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Diabetes Care®

In This Issue of *Diabetes Care*

By Max Bingham, PhD

Maternal Glycemia and Gestational Diabetes Mellitus Results in Subsequent Offspring Glycemia in Adolescence

A commentary by Brown et al. (**p. 393**) on two studies relating to maternal glycemia and gestational diabetes mellitus calls for further research to evaluate how to treat pregnant women to prevent abnormal glucose metabolism in offspring during adolescence. In addition, the authors also call for work on understanding exactly why this phenomenon occurs, citing a string of factors that might be involved. The commentary focuses on two studies related to the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, which originally showed that increasing maternal glycemia that is untreated can result in a range of adverse pregnancy and neonatal outcomes. Now, two long-term follow-up studies of these offspring (published in this issue of *Diabetes Care* [Lowe et al., **p. 372** and Scholtens et al., **p. 381**]) examine the metabolic outcomes when these children were aged 10–14 years. According to the commentary, exposure to gestational diabetes mellitus resulted in offspring having impaired glucose tolerance and reduced insulin sensitivity when they were adolescents but the individuals did not show signs of impaired fasting glucose or type 2 diabetes. Meanwhile, increasing levels of maternal glycemia were associated with impaired glucose tolerance and fasting glucose, raised HbA_{1c} values, and reduced insulin sensitivity in the adolescent offspring. While the commentators call for further research on the phenomenon, they highlight that the findings provide strong argument for better diagnostics for glucose levels in pregnancy, and they remind readers that childhood obesity, metabolic disease, and type 2 diabetes are still difficult to treat and any intervention to prevent their emergence should be considered, including during pregnancy. Commenting further, author Florence M. Brown stated: "The two studies fill a knowledge gap regarding the long-term metabolic outcomes of offspring exposed to increasing degrees of maternal glycemia in pregnancy. Additional strengths of the studies were that mothers and offspring were ethnically/racially diverse and so the results have broad implications. Mothers' blood glucoses in pregnancy are early markers for offspring metabolic risk later in life."

Brown et al. Much to HAPO FUS about: Increasing maternal glycemia in pregnancy is associated with worsening childhood glucose metabolism. Diabetes Care 2019;42:393–395

Lower Cognitive Scores and Altered Brain Growth Following Diabetic Ketoacidosis in Young Children

More serious episodes of diabetic ketoacidosis (DKA) in very young children with type 1 diabetes is associated with altered brain development and lower cognitive scores, according to a study by Aye et al. (**p. 443**). As a result, the authors call for the development of screening programs to identify family members who might be at risk and to increase awareness of type 1 diabetes symptoms, mainly in a bid to avoid DKA in the first place. The study initially involved 144 children aged ~4–10 years with type 1 diabetes. Participants were then grouped according to their severity of DKA, which mostly occurred at the time of diagnosis. They then underwent various MRI scans and cognitive tests at baseline (median time from DKA event was 2.9 years) and after 18 months. The authors found that after grouping the participants according to DKA severity, those with more severe DKA incidents scored worse in the cognitive tests but gained more in terms of total and regional white and gray matter volume over 18 months of follow-up. Explaining the results, they suggest that a DKA event likely results in metabolic disturbances, which might lead to ischemia/reperfusion of the brain or, alternatively, the release of inflammatory factors such as cytokines. In turn, these might lead to the increased brain growth rates, particularly in those with more severe DKA events, as a compensatory event to neural insult. While they do explain a number of limitations with the research, including a small sample size, the authors point out that the differences seen between the groups were statistically significant, but clinical significance is not known at this stage, hence underlining the clear need for further follow-up. According to author Tandy Aye: "The acute complications of DKA are known but we need to learn more about the long-term impact of moderate and severe DKA events. Prevention of DKA is essential."

