Association Between Glycemic Variability, HbA_{1c}, and Large-for-Gestational-Age Neonates in Women With Type 1 Diabetes

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Fetal exposure to hyperglycemia is a major determinant of large-for-gestational-age (LGA; birth weight >90th centile for gender) neonates (1), yet targets for glycemic control beyond the first trimester in type 1 diabetes (T1D) pregnancy remain controversial. As HbA_{1c} represents a summary measure of glycemic control, it might not adequately reflect acute glucose fluctuations or glycemic variability (GV) that contributes to excess fetal growth. Moreover, neonates born to women who attain HbA_{1c} <6% (42 mmol/mol) in the third trimester of pregnancy have an LGA prevalence of 25% (2), with associated adverse perinatal outcomes (3). In contrast to HbA_{1c}, continuous glucose monitoring (CGM) allows precise observation of GV. Several studies have demonstrated an association between higher GV and increased birth weight (1,4,5). The capability of GV compared with HbA_{1c} to identify women likely to have LGA neonates is, however, unclear. We evaluated the association between various measures of GV, HbA_{1c}, and LGA neonates in T1D pregnancy.

Twenty-one pregnant women with T1D were recruited over a 2-year period, and measurements of HbA_{1c} and GV (EasyGV, University of Oxford, Oxford, U.K.) using CGM (Medtronic, Macquarie Park, New South Wales, Australia) were carried out at three time points: 14–18, 24–28, and 32–36 weeks' gestation. The study was approved by the local ethics committee (Northern Sydney Local Health District Human Research Ethics Committee), and all participants gave written informed consent.

The mean ± SD gestational age at delivery was 37.5 ± 1.4 weeks, and birth weight was 3,454 ± 576 g, with eight neonates born LGA. HbA_{1c} at each time point was 6.1 ± 0.9%, 6.0 ± 0.8%, and 6.2 ± 1.0%, respectively. The LGA group had significantly higher mean glucose and GV indices than the non-LGA group at 24–28 weeks' gestation (Fig. 1*A–D*) and higher HbA_{1c} at each time point (Fig. 1*E*).

Linear regression demonstrated a significant association between birth weight centile and each of the glycemic measures at 24–28 weeks of gestation. Because the GV indices demonstrated significant colinearity, we included the J-index alone in subsequent analyses, as it was most strongly correlated with birth weight centile ($r = 0.853$; $P < 0.0001$). Using univariate linear modeling, J-index at 24–28 weeks maintained a significant independent association with birth weight centile ($r^2 = 0.229$; $P < 0.05$), whereas HbA_{1c} did not ($r^2 = 0.008$; $P = 0.713$). The combination of J-index and HbA_{1c} at this time point resulted in a greater association with birth weight centile ($r^2 = 0.477$; $P < 0.01$), with mean values of 31.7% and 5.95%, respectively. Furthermore, using cutoffs of HbA_{1c} >6% and J-index >30 identified all neonates that were born LGA (receiver operating characteristic curve analysis, data not shown).

Despite attaining close to recommended HbA_{1c} target levels for T1D in pregnancy (HbA_{1c} ≤6%), our cohort of women demonstrated an ~40% incidence of LGA neonates, which concurs with the results of recently published studies. We found that the optimal combination of glycemic measures associated with LGA neonates is J-index and HbA_{1c} measured at 24–28 weeks' gestation. These findings were highly statistically significant, even with a small cohort size. Consequently, our results suggest that CGM (to calculate J-index) and HbA_{1c} measured in the late second trimester may be useful clinical tools to identify women with T1D at high risk of LGA neonates; however, this hypothesis should be confirmed in a larger cohort.

