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Original Research

Predictors of Large-for-Gestational-Age Birthweight Among Pregnant Women With Type 1 and Type 2 Diabetes: A Retrospective Cohort Study

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Key Messages

- Little is known about the different risk factors for large-for-gestational-age (LGA) birthweight between women with type 1 and type 2 diabetes.
- We found that glycemic control at delivery was predictive of LGA in women with type 2 diabetes, and there was a trend toward an association of maternal weight gain and continuous subcutaneous insulin infusion with LGA infants in women with type 1 diabetes.
- Further study is warranted to better guide targeted interventions to reduce high rates of LGA birthweight in women with type 1 and type 2 diabetes.

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ABSTRACT

Objective: Our aim in this study was to compare the effects of risk factors for large-for-gestational-age (LGA) birthweight between women with type 1 and type 2 diabetes mellitus (TIDM and T2DM, respectively).
Methods: A retrospective cohort study was conducted for women with T1DM (n=152) and T2DM (n=255) attending a diabetes/pregnancy clinic during the period from 2009 to 2016. Multiple logistic regression analysis was used to identify variables associated with LGA birthweight.
Results: LGA was significantly higher in those with T1DM (39%) than T2DM (17%) ($p<0.001$). Among those with T1DM, there was a nonsignificant association between LGA and continuous subcutaneous insulin infusion (odds ratio, 1.17; 95% confidence interval, 0.99 to 1.39; $p=0.06$) and excess maternal weight gain (T1DM odds ratio, 1.19; 95% confidence interval, 0.99 to 1.43; $p=0.069$). In those with T2DM, there was an association between LGA and glycated hemoglobin at delivery (T2DM odds ratio, 1.10; 95% confidence interval, 1.02 to 1.19; $p=0.01$).
Conclusions: In the study population, glycemic control at delivery was predictive of LGA in women with T2DM, and there was a trend toward an association of maternal weight gain and continuous subcutaneous insulin infusion with LGA infants in T1DM. Further study is warranted to better guide targeted interventions to reduce high rates of LGA birthweight in T1DM/T2DM.

Mots clés:
macrosomie fœtale
grossesse
diabète de type 1
diabète de type 2

RÉSUMÉ

Objectif : Notre objectif dans cette étude était de comparer les effets des facteurs de risque pour le poids à la naissance lors d'une macrosomie fœtale (MF) entre les femmes atteintes de diabète sucré de type 1 et de type 2 (DST1 et DST2, respectivement).
Méthodes : Une étude de cohorte rétrospective a été menée auprès de femmes atteintes de DST1 (n=152) et de DST2 (n=255) qui ont fréquenté une clinique du diabète/de grossesse entre 2009 et 2016. Une

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analyse de régression logistique multinomiale a été utilisée pour identifier les variables associées au poids à la naissance de la MF.
Résultats : La MF était significativement plus élevée pour les femmes atteintes de DST1 (39%) que chez celles atteintes du DST2 (17%) ($p<0.001$). Chez celles atteintes du DST1, une association non significative a été observée entre la MF et la perfusion sous-cutanée continue d'insuline (rapport de cotes, 1.17; intervalle de confiance à 95%, 0.99 à 1.39; $p=0.06$) et le gain de poids excessif chez la mère (rapport de cotes DST1, 1.19; intervalle de confiance à 95%, 0.99 à 1.43; $p=0.069$). Chez les femmes atteintes de DST2, il y avait une association entre la MF et l'hémoglobine glyquée à l'accouchement (rapport de cotes pour le DST2, 1.10; intervalle de confiance à 95%, 1.02 à 1.19; $p=0.01$).
Conclusions : Dans la population de l'étude, le contrôle glycémique à l'accouchement était prédictif de la MF chez les femmes atteintes de DST2, et une tendance a été observée vers une association du gain de poids maternel et de la perfusion sous-cutanée continue d'insuline avec la MF infantile en cas de DST1. Une autre étude demeure nécessaire pour mieux orienter les interventions ciblées visant à réduire les taux élevés de poids à la naissance lors de MF dans les cas de DST1/DST2.

