Contemporary type 1 diabetes pregnancy outcomes: impact of obesity and glycaemic control

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The known Type 1 diabetes in pregnant women is associated with complications for both mother and baby. Optimal glycaemic control reduces the likelihood of these adverse outcomes.

The new The mean body mass index of Australian women with type 1 diabetes is greater than that of women without diabetes. Even with multidisciplinary specialist care and good glycaemic control, their likelihood of adverse outcomes was greater than for women without diabetes because of this additional risk factor.

The implications Pre-conception care is important, but optimising glycaemic control is not sufficient to prevent complications associated with type 1 diabetes during pregnancy. Preventing obesity in childbearing women with type 1 diabetes requires greater attention.

Abstract

Objective: To compare contemporary pregnancy outcomes in women with and without type 1 diabetes, and to examine the effects of obesity and glycaemic control on these outcomes.

Design and setting: Historical cohort study in a specialist diabetes and maternity network in Victoria.

Participants: All singleton births (at least 20 weeks' gestation), 2010–2013, were analysed: 107 pregnancies to women with type 1 diabetes and 27 075 pregnancies to women without diabetes. Women with type 2 diabetes or gestational diabetes were excluded.

Methods: Data were extracted from the Birthing Outcomes System database; associations between type 1 diabetes and pregnancy outcomes were analysed by multivariable regression.

Main outcome measures: Mode of birth; maternal and neonatal outcomes.

Results: The mean body mass index was higher for women with type 1 diabetes than for women without diabetes (mean, 27.3 kg/m^2 [SD, 5.0] *v* 25.7 kg/m^2 [SD, 5.9]; $P = 0.01$); the median gestation period for their babies was shorter (median, 37.3 weeks [IQR, 34.6–38.1] *v* 39.4 weeks [IQR, 38.4–40.4]; $P < 0.001$) and they were more likely to be large for gestational age (LGA) (adjusted odds ratio [aOR], 7.9; 95% CI, 5.3–11.8). Women with type 1 diabetes were more likely to have had labour induced (aOR, 3.0; 95% CI, 2.0–4.5), a caesarean delivery (aOR, 4.6; 95% CI, 3.1–7.0), or a pre-term birth (aOR, 6.7; 95% CI, 4.5–10.0); their babies were more likely to have shoulder dystocia (aOR, 8.2; 95% CI, 3.6–18.7), hypoglycaemia (aOR, 10.3; 95% CI, 6.8–15.6), jaundice (aOR, 5.1; 95% CI, 3.3–7.7), respiratory distress (aOR, 2.5; 95% CI, 1.4–4.4) or to suffer perinatal death (aOR, 4.3; 95% CI, 1.9–9.9). In women with type 1 diabetes, greater obesity was associated with increased odds for an LGA baby or congenital malformation, and increased HbA_{1c} levels were associated with pre-term birth and perinatal death.

Conclusion: Women with type 1 diabetes, even when managed in a specialist setting, still experience adverse obstetric and neonatal outcomes. Poor glycaemic control is not wholly responsible for adverse outcomes, reinforcing the importance of other risk factors, such as obesity and weight gain.

Type 1 diabetes accounts for 5–10% of diabetes diagnoses, and is a well recognised and important risk factor for a number of complications during pregnancy.[1] Women with type 1 diabetes have a higher risk of miscarriage, hypertensive complications and obstetric interventions, and their babies have an increased risk of congenital malformations, stillbirth, macrosomia and birth trauma.[2]

In 1989, the St Vincent Declaration set a 5-year goal of improving pregnancy outcomes for women with type 1 diabetes so that they approximated those of women without diabetes.[3] Although the Diabetes Control and Complications Trial showed that improvements are possible,[4] they have not been seen in observational studies.[5,6]

There are many gaps in the published literature about pregnancy outcomes for women with type 1 diabetes and their babies. Some studies have not distinguished the risks associated with type 1 and type 2 diabetes,[7,8] others have used less informative composite outcomes[7-9] or have not accounted for important confounders, such as maternal age, obesity and glycaemic control.[5,10-12] The interaction between the effects of type 1 diabetes, glycaemic control and body mass index during pregnancy are not well understood, and there are no Australian data on this question. We accordingly aimed to compare contemporary adverse pregnancy outcomes in women with or without type 1 diabetes who were managed in a specialist maternity centre with optimal health care. Further, we explored the influence of obesity and glycaemic control on pregnancy outcomes in women with type 1 diabetes.

Methods

Study design and population

This historical cohort study included all singleton births of at least 20 weeks' gestation at Monash Health, including Clayton, Dandenong and Casey hospitals. Monash Health is one of

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Australia's largest public maternity networks (7500 births each year), providing quaternary care facilities and specialised endocrine, diabetes nurse educator, obstetric, midwifery and neonatal services.

