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Excess foetal growth and glycaemic control in type 1 diabetes and pregnancy

Despite advances in diabetes care for women with type 1 diabetes (T1D) in pregnancy, the incidence of large-for-gestational-age (LGA) neonates (birth weight > 90th centile for gestational age and gender) and macrosomia (birth weight > 4,000 g) remains high. Recent studies have demonstrated rates of LGA between 40% and 80% in T1D pregnancy [1,2], and hyperglycaemia, glycaemic variability and maternal weight gain have all been shown to contribute towards excess foetal growth [3,4]. As a result of the increased tendency towards larger babies in T1D pregnancy, these women are advised to have regular ultrasound scans to monitor foetal growth in the third trimester and to have early term delivery [5].

Several studies have examined the relationship between maternal glycaemic control and acceleration of foetal growth in T1D pregnancy, with conflicting results. All of the studies observed that LGA neonates demonstrate excess foetal growth on ultrasound scans as early as the mid second trimester; however, this was not associated with maternal glycaemic control in two studies [6,7] and was associated with maternal glycaemic control in the first and/or second trimester in two other studies [8,9].

Therefore, the aim of the present study was to determine the relationship between glycaemic control throughout pregnancy in women with T1D and foetal abdominal circumference (AC) as a marker of foetal growth.

We conducted a retrospective cohort study in women aged greater than 18 years with T1D and a singleton pregnancy who attended the multi-disciplinary specialist obstetric clinic (SOC) at Royal North Shore Hospital, a large, tertiary referral hospital in Sydney, Australia, from January 2012 to June 2017. Approval for this study was obtained from the Northern Sydney Local Health District Human Research Ethics Committee (Reference No. LNR/16/HAWKE/191) and the study was carried out in keeping with the STROBE statement for cohort studies.

Data were extracted from patient electronic medical records and included maternal demographics (age, BMI recorded at the first visit to the antenatal clinic, parity, duration of diabetes, mode of insulin therapy) and the following outcomes: maternal outcomes – mode of delivery and complications in delivery, and perinatal outcomes – birth weight, gestational age at delivery, respiratory distress, neonatal hypoglycaemia, jaundice and neonatal intensive care unit (NICU) admission. In addition, ultrasound data including AC were recorded at 22–26, 27–30, 31–33 and 34–37 weeks' gestation during routine foetal growth assessment scans.

The online intergrowth-21st project foetal AC centile calculator was used to assess foetal size relative to population standards and was expressed as AC z-score. Similarly, the online intergrowth-21st project birth weight centile calculators were used to calculate LGA neonates. These centile calculators were chosen as they represent international standards for foetal growth and neonatal size across a multi-ethnic cohort of women [10].

Using the values for foetal AC reported in a previous study of T1D in pregnancy [6], with α 0.05 and power 0.9, a sample size of 13 per group is required to see a significant difference in foetal growth. Differences between groups were compared using Student's *t*-test or the Mann–Whitney test for parametric and non-parametric data, respectively, with Bonferroni correction for multiple comparisons. Fisher's exact test was used to analyse categorical data and Spearman's correlation was carried out to determine the association between AC centile and HbA1c. Receiver operator characteristic (ROC) curves were used to determine the ability of HbA1c at each time point to identify LGA neonates. The optimal HbA1c value for predicting LGA neonates was determined from the ROC curve using Youden's statistic. Statistical analyses were done using GraphPad Prism Version 7 and a P value < 0.05 was considered statistically significant.

Seventy women with T1D in singleton pregnancy were identified. For women with more than one pregnancy during the study time-period ($n = 10$), the first pregnancy was included.

Table 1
Maternal characteristics and perinatal outcomes for women that had LGA compared with non-LGA neonates. Data expressed as means ± SD.

