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ORIGINAL ARTICLE

Continuous Glucose Monitoring, Glycemic Variability, and Excessive Fetal Growth in Pregnancies Complicated by Type 1 Diabetes

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Abstract

Background: To examine trimester-specific associations among glycemic variability, fetal growth, and birthweight in pregnancies with type 1 diabetes mellitus (Type 1 DM).

Methods: In this retrospective cohort study of 41 pregnant women with Type 1 DM, we used continuous glucose monitoring (CGM) data to calculate glycemic variability (coefficient of variation of glucose) over a 7-day interval in each trimester. Clinical data, including fetal biometry, birthweight, and perinatal complications, were extracted from medical records.

Results: Women maintained good glycemic control during pregnancy, with mean HbA1c in the first, second, and third trimester 6.5%, 6.1%, and 6.4%, respectively. Sixty-three percent of infants were large for gestational age (LGA). Estimated fetal weight percentile (EFW%ile) and abdominal circumference percentile (AC%ile) increased during pregnancy, consistent with accelerated prenatal growth. Correlations between trimester-specific glycemic variability and EFW, AC, and birthweight were not statistically significant. After maternal age adjustment, glycemic variability was not associated with birthweight for any trimester (adj. β for first trimester: −38.46, 95% CI: −98.58 to 21.66; adj. β for second trimester: −12.20, 95% CI: −51.47 to 27.06; adj. β for third trimester: −26.26, 95% CI: −79.52 to 27.00).

Conclusions: The occurrence of LGA remains very high in contemporary U.S. women with Type 1 DM, despite the use of CGM and overall good glycemic control. Neither HbA1c nor glycemic variability predicted fetal overgrowth or birthweight. Since LGA is a key driver of maternal and newborn complications in pregnancies with Type 1 DM, our data emphasize the importance of investigating both glucose-dependent and glucose-independent underlying mechanisms.

Keywords: Pregnancy, Type 1 diabetes, Continuous glucose monitoring, Fetal growth, Birthweight.

Introduction

Women with Type 1 diabetes mellitus (Type 1 DM) are at high risk for obstetric and perinatal complications; excessive fetal growth is a major driver of adverse pregnancy outcomes.[1,2] ''Large for gestational age'' (LGA) neonates, defined as birthweight >90th percentile for gestational age and sex, are at increased risk for complications both in the perinatal period and in later life, as LGA is a risk factor for future obesity and type 2 diabetes.[3–5] Fetal exposure to maternal hyperglycemia is thought to be the major driver of fetal overgrowth in Type 1 DM, and the overarching goal of prenatal care in women with Type 1 DM is to achieve tight glycemic control through intensive nutritional and insulin therapy.

However, maternal glycated hemoglobin (HbA1c) may not adequately reflect fetal glycemic exposure, as it does not assess postprandial glucose rise or capture time spent above the normal glucose range. Moreover, shifts in red blood cell

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production during pregnancy reduce the accuracy of HbA1c as a measure of mean glucose levels.[6] The emergence of continuous glucose monitoring (CGM) technology now allows for a more precise understanding of how glycemic patterns, such as mean glucose and variation in glucose levels (glycemic variability), may influence pregnancy outcomes. Law et al. recently reported that in pregnant women with Type 1 and Type 2 DM, LGA was associated with lower mean glucose and less glycemic variability in the first trimester, and higher mean glucose and more variable second and third trimester glucose levels.[7] Other groups have similarly shown that glycemic variability, especially during late pregnancy, may increase risk of LGA.[8,9] A recent randomized trial by Feig et al. demonstrated improved neonatal outcomes in women with Type 1 DM who used CGM during pregnancy, including a lower incidence of LGA infants and a decrease in neonatal hypoglycemia.[10]

It is unclear, however, to what extent CGM-derived measures of glycemic variability may predict LGA in a clinical setting. Moreover, no previous studies have examined how glycemic variability may affect fetal growth patterns. We hypothesized that higher glycemic variability, as measured by trimester-specific CGM data, would be associated with fetal overgrowth, assessed by estimated fetal weight (EFW) and fetal abdominal circumference percentiles (AC%ile) on antenatal growth ultrasounds, and with higher birthweight for gestational age.

