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In This Issue of *Diabetes Care*

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Poor Pregnancy Outcomes With Early Gestational Diabetes Mellitus

A large cohort study suggests that gestational diabetes mellitus (GDM) in early pregnancy seems to be associated with poor pregnancy outcomes that are similar to those seen with pregestational diabetes. Disconcertingly, this was despite intensive intervention and management. The results, reported by Sweeting et al. (**p. 75**), follow a 20-year examination of pregnancy outcomes of ~4,900 women with GDM. According to the authors, previous intervention studies clearly show that treatment for GDM diagnosed after 24 weeks significantly reduces adverse pregnancy outcomes. However, the recommendations on screening and intervention for GDM before 24 weeks are much less clear, and evidence to support specific treatments for such patients is not widely available. Indeed, no study had previously looked at early maternal dysglycemia that would not normally be classed as diabetes, pregnancy outcomes, and, importantly, whether interventions in such a group made any difference. To that end the authors set out to determine the prevalence, clinical characteristics, and pregnancy outcomes of women diagnosed with GDM before 24 weeks and women with preexisting diabetes and then compare with the outcomes of women diagnosed after 24 weeks. Poor pregnancy outcomes associated with GDM (such as preeclampsia, preterm delivery, and neonatal jaundice) were all more prevalent in the early GDM group. Moreover, rates were more comparable to those in the group with preexisting diabetes than with a later diagnosis of GDM. Worryingly, this was despite intensive treatments in the early diagnosis group. Commenting more widely on the outcomes, Dr. Sweeting stated: "The gradation in risk of poor pregnancy outcomes associated with an early diagnosis of GDM suggests a heterogeneity of the phenotype, with women diagnosed with abnormal glucose tolerance prior to 12 weeks' gestation an especially high-risk cohort. Accordingly, these women require increased surveillance throughout pregnancy. These findings also indicate the need for further studies to establish the efficacy of earlier diagnostic processes as well as early and/or alternative management approaches to improve outcomes in these high-risk pregnancies."

Sweeting et al. Gestational diabetes mellitus in early pregnancy: evidence for poor pregnancy outcomes despite treatment. Diabetes Care 2016;39:75–81

Alogliptin for Prevention of Atherosclerosis in Type 2 Diabetes

Results from a randomized controlled trial suggest that alogliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, may be able to inhibit and prevent progression of carotid atherosclerosis in patients with type 2 diabetes. The study by Mita et al. (**p. 139**) investigated the effects of the drug in patients with type 2 diabetes who were free of cardiovascular diseases (CVDs) and compared them with those in equivalent patients who remained on conventional non–DPP-4 inhibitor treatments. Primary outcomes were changes over a 2-year period in a range of measurements of intima-media thickness (IMT) of the carotid artery as measured by echography. Alogliptin resulted in significantly greater reductions in circulating glucose and greater reductions in IMT over the period of the trial. This was in comparison with patients receiving conventional treatments. While clearly resulting in an antiatherogenic effect, the mechanisms behind the effects, as the authors point out, remain to be established, and the limitations in the study design mean that some caution is needed in interpreting the outcome. As a result, the authors call for large-scale prospective trial(s) to "establish the usefulness of DPP-4 inhibitors for primary prevention of CVD in patients with [type 2 diabetes]." Commenting more widely on the study, Dr. Mita stated: "Our data suggest that early and effective intervention with DPP-4 inhibitors before the development of advanced atherosclerosis in patients without history of apparent CVD is likely to be beneficial in prevention of carotid IMT progression. This result may provide some evidence that clinical physicians place priority on the use of this class of agents as one of the optimal oral hypoglycemic agents in terms of preventing the progression of atherosclerosis. However, it is not possible to conclude that the effects of DPP-4 inhibitors on the progression of atherosclerosis found in this study could be generalized to a wider range of patients with type 2 diabetes and therefore more studies are required."