Introduction

Pregnancy outcomes for women with pregestational diabetes have improved considerably in recent decades (1,2); however, women with pregestational diabetes continue to have rates of large-for-gestational-age (LGA) infant birthweight that are substantially higher compared with the general population. Whereas studies have indicated that 8% to 23% of women with type 2 diabetes (T2DM) give birth to LGA infants (3,4), the rate of LGA in studies of women with type 1 diabetes (T1DM) range from 18% to 52% (3,4), and was found to be as high as 63% in one study (5). LGA is associated with maternal complications, such as high rates of cesaerean section and neonatal complications, such as shoulder dystocia, hypoglycemia, birth injury, jaundice and respiratory distress (6–8).

Although the theory of maternal hyperglycemia and subsequent fetal hyperinsulinemia has long been thought to be the primary mechanism of fetal overgrowth in pregnancies affected by diabetes (9), as maternal glycemic control has generally improved in the past decade (10), a coinciding reduction in the rate of LGA infants has not been observed. Studies have since shown that factors, such as maternal weight gain in pregnancy, prepregnancy body mass index (BMI) and parity are important or perhaps even stronger predictors of LGA compared with maternal glycemic control (11–15). LGA has typically been defined as weight >90th percentile adjusted for gestational age and sex, and macrosomia is defined as infant weight >4,000 g. A more recently developed tool for measuring LGA, the Gestation Related Optimal Weight (GROW) method, also accounts for maternal factors that have been shown to affect infant birthweight, such as maternal BMI and ethnicity (16).

Overall, the best predictors of LGA infants for women with pregestational diabetes remains somewhat uncertain. The majority of studies to date that addressed predictors of LGA infants in women with pregestational diabetes have grouped women with T1DM and T2DM together; however, given that the underlying pathophysiology of T1DM and T2DM is quite different, the predictors of LGA in these populations may not be the same. The purpose of this study was to compare the effects of potential risk factors for LGA between women with TIDM and T2DM.

Methods

Study design and participants

A retrospective cohort study was conducted for women with T1DM (n=151) and T2DM (n=253) attending a diabetes and pregnancy clinic in Toronto, Ontario, Canada, from 2009 to 2016, and who were registered in a continuous case series. This study was conducted with the approval of the institutional ethics review board at Mount Sinai Hospital. Inclusion criteria were live, singleton pregnancies of a gestational age of ≥28 weeks for which medical records for antenatal diabetes care and delivery were available. Women with multiple gestations, spontaneous abortion (fetal loss before 20 weeks) or intrauterine fetal death were not included.

Variables

The following data were retrieved from a database of patient medical information: date of birth, maternal ethnicity, parity, self-reported prepregnancy weight and height, smoking before or during pregnancy, delivery date, type of diabetes, duration of diabetes, insulin use before pregnancy, mode of insulin delivery (i.e. multiple daily injection or continuous subcutaneous insulin infusion), first trimester glycated hemoglobin (A1C), A1C at delivery (accepted within 6 weeks from time of delivery), chronic hypertension, pre-eclampsia or pregnancy-induced hypertension, maternal weight within 2 weeks of delivery, gestational age at delivery, baby birthweight from delivery record and sex of offspring.

To examine the potential impact of using different methods to define excessive birthweight, LGA was defined in 2 ways: 1) weight >90th percentile for Canadian population–based data adjusted for gestational age and sex of offspring (Kramer tables) (17); and 2) weight >90th percentile calculated by the GROW method, which accounts for maternal BMI, ethnicity, parity, gestational age at delivery and sex of offspring (18).

Excessive maternal weight gain was defined as weight gain exceeding the Institute of Medicine (IOM) recommendations for total weight gain during pregnancy, which provides guidelines for weight gain based on maternal prepregnancy BMI (19). For preterm births, the presence of excessive maternal weight gain was determined using the IOM recommendations for weekly rate of weight gain in the second and third trimester.