Methods

Participants

This was a retrospective cohort study of women with Type 1 DM who used CGM and delivered between January 2012 and December 2015 at Beth Israel Deaconess Medical Center (Boston, MA). Two hundred seventy-six women with Type 1 DM delivered during this time period, of which 17% ($n=47$) had both CGM and birthweight data available. All women received multispecialty care, including endocrinology, nutrition, and maternal–fetal medicine; glucose targets were between 60–99 mg/dL fasting and 100–129 mg/dL 1-h postmeal, consistent with current guidelines.[11] Exclusion criteria were CGM use in a previous pregnancy ($n=3$), multiple gestations ($n=1$), delivered <28 weeks' gestation ($n=1$), and major fetal anomalies ($n=1$); for a data set of $n=41$. Maternal demographic and clinical data during the index pregnancy were collected from medical records.

Continuous glucose monitoring

We reviewed CGM data from each trimester of pregnancy for ≥7 consecutive days (median 7 days, maximum 30 days). Women used a Medtronic Enlite (Medtronic-MiniMed, Northridge, CA) or a Dexcom 7 or G4 (Dexcom, Inc., San Diego, CA) CGM system. Glycemic variability was defined as the coefficient of variation (standard deviation/mean) of glucose for each data period. We chose to study coefficient of variation as a surrogate of glycemic variability because mean glucose and standard deviation were reported consistently across different CGM systems, whereas the time in range is not consistent across systems; moreover, the coefficient of variation is readily accessible to clinicians.

Fetal growth

We reviewed fetal growth ultrasounds from medical records. EFW in grams and EFW percentile (EFW%ile) for gestational age were computed using the Williams formula.[12] AC percentile (AC%ile) for gestational age was computed using the Hadlock formula.[13] Birthweight in grams was collected from medical records, and LGA was defined as birthweight >90%ile.[14,15]

Statistical analysis

Descriptive statistics were calculated for all continuous and categorical variables. We conducted bivariate analysis to evaluate gestational age by EFW%ile and AC%ile. Pearson correlation coefficients were computed to examine trimester-specific associations between glycemic variability and birthweight. A two-tailed P-value of <0.05 denoted statistical significance.

We used maternal age-adjusted linear mixed models to prospectively assess trimester-specific associations between glycemic variability in first, second, and third trimesters and subsequent EFW%ile and AC%ile. We used linear regression to evaluate the association between trimester-specific glycemic variability and birthweight adjusted for maternal age. As a secondary analysis, we also assessed trimester-specific mean HbA1c and CGM glucose levels with EFW%ile and AC%ile using Pearson correlation coefficients and age-adjusted linear mixed models. In addition, we evaluated trimester-specific mean HbA1c and CGM glucose levels and birthweight by calculating Pearson correlations and linear regression adjusting for maternal age. Analyses were conducted with R 3.3.1.

Results

Maternal and infant data

Clinical characteristics, CGM data, and pregnancy outcomes of the 41 women are displayed in Table 1. Twenty-two (54%) of women had CGM data available in the first trimester (<13 weeks), 36 (88%) in the second trimester (13–26 weeks), and 35 (85%) in the third trimester (≥27 weeks). Twelve women (29%) used a Medtronic Enlite CGM system, 2 (5%) used a Dexcom 7, and 27 (66%) used a Dexcom G4. Forty (98%) used an insulin pump and one (2%) used multiple daily injections. Mean HbA1c in each trimester was 6.5% (47 mmol/mol), 6.1% (43 mmol/mol), and 6.4% (46 mmol/mol), while mean CGM glucose levels for first, second, and third trimesters were 121.5 mg/dL (6.75 mmol/L), 130.7 mg/dL (7.26 mmol/L), and 121.9 mg/dL (6.77 mmol/L), respectively. Mean CGM glucose levels for 75th and 90th percentiles per trimester were also recorded; the 90th percentile was >140 mg/dL in all trimesters. Thirty-three women (80%) of women delivered via cesarean. Of these, 10 were repeat cesarean deliveries and 23 were primary cesarean deliveries, of which 9 were for diabetes-related indications (7 for suspected macrosomia and 2 for retinopathy). The rest were for usual obstetric indications. Sixty-three percent of infants were LGA. Mean birthweight was 4007 ± 735 g and mean birthweight percentile was 93rd ±15th (median 99th percentile interquartile range 92nd–100th). Fifteen (37%) of infants were admitted to the neonatal intensive care unit with a primary diagnosis of hypoglycemia.

