EDITORIAL

Disturbances in insulin secretion and subclinical inflammation in normoglycemic women with a history of pregnancy complicated by gestational diabetes mellitus

Ewa Wender-Ożegowska, Paweł Gutaj

Department of Obstetrics and Women's Diseases, Poznan University of Medical Sciences, Poznań, Poland

Despite several inconsistencies in diagnostic standards, screening for gestational diabetes mellitus (GDM) is recommended in many European countries, including Poland.[1] This is an evidence-based approach because hyperglycemia in pregnancy is associated with unfavorable pregnancy-related outcomes such as macrosomia, birth injuries, neonatal hypoglycemia, and hyperbilirubinemia.[2,3] However, GDM is not only an issue in perinatal medicine. GDM predisposes the offspring to the development of obesity in the future, and this effect seems to be independent of genetic and societal factors.[4,5] This suggests the role of diabetic intrauterine environment in fetal programming. Based on these facts, all women should be informed that their dietary and lifestyle habits could directly impact long-term health outcomes of their children. Screening for GDM also gives us, physicians, an excellent opportunity to diagnose, treat, and educate women at especially high risk of developing type 2 diabetes in their future lives.

There is strong evidence that GDM and type 2 diabetes have common pathophysiology. Both diseases share similar risk factors and susceptibility genes. Chronic low-grade inflammation may also link GDM and type 2 diabetes. In consequence, the incidence of GDM is rising in parallel with the epidemics of obesity and type 2 diabetes.[6] Pregnancy offers the window of opportunity to break the intergenerational cycle of diabetes. However, our attempts to fully achieve that goal should definitely go beyond pregnancy.

The September 2015 issue of the *Polish Archives of Medicine (Pol Arch Med Wewn)* included an interesting research article focusing on the metabolic status of women after pregnancy complicated by GDM.[7] Molęda et al[7] compared 199 women with a history of GDM with 50 normoglycemic controls matched for age, body mass index (BMI), and the number of pregnancies. The patients were studied 5 to 12 years after their pregnancies. This is the period when the risk of developing type 2 diabetes seems to be the highest.

Molęda et al[7] studied several parameters involved in metabolic risk, including anthropometric measures, body composition, insulin resistance and secretion, and serum levels of selected adipokines. As expected, the authors found higher proportions of prediabetes and type 2 diabetes in women with a history of GDM. Moreover, women with a history of GDM showed lower insulin secretion rates and higher concentrations of proinflammatory cytokines (soluble tumor necrosis factor α [sTNF-α] and interleukin 6 [IL-6]). In the next part of their study, Molęda et al[7] divided women with previous GDM into a subgroup of women who were normoglycemic during the oral glucose tolerance test (OGTT; the NGT-pGDM[+] group) and those who had either abnormal fasting glucose levels or abnormal glucose tolerance. Normoglycemic women with previous GDM were then compared with controls (the NGT-GDM[–] group).

Undoubtedly, the most interesting results of the study come from the second part of the analysis. Interestingly, despite having normal BMI and glucose levels in the OGTT, the NGT-GDM(+) group still showed significantly higher levels of sTNF-α and IL-6 and diminished β-cell function in comparison with controls. This is an important finding because it shows a distinct metabolic profile of women who are classified as nondiabetic based on normal OGTT results. Nonetheless, further research is needed to establish whether these alterations may have clinical implications.

Correspondence to:
Prof. Ewa Wender-Ożegowska, MD, PhD, Klinika Położnictwa i Chorób Kobiecych, Uniwersytet Medyczny im. K. Marcinkowskiego w Poznaniu, ul. Polna 33, 60-535 Poznań, Poland, phone: +48 61 841 96 41, fax: +48 61 841 96 47, e-mail: ewaoz@post.pl
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As the authors admit themselves, their study has several limitations. Based on the results, they cannot answer the question of whether metabolic alterations in patients with previous GDM were either observed before pregnancy or were secondary to GDM. Prospective studies of pregnant women with a long-term follow-up postpartum would provide valuable data; however, in our opinion, of major importance is the fact that women who suffered from GDM should be monitored to diagnose metabolic disturbances.

A study that evaluated the risk of metabolic syndrome in women with a history of GDM had already been published in the *Pol Arch Med Wewn* before.[8] Among 153 patients who were treated because of GDM within 6 years after pregnancy, 79 patients had already been treated for diabetes mellitus or because of glucose intolerance. Seventy-four patients, as well as the control group that consisted of 155 subjects in whom GDM during pregnancy was excluded, had been subjected to a 75-gram OGTT. Metabolic syndrome was diagnosed according to the modified 2005 criteria from the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).[9] Patients from the study group were older than those from the control group (P <0.05) and their BMI was higher at the time of the index pregnancy and after the follow-up period (P <0.0001). Metabolic syndrome developed in 47 patients (30.7%) from the study group and 8 patients (5.2%) from the control group (P <0.001). The study group had all components of metabolic syndrome significantly more often than the control group: abnormal waist circumference, 57% vs 37.6% (P <0.005); hypertension, 18.9% vs 1.9% (P <0.001); elevated fasting glycemia, 79.1% vs 1.9%; hypertriglyceridemia, 21.6% vs 2.6% (P <0.0001); and decreased concentrations of high-density lipoprotein cholesterol, 11.1% vs 2.6% (P <0.005). Wender-Ożegowska et al[8] concluded that patients who suffered from GDM are at high risk of carbohydrate disturbances and metabolic syndrome in the following years; therefore, they should be under continuous medical surveillance that would enable early detection and treatment of metabolic disturbances.

There is still no uniform GDM screening approach worldwide, which may lead to inconsistencies in the diagnosis and resultant suboptimal care. Sometimes, there is even no general consensus within a single society. The American Diabetes Association, the leading diabetes society in the world, in their Standards of Medical Care from 2015 accepted 2 different diagnostic strategies—either a 1-step approach (75-gram OGTT) or 2-step approach (50-gram nonfasting screen followed by 100-gram OGTT for those who screen positive).[10] The Polish Diabetes Society approved the 1-step approach based on the results of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study. The ongoing HAPO Follow-up Study will analyze the cohort of 700 pairs of women and their offspring who participated in the HAPO study. The measures of adiposity, glucose, insulin sensitivity and secretion, lipids, inflammation, and blood pressure will be obtained in the mother–offspring pairs 8 to 12 years after participation in the HAPO study. We hope that this study will provide high-quality data and provide new insight into how maternal glucose levels during pregnancy affect mothers and their children.[11]

An increasing number of women who are overweight or obese when becoming pregnant justify an urgent need for interventional trials. The ongoing European multicenter, randomized controlled trial, DALI, will focus on the possible effects of lifestyle intervention (diet, physical activity, and the use of vitamin D) on the development of GDM in a high-risk population of overweight and obese pregnant women.[12] The results of this study will allow to identify measures that might be helpful in the prevention of GDM and, hopefully, will move Europe to adopt common diagnostic and therapeutic standards.

Prospective studies of pregnant women with a long-term follow-up postpartum would provide valuable data that would answer the question of whether metabolic alterations in patients with previous GDM either occur before pregnancy or are secondary to GDM.

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