Statistical analysis

Summary statistics for key demographic and clinical variables were calculated and compared between women with T1DM and women with T2DM using a t test (for means) or a chi-square test (for proportions). Variables for consideration in the multiple logistic regression were chosen by a review of the literature and limited in number by the count of events (the smaller of the number of LGA and non-LGA birthweights), so that there were no fewer than 10 events per variable. Comparisons of these variables between women with LGA and without LGA infants used the same approach as for comparisons of T1DM and T2DM. So that all observations could be used in the multiple regression, the Multiple

Imputation with Chained Equations package (20) was used for imputation of missing data on BMI, A1C, weight gain and parity and ethnicity. All multiple regression logistic results combined estimates from 50 imputed data sets. Odds ratios (ORs), 95% confidence intervals (CIs) and p values were calculated separately for T1DM and T2DM. These comparisons were repeated for LGA, as defined by Kramer tables and LGA, as then defined by GROW. For LGA by GROW, we also combined the data sets for T1DM and T2DM and fitted a model that included type of diabetes, variables of interest and terms representing the interaction between type of diabetes and these other variables. The interaction terms allowed for checking for differential effects of these variables on LGA using GROW. Finally, for variables that did not appear to have a differential effect between T1DM and T2DM, a model was fitted without interaction terms, allowing estimation of a single OR for a risk factor in both T1DM and T2DM for these variables.

Results

A summary of maternal and neonatal characteristics is shown in Table 1. Women with T1DM were an average of 4.1 years younger, more likely to be nulliparous and had a significantly lower prepregnancy BMI (T1DM BMI, 26.2 kg/m^2; T2DM BMI, 31.9 kg/m^2; p<0.001). The proportion of women using CSII from year to year did not consistently increase over the study period (data not shown). Nearly half of the women with T2DM were obese prepregnancy. Women with T1DM, on average, had higher A1C values in the first trimester (T1DM A1C, 7.6%; T2DM A1C, 7.2%; p=0.035) and at delivery (T1DM A1C, 6.5%; T2DM A1C, 6.0%; p<0.001). Women with T1DM had higher rates of excess weight gain in pregnancy (70.9%) than women with T2DM (60.8%) (p=0.015). The population of women with T2DM was more ethnically diverse, with 72% having non-Caucasian ethnicity (South Asian, Asian, Filipino and African backgrounds accounting for the largest groups). Chronic or pregnancy-associated hypertensive disorders were more common in women with T2DM (39.1%) than T1DM (21.2%) (p<0.001).

The average gestational age at the time of delivery differed by half a week between women with T1DM (37.4 weeks) and T2DM (37.9 weeks) (p=0.009). The distribution of birthweight centiles determined using GROW is shown in Figure 1. Women with T1DM had considerably higher rates of LGA (39%) than women with T2DM (17%) (95% CI for difference, 12.4% to 31.5%; p<0.0001).

The relationships between maternal factors and LGA were analyzed using national growth curves (17). For women with T1DM, non-Caucasian ethnicity (p=0.001) and the use of CSII (p=0.003) were significantly associated with LGA (Table 2). For women with T2DM, non-Caucasian ethnicity (p=0.001), multiparity (p=0.02) and excess maternal weight gain (p=0.046) were significantly associated with LGA (Table 2). Multivariable analysis for women with T1DM showed a strong association between LGA and non-Caucasian ethnicity (OR, 4.07; 95% CI, 1.46 to 11.35; p=0.008) and a nonsignificant trend toward association with use of CSII (OR, 2.08; 95% CI, 0.94 to 4.61; p=0.07) (Table 3). Multivariable analysis for women with T2DM showed a significant association between LGA and non-Caucasian ethnicity (OR, 2.47; 95% CI, 1.15 to 5.32; p=0.02) and nulliparity (OR, 0.32; 95% CI, 0.13 to 0.77; p=0.01), and a nonsignificant trend toward association with each point increase in prepregnancy BMI (OR, 1.05; 95% CI, 0.99 to 1.11; p=0.09) (Table 2).

Given that primarily nonmodifiable risk factors, such as ethnicity and parity, seemed to be most strongly associated with excess infant birthweight, the analysis was repeated using GROW as a means of defining LGA, as GROW takes into account these nonmodifiable risk factors (parity, ethnicity and prepregnancy BMI) when determining the cutoff for high infant birthweight. Using GROW, multiple regression analysis for women with T1DM showed a nonsignificant trend toward association between LGA and CSII (OR, 1.17; 95% CI, 0.99 to 1.39; p=0.06) (Table 3). Excess maternal weight gain also showed a nonsignificant trend toward association with LGA in women with T1DM but no association in T2DM (T1DM OR, 1.19; 95% CI, 0.99 to 1.43; p=0.06; T2DM OR, 1.04; 95% CI, 0.91 to 1.18; p=0.54). A1C at delivery was associated with LGA birthweights in women with T2DM (T1DM OR, 0.99; 95% CI, 0.90 to 1.08; p=0.77; T2DM OR, 1.10; 95% CI, 1.02 to 1.19; p=0.01) (Table 3).