Table 1. Maternal and Infant Characteristics, Continuous Glucose Monitoring Data, and Pregnancy Outcomes

Maternal characteristics	n = *41*
Age (years)	32.5 ± 3.2
Race	
White	37 (90.2)
Non-white	4 (9.8)
Body mass index (kg/m^2)	28.3 ± 5.6
Gestational weight gain (kg)	13.4 ± 5.5
Parity	1 ± 1
Years with Type 1 DM	21.4 ± 7.9
Retinopathy	
Yes	27 (66)
No	14 (34)
Nephropathy	
Yes	1 (2.4)
No	40 (97.6)
Chronic hypertension	
Yes	7 (17)
No	34 (83)
Hemoglobin A_{1c},% (mmol/mol)	
First trimester	6.5 ± 0.7 (47 ± 8.1)
Second trimester	6.1 ± 0.5 (43 ± 5.5)
Third trimester	6.4 ± 0.6 (46 ± 6.7)
Mean CGM glucose, mg/dL (mmol/L)	
First trimester	121.5 ± 19.0 (6.75 ± 1.1)
Second trimester	130.7 ± 20.7 (7.26 ± 1.2)
Third trimester	121.9 ± 19.0 (6.77 ± 1.1)
75th percentile CGM glucose, mg/dL (mmol/L)	
First trimester	131.8 (7.31)
Second trimester	143.8 (7.98)
Third trimester	132.0 (7.33)
90th percentile CGM glucose, mg/dL (mmol/L)	
First trimester	145.7 (8.09)
Second trimester	153.5 (8.52)
Third trimester	144.6 (8.03)
Glycemic variability CGM glucose (coefficient of variation, %)	
First trimester	35.5 ± 6.2
Second trimester	35.5 ± 6.6
Third trimester	33.3 ± 5.3
Gestational age at delivery (weeks)	38.0 ± 1.9
Preeclampsia	
Yes	10 (24)
No	31 (76)
Cesarean delivery	
Yes	33 (80)
No	8 (20)
Infant characteristics	
Birthweight (g)	4007 ± 735
Birthweight percentile, mean	93 ± 15
LGA	
Yes	26 (63)
No	15 (37)
Neonatal intensive care unit admission for hypoglycemia	
Yes	15 (37)
No	26 (63)

All data are *n* (%) or mean ± SD unless otherwise specified.
CGM, continuous glucose monitoring; LGA, large for gestational age; Type 1 DM, type 1 diabetes mellitus.

Glycemic variability and fetal growth

Based on analysis of serial prenatal ultrasounds, fetal growth parameters (i.e., EFW%ile and AC%ile) increased during pregnancy, consistent with accelerated prenatal growth (Fig. 1). There was no association between first, second, or third trimester maternal age-adjusted continuous glycemic variability and EFW%ile or AC%ile, which remained unchanged when glycemic variability was categorized as ≥ and < median levels (Fig. 2). In our secondary data analysis, there was no association between HbA1c and EFW%ile or AC%ile for any trimester. There was a significant association between first trimester mean CGM glucose levels and EFW%ile ($P = 0.03$); however, there was no association between second and third trimester mean CGM glucose levels and EFW%ile or AC%ile for any trimester.