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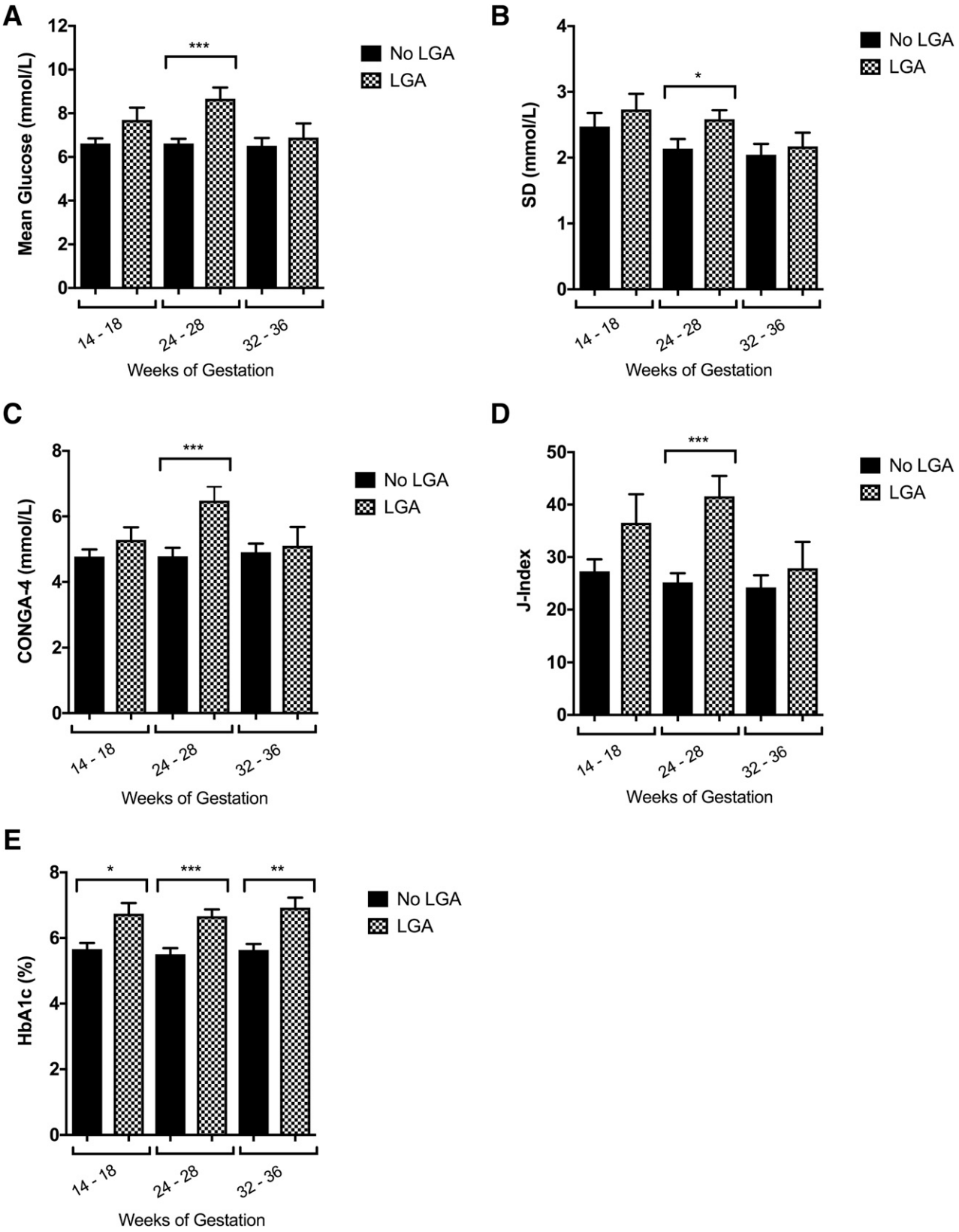

Figure 1—Indices of glycemic variability and HbA_{1c} at 14–18, 24–28, and 32–36 weeks of gestation were compared between women with and without LGA neonates using the Mann-Whitney *U* test. Results presented as mean ± SEM. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. CONGA-4, continuous overall net glycemic action at 4 h.

Our results provide an opportunity for future studies to determine whether targeting GV, as well as lowering HbA_{1c}, could reduce fetal overgrowth in T1D pregnancy.

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