There were no significant interactions between diabetes type and any of the risk factors examined. Figure 2 shows the ORs for each of the predictors within each diabetes type and the ORs from the single model that included both women with T1DM and those with T2DM.

Table 1
Maternal and fetal characteristics

	T1DM	T2DM	p value
Number of patients	151	253	
Age, years (mean [SD])	31.0 (5.5)	35.1 (5.1)	<0.001
Nulliparous (%)	81 (54.7)	91 (36.0)	0.002
Ethnicity (%)			
Caucasian	106 (71.6)	65 (26.3)	<0.001
Prepregnancy BMI (mean [SD])	26.2 (5.8)	31.9 (7.5)	<0.001
BMI category (%)			<0.001
Normal	70 (51.5)	43 (17.0)	
Overweight	39 (28.7)	52 (20.6)	
Obese	27 (19.9)	116 (45.8)	
Excess weight gain (%)			0.015
Yes	90 (70.9)	115 (60.8)	
Duration of diabetes, years (mean [SD])	15.4 (8.5)	5.4 (5.1)	<0.001
Insulin use prepregnancy (mean [SD])	1.0 (0.0)	0.2 (0.4)	<0.001
Mode of insulin delivery (%)			<0.001
CSII	73 (48.3)	0 (0.0)	
First trimester A1C (mean [SD])	7.6 (1.6)	7.2 (1.6)	0.035
Delivery A1C (mean [SD])	6.5 (1.0)	6.0 (0.9)	<0.001
Hypertension* (%)	32 (21.2)	99 (39.1)	<0.001
Smoking (%)	25 (16.6)	26 (10.3)	0.092
Gestational age at delivery (weeks)	37.4 (1.9)	37.9 (1.8)	0.009
LGA infant birthweight (%)	59 (39.1)	42 (16.6)	<0.001

A1C, glycated hemoglobin; *BMI*, body mass index; *CSII*, continuous subcutaneous insulin infusion; *GROW*, Gestation Related Optimal Weight; *LGA*, large for gestational age; *SD*, standard deviation; *T1DM*, type 1 diabetes mellitus; *T2DM*, type 2 diabetes mellitus.

*Hypertension defined as chronic hypertension, pre-eclampsia or pregnancy-induced hypertension.

Discussion

Advancing the understanding of the potential predictors of LGA birthweight is of considerable importance, as this may allow for targeted interventions aimed at altering modifiable factors that may be contributing to LGA. In this study, the incidence of LGA was higher in women with T1DM compared to women with T2DM. Parity and ethnicity were significantly associated with LGA in both types of diabetes when using national growth curves that do not account for maternal characteristics. When these variables were taken into account using a customized growth curve, other factors, such as glycemic control, use of CSII and maternal weight gain, showed potential relationships to LGA birthweight. Specifically, in women with T1DM, there was a nonsignificant trend toward association between LGA and CSII use as well as LGA and excess maternal weight gain. In women with T2DM, LGA was significantly associated with a higher A1C near the time of delivery.

Definition of LGA can influence results

These results may be the first to demonstrate that predictors of LGA infants may be influenced by the method used to define fetal overgrowth. The initial results showed that nonmodifiable risk factors, such as ethnicity and parity, were more strongly linked