Glycemic variability and birthweight

Pearson correlation coefficients between glycemic variability and birthweight per trimester were $r = 0.08$ ($P = 0.71$), $r = 0.01$ ($P = 0.93$), and $r = 0.05$ ($P = 0.76$), respectively (Fig. 3). Even after maternal age-adjustment, glycemic variability was not associated with birthweight for any trimester (adj. β for first trimester: −38.46, 95% CI: −98.58 to 21.66; adj. β for second trimester: −12.20, 95% CI: −51.47 to 27.06; adj. β for third trimester: −26.26, 95% CI: −79.52 to 27.00).

With respect to secondary data analyses, correlations between trimester-specific HbA1c and birthweight were not statistically significant ($r = 0.05$, $P = 0.72$; $r = 0.10$, $P = 0.51$; $r = 0.78$, $P = 0.78$). Trimester-specific mean CGM glucose levels and birthweight also showed no correlation ($r = 0.37$, $P = 0.07$; $r = 0.08$, $P = 0.59$; $r = 0.19$, $P = 0.25$) (Fig. 3). After maternal age-adjustment, no associations existed for neither trimester-specific HbA1c and birthweight nor trimester-specific CGM glucose levels and birthweight.

Discussion

We report, in a contemporary cohort of U.S. women, that the risk of high birthweight and LGA remains extremely high in pregnancies complicated by Type 1 DM, with mean birthweight >4000 g, despite overall good glycemic control, CGM use, and multispecialty care. Our findings are concerning given the strong associations between LGA and risk for perinatal complications,[16] neonatal intensive care unit admission,[17] and complications during later life, including obesity, insulin resistance, and diabetes[3,4] Surprisingly, we did not observe trimester-specific associations among glycemic variability, mean glucose, or HbA1c and birthweight nor with prenatal ultrasound-derived measures of fetal growth, with the exception of an association between higher first trimester mean glucose and higher EFW%ile. Our findings contrast with those of Law et al.[7]; this difference may have arisen because we chose to use coefficient of variation as a surrogate for glycemic variability, whereas Law et al. relied on a variety of other CGM-derived measures.

To our knowledge, we are the first to examine detailed prenatal ultrasound data in pregnancies complicated by Type 1 DM. Our results suggest that fetal overgrowth may emerge earlier in pregnancy than previous reports. Surprisingly, the good glycemic control attained in our cohort did not prevent fetal growth acceleration, which highlights the importance of

