COMMENTS AND RESPONSES

Response to Comment on: Goldberg et al. Circadian Variation in the Response to the Glucose Challenge Test in Pregnancy: Implications for Screening for Gestational Diabetes Mellitus. Diabetes Care 2012; 35:1578–1584

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We thank Dokus and Dokusova (1) for their interest in our recent article on circadian variation in the response to the glucose challenge test (GCT) in pregnancy and its implications for screening for gestational diabetes mellitus (GDM) (2). In this study, 927 pregnant women with a positive GCT underwent metabolic characterization with a 3 h 100-g oral glucose tolerance test (OGTT). Metabolic characteristics were compared across the following four groups that were defined based on time of day of the GCT: before 9:00 (n = 171); 9:00–10:59 (n = 288); 11:00–12:59 (n = 189); and after 13:00 (n = 279). This analysis revealed that, when compared on subsequent OGTT, women with a positive GCT in the afternoon have a better metabolic profile and lower risk of GDM than those with a positive GCT earlier in the day.

In their letter, Dokus and Dokusova suggest that, since the GCT is not necessarily performed in the fasted state, food intake during the day could have contributed to women with normal glucose tolerance (NGT) or gestational impaired glucose tolerance (GIGT) having a positive GCT in the afternoon. Indeed, in the original publication (2), we acknowledged that a limitation of the study was the lack of data on the time since participants' last meal. However, we also noted three factors that potentially argue against this basis for the observed findings. First, we demonstrate that there exist graded relationships across the day between the four GCT time groups and glycemia, insulin sensitivity (IS_{OGTT}), and β-cell function (insulin secretion-sensitivity index-2 [ISSI-2]), respectively. Second, upon sensitivity analysis restricted to only women whose GCT was performed in the afternoon, there were no significant differences in mean adjusted area under the glucose curve on the OGTT (AUC_{gluc}), IS_{OGTT}, or ISSI-2 between women tested from 13:00 to 13:59 (n = 112), those tested from 14:00 to 14:59 (n = 81), and those tested after 15:00 (n = 86) (i.e., potentially arguing against a confounding effect of lunch-time food intake). Third, diurnal variation in glucose metabolism has been previously demonstrated in other settings and provides biologic plausibility for the observed findings (3–5).

Finally, the suggestion that the analyses relating time of day of the GCT to metabolic function should be adjusted for glucose tolerance status (NGT, GIGT) cannot be undertaken because the metabolic features under study (insulin sensitivity and β-cell function) are the pathophysiological determinants of glucose tolerance status. Instead, however, a statistically acceptable approach is to repeat the adjusted analyses in only those women without GDM. Indeed, in the 708 women with NGT and GIGT, mean adjusted AUC_{gluc} decreased across the GCT groups from before 9:00 to 9:00–10:59 to 11:00–12:59 to after 13:00 ($P < 0.0001$), while insulin sensitivity (IS_{OGTT}) and β-cell function (ISSI-2) both progressively increased (P = 0.0002 and $P < 0.0001$, respectively). Furthermore, even when restricting to only the 533 women with NGT, the same graded decrease in AUC_{gluc} ($P < 0.0001$) and progressive increase in IS_{OGTT} (P = 0.0043) and ISSI-2 (P = 0.0016) is observed. Thus, differences in glucose tolerance status are not the basis for the observed relationships between time of day of the GCT and metabolic function in pregnant women.

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