening for gestational diabetes at 19 to 20 weeks, and potentially initiating therapy, then has advantages over screening for gestational diabetes per current guidelines at 24 to 28. Is that right?

Dr. Simmons:
That's exactly right. And the hypothesis is that we're testing, is exactly that, that early treatment of hyperglycemia in pregnancy results in improvements in perinatal outcomes was our primary outcome and without any harm to the baby. So there's always this worry about small for gestational age, and babies having reduced neonatal lean mass, for example. And we also obviously within this design, if you were a control woman, you can imagine that people say, "Oh, look, you're in the trial; you must have high glucose. We'll do A, B, or C." So we also ensured that we recruited decoys to mess them up, so you couldn't tell who had the high glucose early on and who didn't. They were just ordinary women who were in our bigger TOBOGM study. And so we used as our primary outcome—we used a composite of what most people would consider serious endpoints—so a composite of birth less than 37 weeks gestation, so prematurity; birth weight 4.5 kilos or more, seriously big baby; birth trauma using international criteria; neonatal respiratory distress, and that is particularly those that ended up in the neonatal intensive care unit for supportive breathing, but also those who required four hours or more of oxygen; need for phototherapy for jaundice; stillbirth or neonatal deaths; and shoulder dystocia. And we had 80 percent power to identify six percent reduction assuming a 10 percent loss to follow-up. But actually, when you had six percent loss to follow-up, so it's pretty well-powered. Also in this trial, we knew that many women would be treated from 24 to 28 weeks. So we know that treatment at 24 to 20 weeks can be successful, and can reduce LGA, so we wanted to really go for the really serious endpoints. And then our secondary outcome was hypertension, gestational hypertension, including preeclampsia and other forms of hypertension in pregnancy. And we use something called a gateway approach, which is if the primary outcome is positive, then we can look at the second. Our primary outcome was substantially positive, and then we went to the second, and there was no difference in hypertension in pregnancy between the two groups, and we think that's most likely because of the treatment that those women received once they had their GDM diagnosed at 24 to 28 weeks.

Dr. Buse:
Can you give us a little bit more detail on that primary outcome and your findings?

Dr. Simmons:
Yes. What we found was that there was overall an 18 percent reduction in those severe adverse pregnancy outcomes as the primary outcome. So in absolute terms, it's about 1 in 18 or 1 in 19 babies, no longer had those severe adverse neonatal outcomes, so we were very pleased with that, and that was obviously significant.

Some of our secondary outcomes though were significant. One of these, which was surprising, was the degree of reduction in third or fourth perineal injury. So usually, perineal tears are around two to three percent, and in this cohort in the controls, it was 3.6 percent, but in our treated group, it was down to .8 percent. I mean, that's pretty important that 1 in 50 women no longer has those lifelong, potentially lifelong, impacts of perineal injury.

Other secondary outcomes—there was no difference in the neonatal hypoglycemia—but once babies were admitted to neonatal intensive care unit, which there was no difference in admission rates, they were in there for a shorter time by about .8 days. So that's really important from obviously health economic perspective, and those analyses are underway at the moment.

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. David Simmons from Australia about the treatment of gestational diabetes in pregnancy.

So that's remarkable. You had better outcomes for the babies, better outcomes for the moms, better outcomes for the healthcare system. Were there any important subgroup analyses, women that particularly benefited or did not?

Dr. Simmons:
Thank you, John. And we think these findings in particular will influence policy, and we think that everyone should be aware of two sets of secondary analyses. One of them was we actually set up secondary analyses, which are essentially small randomized controlled trials in glucose bands, so we set up the randomization so that those within the fasting glucose of 92 to 94, the one-hour of 180 to 190, the

two-hour glucose of 153 to 161, they had a randomization within that, what we call the lower band, and it was about 40 percent of the women were in this lower band. And the rest of the women were in the upper band, which was a fasting glucose of 95 to 109, one-hour glucose of about 191, and a two-hour glucose of 162 to 199. We had excluded those women with a glucose above 200 milligrams per deciliter on the two-hour glucose, and we also excluded those with a fasting glucose of 110 milligrams per deciliter or more. And within these two bands in the higher glycemic range, the reduction in that primary composite was greater. It was a .78, so a 22 percent reduction in those severe adverse pregnancy outcomes. The absolute terms, that was a reduction in 7.8 percent so about 1 in 12, so that's pretty major.

We think of major importance in that particular band was the small-for-gestational-age incidents. And in that, the small for gestational age was increased by 75 percent, and that was significant, whilst there was no significant increase in the odds ratio. It was a nonsignificant 1.10 in the upper range. So we think that that lower range currently being used is associated with less benefit when used in early pregnancy, and also we think it's probably associated with harm. However, the upper range is associated with substantial benefits in terms of severe adverse pregnancy outcomes and is not associated with harm. So we feel that we need to review those odds ratios of 1.75 based on HAPO and go up to the odds ratio of two, and that's really what we're looking at the moment is how to do that, and what's the cost-effectiveness of that, and what are the wider issues there.

But we also undertook another secondary analysis, which was the timing of that early GTT, and in the first trimester, so before 14 weeks, which was only about 23 percent of our pregnancies—and that was across a number of countries—they were across Sweden and Austria and India and Australia, so this really is a big international study. And across all of us, what we found when we put these together, the reduction in severe adverse pregnancy outcomes, that composite, was .75, so a 25 percent reduction. After 14 weeks was a nonsignificant reduction to .82, the same as the wider group. So we think that within that 14-week slot, this is where the sweet spot is that we should really be starting our screening and treatment using a single glucose tolerance test. Using the odds ratio of two, we think is what our findings suggest.

Dr. Buse:
Well, that's a lot of results. This is going to give the guideline writers a great deal to think about. What do you think they should do with regards to future recommendations for women at high risk for elevated glucoses in pregnancy?

Dr. Simmons:
So we feel that along with the other studies, we feel that this is sufficient evidence to say not only should we obviously continue screening and testing for gestational in America, we should review the Carpenter and Coustan approach of 100 grams test of the 50 grams glucose challenge test, which misses a lot of women with a high fasting glucose, which is actually those we feel at the greatest risk. And what we should do is we should move our paradigm and realize that somewhere between 30 and 70 percent of these women who have gestational diabetes have already got hyperglycemia early in pregnancy, so we feel that we should start introducing the glucose tolerance test early in pregnancy as a 75 grams test rather 100 grams test as a one-step test. And then we feel that our data would support the use of the odds ratio of two early in pregnancy. We have had a large international meeting discussing what does that mean at 24 to 28 weeks, and the general consensus is that we should really use the same set of approaches and criteria early and late in pregnancy.

Dr. Buse:
Wow, this has been a really impactful conversation. I'd like to thank my guest, Dr. David Simmons, for being here and for sharing his key insights on the treatment of gestational diabetes and pregnancy.

David, thank you so much for joining us today.

Dr. Simmons:
Thank you very much for having me and allowing me to present on this work.

Dr. Buse:
For ReachMD, I'm Dr. John Buse. To access this episode and others from our series, visit ReachMD.com/DiabetesDiscourse where you can Be Part of the Knowledge. Thanks for listening.