Mita et al. Alogliptin, a dipeptidyl peptidase 4 inhibitor, prevents the progression of carotid atherosclerosis in patients with type 2 diabetes: the Study of Preventive Effects of Alogliptin on Diabetic Atherosclerosis (SPEAD-A). Diabetes Care 2016;39:139–148

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ZnT8A Associations in Type 1 Diabetes Suggest More Aggressive Disease Progression

Positivity for zinc transporter 8 autoantibodies (ZnT8A) at diagnosis of type 1 diabetes may reflect a more aggressive form of disease progression, particularly in relation to β-cell function and increased insulin requirements. Moreover, a combination of assays for ZnT8A and two other antibodies may represent a cost-effective method for detecting β-cell autoimmunity. These are the conclusions of a population-based study by Juusola et al. (**p. 118**) that investigated the relationship between ZnT8A and type 1 diabetes progression in Finnish children over a period of 2 years. Using serum samples collected at the time of diagnosis from 723 children, the authors found that ~73% were positive for ZnT8A. These children were likely to have lower blood pH, more frequent ketoacidosis, and lower serum C-peptide concentrations and required higher insulin doses over time than the ZnT8A-negative children. The HLA DR3 allele was associated less often with being ZnT8A positive. According to the authors, this suggests, when taken together, that a strong initial immune response against ZnT8A might suppress β-cell function and that ZnT8 might act as some kind of cellular regulator of β-cells. Combined with the observations around ketoacidosis rates, they suggest that positivity for ZnT8A may indicate that a more aggressive disease progression is likely. The study also included an analysis of a range of other antibodies relevant to type 1 diabetes. These included ICA, GADA, IA-2A, and IAA and when analyzed alongside ZnT8A, the authors found that a combination of ZnT8A, GADA, and IA-2A allowed them to detect 97.9% of cases. On the basis of these results, they suggest that this strategy could represent a cost-effective approach toward the detection of β-cell autoimmunity. Commenting more widely on the outcome of their analysis, Dr. Knip stated: "Autoantibodies not only are predictors of clinical type 1 diabetes in subjects at risk but may even function as markers of the aggressiveness of the disease process in both preclinical and clinical type 1 diabetes."

Juusola et al. Positivity for zinc transporter 8 autoantibodies at diagnosis is subsequently associated with reduced β-cell function and higher exogenous insulin requirement in children and adolescents with type 1 diabetes. Diabetes Care 2016;39:118–121

Depressive Symptoms and Stress Increase Incidence of Adverse Cardiovascular Outcomes in Diabetes

Elevated stress levels and depressive symptoms either combined or alone are common in individuals with diabetes and may be associated with increased risk for adverse cardiovascular disease outcomes, according to an analysis by Cummings et al. (**p. 101**) who examined the relationship between depressive symptoms and stress in adults with or without diabetes and incidence of cardiovascular outcomes, such as stroke, heart attack, and death. The analysis was part of the wider 22,000-strong REGARDS population-based, cohort study. The authors report that individuals with diabetes were more likely to report stress and/or depressive symptoms and that these comorbidities were associated with significantly increased incidence of stroke and death due to cardiovascular complications. No such associations existed in those without diabetes. "Behavioral comorbidities are common in individuals with diabetes, and the present study demonstrates that these comorbidities are associated with substantially increased risk for adverse cardiovascular outcomes in subjects with diabetes. These findings raise important issues that bear consideration," said Dr. Cummings. "The first is that providers need to be more cognizant of the emotional side of diabetes in their patients. Despite the availability of screening instruments, screening for emotional and behavioral health is unfortunately an uncommon practice in most primary care settings. Further, more research is needed to understand the extent to which increasingly complex glycemic, blood pressure, and lipid medication regimens in individuals who are already struggling to successfully implement lifestyle changes and disease monitoring behaviors—often in the midst of complex lives with multiple competing priorities and inadequate support—may contribute to these emotional problems. Once present, we also need to better understand the extent to which these behavioral comorbidities interfere with important care-taking behaviors, including lifestyle and medication adherence behaviors, that may contribute to adverse cardiovascular outcomes." Turning to implications Dr. Cummings stated: "Finally, future research needs to investigate new models of integrated care delivery that consistently identify and successfully manage these comorbidities in primary care settings where most diabetes is managed."

Cummings et al. Consequences of comorbidity of elevated stress and/or depressive symptoms and incident cardiovascular outcomes in diabetes: results from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. Diabetes Care 2016;39:101–109

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