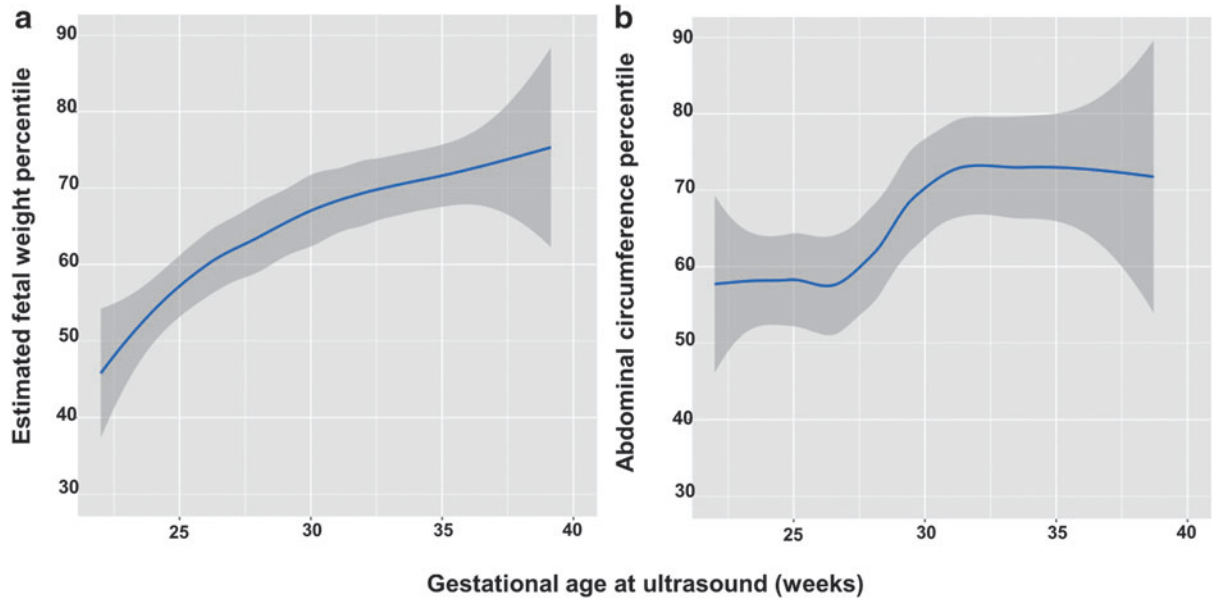

FIG. 1. Fetal growth parameters by gestational age. **(a)** Change in EFW%ile during pregnancy. **(b)** Change in AC%ile during pregnancy. AC%ile, abdominal circumference percentile; EFW%ile, estimated fetal weight percentile.

identifying additional strategies to prevent this complication. Accelerated prenatal growth has been reported previously in pregnancies complicated by diabetes, but not specifically in pregnancies with Type 1 DM. Landon et al. reported an accelerated fetal AC by 32 weeks' gestation in LGA infants whose mothers had diabetes during pregnancy.[18] Langer et al. described two patterns of accelerated growth; ''early'' (EFW >90%ile at 30 weeks' gestation) and ''late'' (36 weeks' gestation) in 522 women with diabetes in pregnancy. However, of the 81 women with insulin-dependent diabetes,

