COMMENTARY

Metabolomic Markers in Early Pregnancy for Gestational Diabetes Mellitus

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Gestational diabetes mellitus (GDM) is one of the most common pregnancy complications, affecting 2–22% of all pregnancies depending on diagnostic criteria and study populations (1). GDM reflects an increased risk of type 2 diabetes (T2D) and cardiovascular diseases after the index pregnancy in women (2–4). Offspring born to mothers with GDM have an elevated risk of developing T2D and cardiovascular diseases, likely before reaching reproductive age (5–8). Thus, GDM has been considered one of the key contributors to the vicious intergenerational cycle of cardiometabolic diseases and a major challenge in obstetric care. Currently, tools are lacking to identify women in early pregnancy with a higher risk of developing GDM. As a result, neither mothers nor fetuses are treated until late in the second trimester (usually 24–28 gestational weeks), when GDM is diagnosed.

Although emerging evidence tends to indicate that women with GDM exhibit metabolic alterations earlier in pregnancy, the efforts to identify biomarkers for GDM in early pregnancy have achieved only limited success (9,10). GDM is a multifactorial condition, and there is no single pathway that contributes to the development of GDM (11). This complexity presents a challenge for the examination of one or several targeted molecules using the traditional approaches. The recent advances in metabolomics, an approach involving systematic analysis of numerous metabolites that detects subtle changes in the metabolic network, provides a new opportunity (12). Metabolomics has a unique advantage over other "omics" technologies (i.e., genomics, transcriptomics, and proteomics) because it measures molecular phenotypes that are the net results of other omics, therefore providing the most integrated profile of pathophysiologic status. Additionally, metabolites are more stable in most biospecimens than proteins and RNA. We conducted a systematic review of studies using the metabolomics approach to investigate early biomarkers for predicting GDM in 2018 (13) and updated our review in 2021. As indicated by other reviews on this topic (14–16), the emerging evidence has suggested metabolomics is a promising tool for identifying novel metabolic pathways for GDM risk. Previous studies have consistently identified metabolites that are involved in several important pathways, including amino acids, bile acids, carbohydrate metabolism, lipid metabolism, inflammation, oxidative stress, and gut microbiota–generated metabolites. However, available studies only yielded minimally consistent findings for specific metabolites or metabolite panels in early pregnancy with high predictive powers for GDM. There are multiple explanations for such highly inconsistent results. First, studies in this area have used different biospecimens (e.g., plasma/serum, urine, amniotic fluids, and hair samples) and employed different instruments and technologies for metabolomic profiling (i.e., mass spectrometry or nuclear magnetic resonance spectroscopy). Even among studies using blood biospecimens, the majority used nonfasting samples, which could be influenced largely by an individual's last meal and the time between that meal and biospecimen collection. Second, the criteria for GDM diagnosis are different across studies and countries. Third, most studies only included one racial group (e.g., Caucasian or Chinese), which could limit the generalizability of the findings. Fourth, most studies have relatively small sample sizes (most had <100 GDM cases), which could increase the chance of random errors. Last but most importantly, only a few studies included validation, either internally or externally. Validation is critical for identifying predictive biomarkers, and external validation is considered the gold-standard approach to show the generalizability of the study findings. Unfortunately, the three studies with validations have considerable design issues. The first U.K. study (Cambridge Baby Growth Study [CBGS]) had a small sample size, only internal validation (13 and 35 GDM cases in the discovery and validation data set, respectively), only lipid metabolites, and nonfasting

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serum biospecimens (17). Another U.K. study had large sample sizes in both the discovery data set (Born in Bradford [BiB] cohort) and validation data set (UK Pregnancies Better Eating and Activity Trial [UPBEAT]); however, the blood biospecimens in both were examined at the same time, when GDM was diagnosed, which is less meaningful for GDM prediction (18). The recent study conducted in Poland had a very small internal validation data set (25 GDM cases), and the time windows of biospecimen collection were different in the discovery data set (24–28 gestational weeks when GDM has been diagnosed) and the validation data set (8–14 gestational weeks), which is pragmatic (19).

In this issue of *Diabetes*, Zhu et al. (20) filled several of the abovementioned research gaps by conducting a well-designed metabolomics study with a total of 203 GDM case subjects and 622 non-GDM control subjects. In this study, the investigators included two independent studies of pregnant women in the U.S. (i.e., the Pregnancy Environment and Lifestyle Study [PETALS] and the Gestational Weight Gain and Optimal Wellness [GLOW] study). The unique strength of this study is that investigators divided the study data sets into a discovery data set (a nested case-control sample from PETALS), an internal validation data set (a random subsample from PETALS), and an external validation data set (a nested case-control sample from GLOW). Additional strengths of this study included the following: *1*) all participants had fasting serum biospecimens (overnight fasting for 8–12 h) collected prospectively before (<19 gestational weeks) the diagnosis of GDM, *2*) all individuals with GDM were screened and diagnosed using the same approach and criteria, *3*) untargeted metabolomic profiling for the discovery and validation data were performed by the same laboratory and utilized the same platforms and technologies, and *4*) the study population was racially diverse, with 78% being Hispanic, Black, and Asian individuals. This study identified a 17-metabolite panel at 10–13 gestational weeks that outperformed the model using conventional risk factors (area under the curve [AUC] 0.832 vs. 0.742) in the discovery data set. This 17-metabolite panel also had good to excellent performance in the internal validation data set (AUC 0.771) and the external validation data set (AUC 0.907). This study confirmed several metabolic pathways reported in previous studies, but more importantly, several metabolites included in the panel were reported in previous studies, including 1,5-anhydroglucitol, alanine, β-alanine, β-sitosterol, citric acid, β-tocopherol, uric acid, and urea (13). With its rigorous design, this study offers a piece of important evidence that shows the robustness of these highly predictive and replicable metabolites in the development of GDM. A couple of study limitations are worth mentioning. This study only included 144 known metabolites, which may limit its capacity to replicate findings from previous studies that included much larger numbers of metabolites. PETALS had fasting serum metabolomic profiling at two time points in early pregnancy. This study selected two GDM predictive metabolite panels separately (i.e., 17-metabolite panel at 10–13 and 10-metabolite panel at 16–19 gestational weeks). Although several metabolites were selected in both panels (e.g., 1,5-anhydroglucitol, 2,3-dihydroxybutanoic acid, α-aminoadipic acid, and citric acid), the investigators did not evaluate the predictive performance and estimate the reproducibility of these important metabolites. Like other biomarkers, predictive metabolomic markers should have high discrimination capacity and good reproducibility.

In summary, metabolites are the end products of biological regulatory and metabolic processes; thus, their levels can reflect the biological responses to genetic, lifestyle, and environmental exposures. Because metabolites are closely related to an individual's phenotype, the metabolomics approach offers a valuable tool for early prevention and treatment of GDM that intends to improve maternal and infant outcomes. Future studies should *1*) identify the optimal timing for collecting biospecimens, *2*) investigate the GDM predictive metabolites that have been replicated in multiple studies using the targeted method, which can provide more accurate quantitative values, and *3*) investigate whether these metabolites serve as early intervention targets by identifying their modifiable upstream determinants (such as diet, physical activity, sleep, stress, and air pollution). To be applied in clinical practice, the key GDM predictive metabolomic markers or metabolite panels also need to be evaluated by their sensitivity, specificity, and reproducibility in large and racially diverse populations.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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