Aye et al. Impact of early diabetic ketoacidosis on the developing brain. Diabetes Care 2019;42:443–449

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Time in Range as a Blood Glucose Metric and Predictor of Microvascular Complications in Diabetes

There is a compelling case that time in range for blood glucose levels is associated with certain microvascular complications of diabetes, according to Beck et al. (**p. 400**). Specifically, they found that time in a range of 70–180 mg/dL for blood glucose was strongly associated with (reduced) risk of the development and progression of retinopathy and the development of microalbuminuria. The conclusions come from an analysis of data from the Diabetes Control and Complications Trial (DCCT) and involved 1,440 individuals who provided 7-point blood glucose concentration blood samples every 3 months over the 10-year trial. Outcome measures included retinopathy gradings from fundus photography obtained every 6 months, and for microalbuminuria, albumin excretion rate was assessed every 12 months. They found that the overall mean time in range was 41 ± 16%. Participants who received intensive treatment in trial were 52 ± 10% time in range while those on conventional treatment were 31 ± 12% time in range. Most measurements that were outside of the target range indicated hyperglycemia. For those who developed microvascular complications, time in range was substantially lower than it was in individuals who remained free of complications. In terms of hazard rates, the retinopathy outcome was increased by 64% and microalbuminuria by 40% for each 10% lower time in range. Other glycemic metrics such as mean glucose concentrations, amount of hyperglycemia, and A1C all strongly correlated with time in range. Based on the analysis, the authors suggest that although A1C remains a valuable metric, it now should be recognized that with wider usage of continuous glucose monitoring devices, time in range has advantages as an outcome metric and is strongly associated with predicting risk of microvascular complications associated with diabetes. Commenting further on the research, author Roy W. Beck said: "Based on these results, a compelling case can be made that time in range is strongly associated with the risk of microvascular complications. I hope that the U.S. Food and Drug Administration will find this evidence convincing to begin accepting time in range, measured with continuous glucose monitoring, as an acceptable end point for clinical trials."

Beck et al. Validation of time in range as an outcome measure for diabetes clinical trials. Diabetes Care 2019;42:400–405

Legacy Effects of Intensive, Early Treatment of Glycemia in Type 2 Diabetes Exists in the Real World

The legacy effect of early intensive treatment for glycemia in type 2 diabetes likely exists in real-world patient populations, according to Laiteerapong et al. (**p. 416**). Specifically, patients newly diagnosed with diabetes and HbA_{1c} >6.5% in year one had significantly greater risk for macrovascular and microvascular complications and in some cases mortality at 10 years. As a result, the authors stress the importance of intensive treatment for newly diagnosed patients to avoid complications later on that are difficult to fully cure. The conclusions come from a cohort study involving just under 35,000 patients in the Kaiser Permanente Northern California health system with newly diagnosed type 2 diabetes and 10 or more years of survival. The authors looked for any associations between bands of HbA_{1c} measurements stretching from <6.5 to ≥9.0% taken shortly after diagnosis and up to many years later and future incidence of microvascular and macrovascular complications and mortality. They found that compared with the group with HbA_{1c} <6.5% shortly after diagnosis, any level of HbA_{1c} above 6.5% was associated with increased microvascular and macrovascular events. These included complications such as renal disease, eye disease, amputation, stroke, and heart or vascular diseases. Risk of more serious events including certain macrovascular issues and death emerged for higher levels of HbA_{1c} and longer exposure times. This followed adjustment for a range of potential confounding factors such as age, various cardiovascular risk factors, and other comorbidities. While acknowledging a number of study limitations, the authors conclude that elevated HbA_{1c} levels risk later complications, particularly following diagnosis. They suggest that based on this conclusion, the legacy effect of intensive early treatment, only seen so far in trials, actually does exist in the real world. Commenting further, author Neda Laiteerapong told *Diabetes Care*: "These results suggest that patients and providers should take a new diagnosis of diabetes seriously and work aggressively to achieve an HbA_{1c} <6.5% as soon as possible."

Laiteerapong et al. The legacy effect in type 2 diabetes: impact of early glycemic control on future complications (the Diabetes and Aging Study). Diabetes Care 2019;42:416–426

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