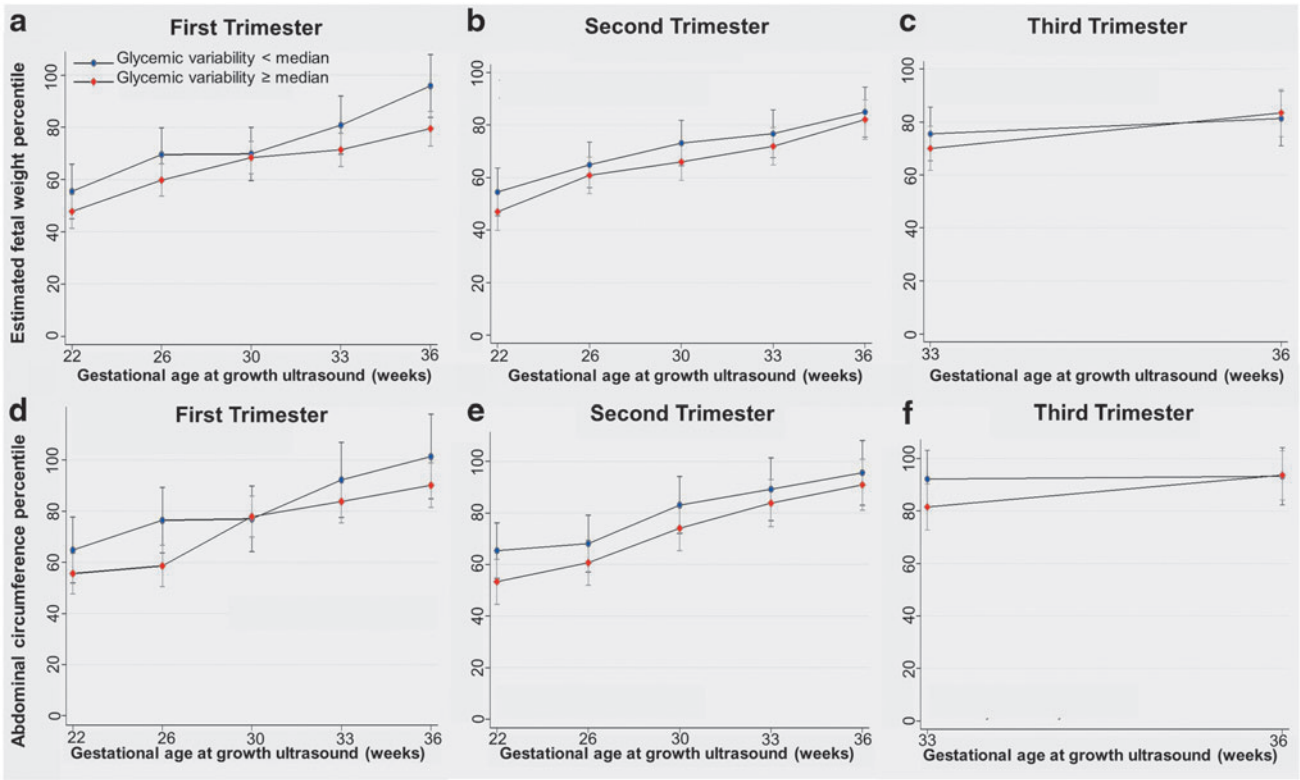

FIG. 2. Trimester-specific glycemic variability and fetal growth. **(a)** First trimester glycemic variability and change in EFW%ile during pregnancy, **(b)** Second trimester glycemic variability and change in EFW%ile during pregnancy, **(c)** Third trimester glycemic variability and change in EFW%ile during pregnancy, **(d)** First trimester glycemic variability and change in AC%ile during pregnancy, **(e)** Second trimester glycemic variability and change in AC%ile during pregnancy, **(f)** Third trimester glycemic variability and change in AC%ile during pregnancy.

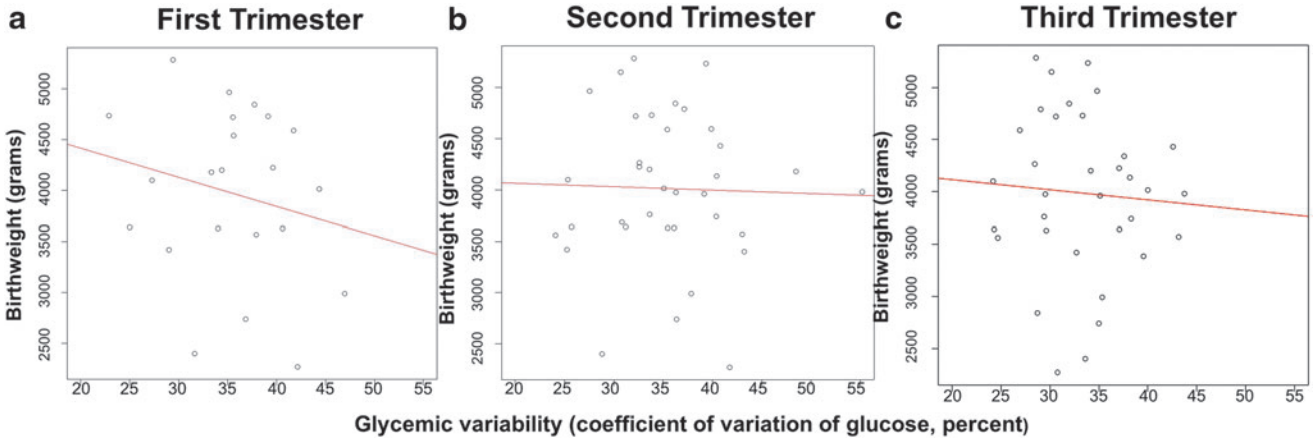

FIG. 3. Trimester-specific glycemic variability and birthweight. **(a)** Association between first trimester glycemic variability and birthweight. **(b)** Association between second trimester glycemic variability and birthweight. **(c)** Association between third trimester glycemic variability and birthweight.

only 11 infants were LGA.[19] Our observed high incidence of LGA is comparable to the CGM arm of the recently published Feig et al. randomized controlled trial; including LGA (63% vs. 53%), and neonatal intensive care unit admission (37% vs. 27%). Although the Feig et al. trial demonstrated that CGM improved neonatal outcomes, over half of infants in the CGM arm were LGA.[10] Similarly, Persson et al. reported a 47% rate of LGA in a population-based cohort of 3705 infants born to mothers with Type 1 DM in Sweden,[2] while a smaller study ($n=221$) by Ladfors et al. reported a 50% LGA prevalence.[20] Taken together, these data indicate that the prevalence of fetal overgrowth in Type 1 DM remains alarmingly high, even with modern diabetes management.