	LGA ($n = 34$)	Non-LGA ($n = 26$)	P
Maternal characteristics			
Age (years)	32.6 ± 6.1	32.7 ± 4.1	0.999
Duration of diabetes (years)	16.5 ± 9.3	14.5 ± 10.3	0.918
Early pregnancy BMI (kg/m^2)	26.0 ± 4.0	25.4 ± 5.7	0.490
Parity	0.6 ± 0.8	0.2 ± 0.7	0.122
Ethnicity			
Caucasian	91.2%	76.9%	0.442
Asian	2.9%	7.7%	
South East Asian	2.9%	11.5%	
Aboriginal and Torres Strait Islander	2.9%	3.8%	
Insulin treatment modality			
Multiple daily injections	44.1%	65.4%	0.123
Insulin pump therapy	55.9%	34.6%	
Mode of delivery			
Caesarean section	88.2%	73.1%	0.182
Vaginal birth	11.8%	26.9%	
HbA1c (%)			
Pre-pregnancy	7.7 ± 1.5	6.9 ± 1.0	0.374
First trimester	7.4 ± 1.0	6.3 ± 0.9	0.002
Second trimester	6.4 ± 0.7	5.6 ± 0.6	0.0004
Third trimester	6.5 ± 0.9	5.8 ± 0.6	0.025
Neonatal outcomes			
Birth weight (g)	3,972 ± 366	3,071 ± 543	0.0007
Gestational age at delivery (weeks)	37.5 ± 0.8	37.2 ± 2.3	0.773
Birth weight centile	97.1 ± 3.2	66 ± 20.5	0.0007
Neonatal hypoglycaemia	55.8%	53.9%	0.999
Respiratory distress	26.5%	15.4%	0.954
Jaundice	29%	30.8%	0.999
Admission to neonatal intensive care unit	32.3%	46.2%	0.906

LGA: large-for-gestational-age.

Thus, 60 pregnancies comprised the final study cohort. The mean ± SD maternal age was 32.6 ± 5.3 years, with median diabetes duration of 15.6 years (range: 1–35) and mean ± SD first trimester BMI of 25.8 ± 4.8 kg/m^2. Thirty-four neonates (56.7%) were born LGA with a mean birth weight of 3,972 g and 18 of these neonates (52.9%) had macrosomia. Maternal characteristics and perinatal outcomes for women that did or did not have LGA neonates are outlined in Table 1. There was no significant difference in maternal age, duration of diabetes, ethnicity, early pregnancy BMI, parity, insulin treatment modality or mode of delivery between groups. There were similar rates of caesarean section in both groups, in keeping with the high rate of caesarean sections at our hospital. Furthermore, LGA neonates were born at the same gestational age as non-LGA neonates, and experienced the same rate of adverse perinatal outcomes.

Mothers of LGA neonates had significantly higher HbA1c levels in the first ($P = 0.002$), second ($P = 0.0004$) and third ($P = 0.025$) trimesters, yet no difference was observed pre-pregnancy (Table 1). Ultrasounds scans were available for 43 pregnancies at 22–26 weeks, 48 pregnancies at 27–30 weeks, 47 pregnancies at 31–33 weeks and 54 pregnancies at 34–37 weeks. Neonates born LGA had significantly greater AC z-scores by 30 weeks' gestation compared to non-LGA neonates ($P = 0.0036$) and this difference was observed for the remainder of pregnancy. Furthermore, foetal AC centile at 27–30 weeks was positively associated with second trimester HbA1c (r = 0.378; $P = 0.021$). Likewise, foetal AC centile at 34–37 weeks' gestation correlated with third trimester HbA1c (r = 0.589; $P < 0.0001$). Following adjustment for maternal age, BMI, duration of diabetes, parity, and insulin treatment modality, second trimester HbA1c retained its significant association with LGA neonates ($P = 0.01$), whereas first trimester HbA1c ($P = 0.862$) and third trimester HbA1c ($P = 0.221$) did not.