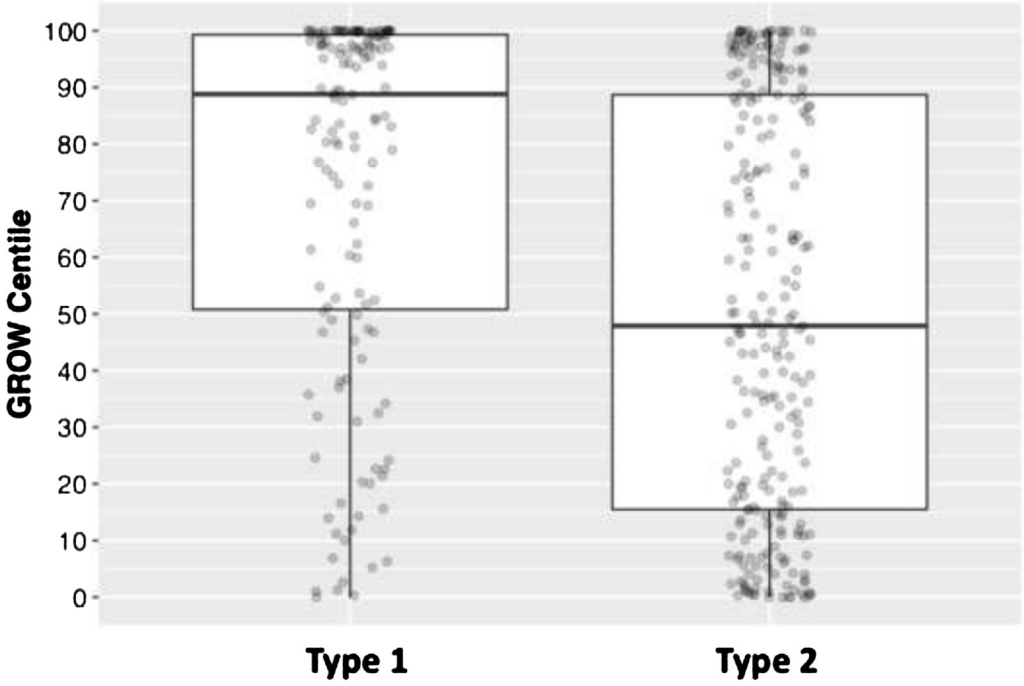

Figure 1. Distribution of birthweight centiles using the Gestation Related Optimum Weight (GROW) method for type 1 and type 2 diabetes mellitus.

with LGA; however, by using a method that accounted for these factors, other factors associated with LGA that could potentially be modified through intervention were identified. The use of varied means of defining LGA may explain some of the variability in the literature regarding the predictors of LGA in women with pregestational diabetes.

Prevalence of LGA

Consistent with previous studies (3,4,13), the incidence of LGA was considerably higher among women with T1DM in this population compared with T2DM. In this study, 39.1% of women with T1DM had infants with LGA compared to 16.6% of women with T2DM ($p<0.001$). As discussed in what follows, differences in glycemia and pregnancy weight gain between these groups may in part explain the higher incidence of LGA birthweights among women with T1DM. Also, hypertension has been associated with lower infant birthweight in previous studies (21). In this population, there were considerably more patients with hypertension (either chronic or gestational) among women with T2DM (39.1%) vs T1DM (21.2%) ($p<0.001$); however, in the multivariate analysis, hypertension was not significantly associated with a lower likelihood of LGA.

Role of A1C

In this cohort, having a higher A1C at delivery was associated with LGA birthweight in women with T2DM but not T1DM. Women with T2DM in this sample, on average, had significantly lower A1C values at delivery (6.0%) vs women with T1DM (6.5%), although both groups had mean values close to the targets set forth by Canadian practice guidelines (22).

According to the hypothesis of "maternal hyperglycemia–fetal hyperinsulinemia" (9), one may expect that the women with T1DM who generally exhibited less optimal glycemic control in the current study would have shown a stronger association between A1C at delivery and LGA, but there is conflicting evidence regarding the degree to which maternal hyperglycemia explains the variance in infant birthweight. For example, in a study of 510 women with T1DM in Poland, Cyganek et al (23) found that, in multiple regression analysis, third trimester A1C and mean fasting self-monitored blood glucose were independent predictors of macrosomia. Similarly, Morrens et al (24) found that, in a population of 180 women with T1DM in Belgium, A1C early in pregnancy and at delivery were independent predictors for LGA. On the other hand, Gold et al (25) found that A1C accounted for only 23% of the variance in birthweight in a cohort of 57 women with T1DM in Scotland. Also, Scifres et al (11) found that, among 175 women in the United States with T1DM, there were similar rates of LGA birthweight among women with A1C $<6.5\%$ and $>6.5\%$, suggesting that other factors may be playing a role.

Previous studies regarding the relationship between maternal glycemic control and LGA for women with T2DM are also conflicting. Although 1 study of 51 women with T2DM in Chile found that A1C was not predictive of LGA (13), another study of 90 women in the United States with either insulin-dependent gestational diabetes or T2DM found that self-monitored blood glucose measures in the third trimester were associated with birthweight (26).