Although maternal hyperglycemia is a key pathway associated with fetal overgrowth,[21–23] factors other than glycemic control may contribute to LGA. We previously reported that third trimester maternal placental growth factor levels were predictive of birthweight, independent of HbA1c.[24] These data, together with the low rate of diabetes complications in our study population, point to the possibility that this contemporary group of women with Type 1 DM has better vascular function and placental blood flow than historical controls. Others have reported that Type 1 DM is associated with increased placental weight, altered placental structure, altered expression of vascular endothelial growth factor and other angiogenic factors, and changes in the placental growth hormone-insulin-like growth factor axis, which further supports the possibility that differences in placental function could contribute to macrosomia risk.[25–28] Other mechanisms for fetal overgrowth may be related to the rising prevalence of obesity in the Type 1 DM population.[29,30] Indeed, the mean prepregnancy body mass index (BMI) in our study population was 28.3 kg/m^2, and 68% of women were overweight or obese (BMI ≥25 kg/m^2) at the first prenatal visit. Obesity may cause insulin resistance,[31] altered levels of adipokines (e.g., adiponectin, leptin),[32–34] altered appetite regulating factors such as ghrelin,[35] inflammation,[36] and differences in placental nutrient transport,[37] each of which is associated with fetal growth.

We recognize some limitations to our study. First, this was a clinically based observational study, in which we relied on coefficient of variation as a measure of glycemic variability, since other measures (e.g., mean amplitude of glycemic excursion (MAGE, time within target range, etc.) were not accessible from the clinical CGM data. We acknowledge that use of coefficient of variation limits our ability to directly compare our results to some other studies. However, as a metric that can be easily accessed from CGM download data in clinical settings, it is important to document the utility (or lack thereof) of coefficient of variation (CV) as predictor of LGA in Type 1 DM pregnancies. The use of clinical CGM downloads also limited our ability to examine the effects of specific glucose thresholds; this will be an important area for future study. Another limitation is that women did not use the same CGM brand, which might have affected glycemic variability measurements. Previous studies have shown that the Dexcom G4 CGM system is more accurate than the Medtronic Enlite, including in the hypoglycemic range.[38,39] Our small population limited our ability to fully adjust for potential confounders, including maternal obesity; 68% of women were overweight or obese (BMI ≥25 kg/m^2) at the first prenatal visit. Future studies will need to account for these factors to better assess these associations. The majority of women were white, age ≥30, and college educated, which may potentially limit generalizability to other populations. Despite these limitations, our study has several strengths, including assessment of glycemic variability in each trimester to evaluate trimester-specific associations with birthweight. Our analysis of the timing of accelerated growth across AC%ile and EFW%ile may help predict when fetal overgrowth starts to occur, which may identify important therapeutic windows for future intervention studies.

In conclusion, glycemic variability based on CGM data did not predict birthweight or fetal overgrowth. Mean birthweight and LGA prevalence were extremely high despite use of CGM technology and multispecialty care with intensive insulin management. As LGA is a key driver of maternal and newborn complications in pregnancies with Type 1 DM, our data indicate the urgency of investigating the underlying mechanisms.

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Authors' Contributions

B.M.M. collected the data and wrote the article. N.N. analyzed and interpreted the data, and reviewed/edited the article. T.J.T. analyzed and interpreted the data, and reviewed/edited the article. E.I. contributed to the introduction and discussion sections of the article and reviewed/edited the article. T.T. collected the data and reviewed/edited the article. A.C. collected the data and reviewed/edited the article. C.W. collected the data and reviewed/edited the article. K.E.O. designed the study and reviewed/edited the article. F.M.B. designed the study and reviewed/edited the article. B.M.M., K.E.O., and F.M.B. are the guarantors of this work and had full access to all of the data (B.M.M. and K.E.O. to the Beth Israel Deaconess Medical Center data, and F.M.B. to the Joslin Diabetes Center data) and take responsibility for the integrity of the data and the accuracy of the data analysis.

Author Disclosure Statement

There are no reported potential conflicts of interest relevant to this article for any of the authors. No competing financial interests exist.

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