ROC curve analysis showed that the optimal HbA1c value in the second trimester for detecting neonates born LGA was 6.05%, with a Youden's index of 0.556 and an area under the curve of 0.831 (sensitivity 69.23% and specificity 86.36%; $P < 0.0001$). Furthermore, first and third trimester HbA1c levels of 7% and 5.75%, respectively, had the highest sensitivity and specificity for predicting LGA neonates (sensitivity 67.86% and specificity 85%; $P = 0.001$ and sensitivity 84% and specificity 61.11%; $P = 0.0073$, respectively).

In the present study, we have identified that women with T1D that had LGA neonates have higher HbA1c levels throughout pregnancy, and that raised HbA1c levels are associated with foetal overgrowth in the late second and third trimesters. Other studies have observed excess growth in neonates born LGA in T1D pregnancy, yet there have been inconsistent findings regarding the association between maternal glycaemic control and foetal growth (6–9). In addition, ROC curve analysis showed that second trimester HbA1c of > 6.05% was the best predictor of LGA neonates, compared with HbA1c measured at other time points in pregnancy.

We found that HbA1c in the second trimester was significantly associated with LGA neonates following adjustment for maternal confounding factors, which is similar to the results of our previous prospective study in T1D pregnancy examining the association between glycaemic variability and HbA1c with LGA neonates [3]. Of note, previously we showed that HbA1c < 6% was necessary, though not sufficient to ensure normal neonatal size, and that glycaemic variability, especially in the second trimester of pregnancy, was an important determinant of LGA. Taken together, these findings suggest that achieving an HbA1c below 6.05% by 24 weeks of gestation, as well as minimising glycaemic excursions, may result in a lower likelihood of foetal overgrowth occurring in T1D pregnancy; however, this should be confirmed in future studies. Our results are similar to those of Maresh et al., who found that an HbA1c > 6% in the second trimester was significantly associated with LGA neonates in a large cohort of women with T1D [11]. Conversely, several studies have demonstrated no relationship between maternal glycaemic control and the likelihood of LGA neonates [12] nor excess foetal growth in T1D pregnancy [6,7]. Thus, additional work is required to elucidate the contribution of glucose, along with other maternal factors such as BMI and maternal age [13], towards foetal overgrowth in T1D pregnancy.

LGA and macrosomic neonates are more likely to experience adverse outcomes, both at the time of delivery and later in adult life, including obesity, diabetes and cardiovascular disease. Furthermore, a previous study at our hospital (between 1989 and 1998) demonstrated the rate of LGA neonates for women with T1D in pregnancy was 39.6% [14], showing that increased birth weight is now occurring more frequently. Thus, minimising excess foetal growth in T1D pregnancy such that birth weight falls within the normal range is of direct clinical relevance. Feig et al. recently showed that use of real-time continuous glucose monitoring in T1D pregnancy not only reduced time spent in hyperglycaemia and glycaemic variability, but also gave rise to a significantly lower incidence of LGA neonates [15]. We found no difference in adverse neonatal outcomes between those born LGA and non-LGA, which may be due to the small sample size; yet reductions in birth weight might give rise to benefits in later life, by ameliorating susceptibility to chronic disease in those born LGA.

A limitation of this study is the small sample size; however, it is in keeping with other studies examining foetal growth in T1D pregnancy [7,8]. Furthermore, we did not have information on gestational weight gain, which has previously been shown to be a contributor towards foetal overgrowth in pregnancy complicated by T1D [4].

In summary, maternal glycaemic control in T1D pregnancy, specifically an HbA1c > 6% in the second trimester, is associated with an increased risk of neonates being born LGA. Furthermore, foetal overgrowth is apparent on ultrasound from the late second trimester and there is a significant relationship between foetal abdominal circumference and maternal HbA1c. Future research directed towards minimising maternal hyperglycaemia whilst also measuring foetal size would further elucidate the contribution of glucose towards foetal growth in T1D pregnancy.

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Disclosure of interest

The authors declare that they have no competing interest.

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