One possible explanation for why studies have failed to consistently show an association between A1C and LGA may be because A1C may not be the best measure of glycemic control. Multiple studies have shown that people with diabetes can have considerable episodic hyperglycemia and maintain normal A1C values (27–29). Kerssen et al (30) showed that 41% of readings on continuous glucose monitoring (CGM) were above target for women with an A1C that was in target. Also, Law and colleagues (29) in their examination of temporal blood glucose patterns using CGM for women with pregestational diabetes, found that trimester-specific maternal glucose excursions at certain times of day were associated with LGA, and that this glucose variation was not reflected in A1C values.

Overall, although studies examining the role that glycemic control plays as a predictor of LGA in women with T1DM and T2DM have yielded conflicting results, this may reflect the fact that A1C as

Table 2
Associations between maternal factors and birthweight corrected for gestational age and infant sex for type 1 and type 2 diabetes

	Comparisons of LGA and non-LGA mothers and infants			Multivariable analysis		p value
	Non-LGA	LGA	p value	OR	CI	
Type 1 diabetes	(n=92)	(n=59)				
Non-Caucasian ethnicity	54 (60.7)	52 (88.1)	0.001	4.07	1.46-11.35	0.008
Nulliparous	53 (58.2)	28 (49.1)	0.36	0.59	0.27-1.29	0.19
CSII	35 (38.0)	38 (64.4)	0.003	2.08	0.94-4.61	0.07
Hypertension	20 (21.7)	12 (20.3)	0.99	0.70	0.27-1.84	0.47
Prepregnancy BMI	26.8 (6.3)	25.2 (4.88)	0.12	0.94	0.87-1.01	0.10
First trimester A1C	7.67 (1.68)	7.49 (1.5)	0.52	0.98	0.72-1.35	0.91
Delivery A1C	6.44 (1.2)	6.52 (0.72)	0.65	1.32	0.83-2.10	0.25
Type 2 diabetes	(n=211)	(n=42)				
Non-Caucasian ethnicity	45 (22.0)	20 (47.6)	0.001	2.47	1.15-5.32	0.02
Nulliparous	83 (40.1)	8 (19.5)	0.02	0.32	0.13-0.77	0.01
Hypertension	81 (38.4)	18 (42.9)	0.71	1.15	0.54-2.43	0.72
Prepregnancy BMI	31.3 (7.3)	35.1 (7.4)	0.12	1.05	0.99-1.11	0.09
First trimester A1C	7.23 (1.62)	7.17 (1.3)	0.83	0.95	0.71-1.29	0.76
Delivery A1C	6.00 (0.84)	6.18 (0.91)	0.25	1.40	0.86-2.30	0.18
Excess weight gain	90 (57.3)	25 (78.1)	0.046	2.26	0.85-5.97	0.11

A1C, glycated hemoglobin; *BMI*, body mass index; *CI*, confidence interval; *CSII*, continuous subcutaneous insulin infusion; *GROW*, Gestation Related Optimal Weight; *LGA*, large for gestational age; *OR*, odds ratio.
Notes: Data for single-variable analysis are presented as count (%) except for A1C values and BMI, which are presented as mean (standard deviation). LGA was determined using population-based Canadian data adjusted for gestational age and sex of offspring (17).

a measure of glycemia is somewhat flawed. More sensitive measures of glycemic control are needed, such as CGM. Encouragingly, some studies have shown that women with pregestational diabetes who use CGM attain improved glycemic control and have a lower incidence of LGA birthweights (31,32).

Excess maternal weight gain

In this study, there was also a nonsignificant trend toward association between excess weight gain in pregnancy beyond the IOM recommendations and LGA infants in women with T1DM but not in T2DM. For women with T1DM, the majority of studies in this domain have shown an association between LGA infants and total weight gain in pregnancy or weight gain in pregnancy beyond the IOM recommendations (11,12,23,24,33). However, studies of the relationship between maternal weight gain and LGA birthweight in women with T2DM have been less consistent. For example, a Danish study of 142 women with T2DM found that maternal weight gain beyond the IOM guidelines was associated with higher infant birthweight after adjustment for prepregnancy BMI, smoking, A1C, insulin dose at last visit, ethnicity and parity (15). On the other hand, in a study from Chile that included 51 women with T2DM, the authors did not find an association between pregnancy weight gain and macrosomia (13).

Certain prepregnancy and pregnancy-related factors may help to explain why excess maternal weight gain may be less strongly associated with LGA birthweight in women with T2DM compared to T1DM. Among the population in this study, and as found by each previous study that compared predictors of LGA among women with T1DM and T2DM (3,4,13), although women with T2DM had more obesity at the outset of pregnancy, they had less weight gain in pregnancy, on average, than women with T1DM. More specifically, in this sample, whereas the incidence of excess weight gain in women with T2DM was still quite high, significantly fewer women with T2DM had excess weight gain compared to women with T1DM (T1DM, 59.6%; T2DM, 45.5%; p=0.015). One may presume that women with type 2 diabetes may be more prone to excess weight gain in pregnancy due to the metabolic syndrome that typically accompanies type 2 diabetes; however, after the release of the IOM guidelines in 2009 that emphasized BMI-based targets for recommended weight gain in pregnancy, it is possible that women with T2DM, who tend to be more obese at the outset of pregnancy, are gaining less weight because they are receiving more education about appropriate weight gain in pregnancy than their leaner counterparts with T1DM. As a result, for women with T2DM who do not gain excess weight in pregnancy, perhaps other metabolic factors, such as glycemia, as found in the current study, may play a greater role in the LGA birthweight than weight gain. Future studies could attempt to quantify differences in lifestyle changes adopted by women with T1DM and T2DM in pregnancy to help determine whether women with T2DM may implement more substantial lifestyle changes in pregnancy.

Table 3
Factors associated with LGA defined using GROW in multiple logistic regression for women with T1DM and T2DM

	T1DM			T2DM		
	OR	CI	p value	OR	CI	p value
CSII	1.17	0.99-1.39	0.06	—	—	—
Hypertension	0.98	0.80-1.20	0.85	0.99	0.89-1.10	0.85
First trimester A1C	1.03	0.97-1.10	0.29	0.99	0.95-1.03	0.60
Delivery A1C	0.99	0.90-1.08	0.77	1.10	1.02-1.19	0.01
Excess weight gain	1.19	0.99-1.43	0.06	1.04	0.91-1.18	0.54

A1C, glycated hemoglobin; *CI*, confidence interval; *CSII*, continuous subcutaneous insulin infusion; *GROW*, Gestation Related Optimal Weight; *LGA*, large for gestational age; *OR*, odds ratio.

Use of continuous subcutaneous insulin infusion

Finally, among the women with T1DM in this study, there was a nonsignificant trend toward association between the use of CSII and LGA. There have been several meta-analyses exploring this relationship. For example, a meta-analysis from 2015 that included 5 studies did not find a statistically significant difference in birthweight among women with T1DM using CSII or multiple daily injections (34). A more recent meta-analysis of randomized and nonrandomized, controlled trials by Rys et al that examined 47 studies reporting on 7,824 pregnancies found that women with T1DM using CSII were more likely to have an LGA infant (relative risk, 1.16; 95% CI, 1.07 to 1.24) (35). One hypothesis is that women on CSII typically achieve better glycemic control in the first trimester, which may lead to a better-functioning placenta and improved fetal growth later in pregnancy (35). From our clinical

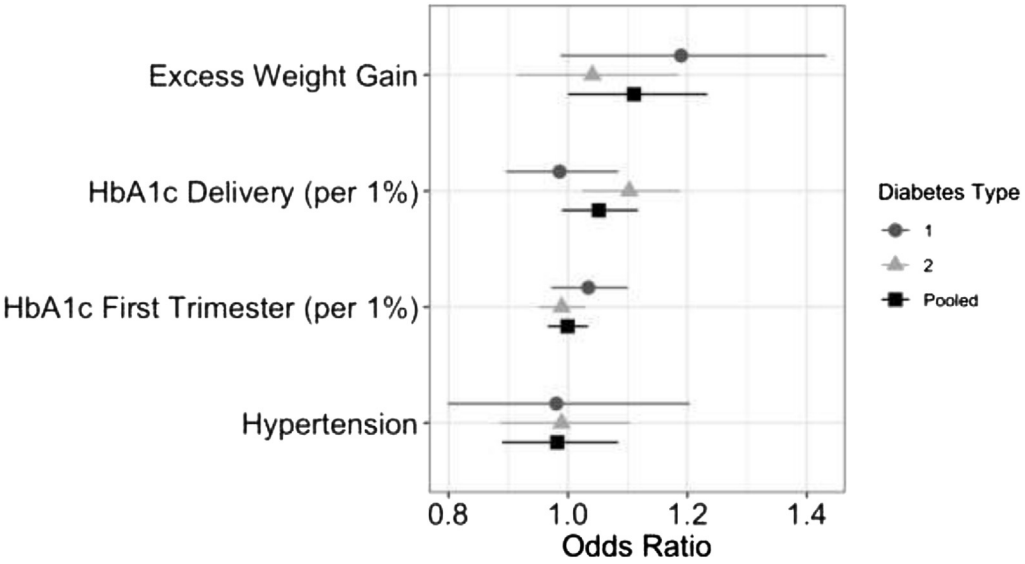

Figure 2. Odds ratio estimates relating LGA (defined by GROW) to excess weight gain during pregnancy, A1C in the first trimester and at delivery and hypertension. Estimates are shown for models in T1DM, T2DM separately and then from a model in a combined cohort that also contains a variable for diabetes type. *A1C*, glycated hemoglobin; *GROW*, Gestation Related Optimum Weight; *LGA*, large for gestational age; *T1DM*, type 1 diabetes mellitus; *T2DM*, type 2 diabetes mellitus.

experience, we have also observed that pregnant women on CSII will at times have a more liberal diet, as bolusing insulin for more frequent food intake is more convenient with CSII than with multiple daily injections. This increased caloric intake could also be playing a role in fetal overgrowth. It should be noted that many participants in previous trials of CSII were not using CGM. Given that some studies have shown that CGM can reduce the incidence of LGA in both women with CSII and multiple dose injections (31), perhaps future studies examining the role of CSII in pregnancy that make use of CGM will yield different results.

Study strengths and limitations

This study has several strengths. Patients were identified from a prospectively collected database and were all from one centre, so a similar treatment approach was used for all women. Important variables, such as prepregnancy BMI, pump use, A1C, parity and ethnicity, were included and could be used in the multiple regression analysis. Another advantage of the current study is the use of GROW to assess for fetal overgrowth. Arguably, GROW provides a more physiological assessment of fetal overgrowth, as it accounts for fetal sex, gestational age at delivery and key maternal factors that have been shown to impact fetal size, such as ethnicity, BMI and parity.

However, as a retrospective cohort study, there are limitations to our analyses. For example, we did not have data regarding insulin dose during pregnancy. Other potentially important predictors of LGA that were not captured in the database include paternal demographics, immigration status or maternal iron deficiency and hemoglobinopathy that could affect A1C values. Also, metformin use during pregnancy, which may have influenced maternal weight gain and insulin doses, was not recorded; however, metformin use during pregnancy in this time frame was not recommended at our study centre unless patients were enrolled in a clinical trial. Other changes in general diabetes care, such as education, provided on nutrition or weight gain in pregnancy may have changed slightly over the study period. Access to nurse and dietitian support did not change. Fasting and postprandial glycemic targets recommended by Canadian practice guidelines did not change over the study period (36,37).

The sample population in this study was ethnically diverse and may not be generalizable to less diverse populations. Most studies to date on the predictors of LGA birthweight in women with T1DM and T2DM did not report the ethnicity of study participants. Future studies may benefit from reporting the ethnicity of the patient population and controlling for ethnicity when assessing for LGA by using a measure such as GROW.

Conclusions

The results of this study show that non-Caucasian ethnicity and multiparity were associated with LGA birthweight. After controlling for these nonmodifiable maternal factors, A1C near delivery was associated with LGA in women with type 2 diabetes. Other factors, such as prepregnancy BMI, maternal weight gain in pregnancy or use of CSII may be associated with LGA. Given that the incidence of LGA birthweights remains high, further study is warranted with regard to these and other potential predictors.

Author Disclosures

Conflicts of interest: None.

Author Contributions

LA, DSF and GT designed the study, LA did the retrospective chart review and put the data in the database, GT designed the statistical analyses plan and performed the analyses. LA, DSF and GT wrote the first draft manuscript; LA, DSF and GT are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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