Data were obtained from the Birthing Outcomes System (BOS) database for the period 1 January 2010 – 31 December 2013. Data were collated prospectively by midwives from the first antenatal visit until delivery and discharge. The database contains routinely recorded standardised pregnancy and neonatal health information collected for statutory data reporting, including demographic data, medical history, and information about antenatal care and complications.

More than 80% of women with type 1 diabetes attended pre-conception care, half of whom attended a pre-conception and early pregnancy clinic at our service. From 12 weeks' gestation, all attended a specialised multidisciplinary diabetes and maternity service. Care for women without diabetes was provided by midwives and obstetric staff at general antenatal clinics. Following delivery, babies were admitted to the special care nursery if they needed specialised care and observation; this is routine for babies of women with type 1 diabetes. Babies were admitted to the neonatal intensive care unit (NICU) only if they had potentially life-threatening conditions.

Antenatal characteristics and maternal and neonatal outcomes for mothers with type 1 diabetes and women with normal glucose tolerance were compared. Women with type 2 diabetes and gestational diabetes mellitus (GDM) were excluded. All women were screened for GDM at 24–28 weeks' gestation with a 75 g oral glucose tolerance test; GDM was diagnosed if the fasting blood glucose concentration was 5.5 mmol/L or more, or the 2-hour level was 8.0 mmol/L or more. Women with risk factors were screened early for GDM and unrecognised diabetes. "Pre-existing diabetes" was recorded if reported by the woman and validated by a clinician reviewing individual medical records for type of diabetes, treatment, and the presence of microvascular complications. Glycated haemoglobin (HbA_{1c}) levels were measured at booking and every 4–6 weeks thereafter by high performance liquid chromatography (HA-8160 Automatic Glycohemoglobin Analyzer, Arkray Adams; coefficient of variation, 1.4%).

Outcomes

The primary outcomes were large for gestational age (LGA; > 90th percentile) and small for gestational age babies (SGA; < 10th percentile), with weights adjusted for gestational age and sex according to Australian birthweight percentiles.[13] Secondary maternal outcomes were induction of labour (IOL), caesarean delivery, pre-term birth (< 37 weeks' gestation), gestational hypertension (new onset hypertension from 20 weeks' gestation, with blood pressure ≥ 140/90 mmHg) and pre-eclampsia (hypertension with proteinuria > 300 mg/24 hours, spot urine protein:creatinine ratio ≥ 0.03 g/mmol, or renal, hepatic, neurological or haematological involvement). Secondary neonatal outcomes were admission to an NICU, hypoglycaemia (blood glucose level < 2.6 mmol/L), jaundice requiring phototherapy, and respiratory distress syndrome. Shoulder dystocia and Apgar scores below 7 at 5 minutes were reported for vaginal deliveries. Major congenital malformations and perinatal death (stillbirths at 20 weeks' gestation or later, and neonatal deaths up to 28 days post partum or while the mother was an inpatient) were reported.

Statistical analyses

Maternal characteristics are reported for the two groups of women as descriptive statistics. Categorical data were compared using Pearson χ^2 or Fisher exact tests; continuous data were compared using Student t tests or Mann–Whitney U tests as appropriate. Multivariable logistic regression analysis generated crude and adjusted odds ratios (ORs, aORs respectively) and 95% confidence intervals (CIs) for each outcome for women with type 1 diabetes (reference category: women without diabetes). Covariates that were clinically or statistically significant ($P < 0.1$) in the univariable analysis were included in multivariable models. Area under the curve and the likelihood ratio test were used to determine the most parsimonious multivariable models. Potential confounders analysed included maternal age, body mass index (BMI) at the first antenatal visit, region of birth, parity, smoking status, and gestational age. We accounted for repeated measurements in an individual by adjusting analyses for clustering. A subanalysis of data for women with type 1 diabetes assessed the effect of obesity and glycaemic control. $P < 0.05$ (two-sided) was deemed statistically significant. Analyses were performed in Stata 12 (StataCorp).

Ethics approval

The study was approved by the Monash Health Human Research Ethics Committee (reference, 14001Q, 2013).

Results

Maternal and neonatal health characteristics

Outcomes for 107 pregnancies in 94 women with type 1 diabetes and 27 075 pregnancies in 21 370 women without diabetes were analysed. The mean BMI was higher for women with type 1 diabetes than for women without diabetes ($P = 0.01$) (Box 1); 66% were overweight or obese, compared with 45% of women without diabetes (data not shown). Women with type 1 diabetes were more likely to have been born in Australia ($P < 0.001$), but there were no significant differences in age, parity or smoking status. A greater proportion of babies born to women with type 1 diabetes were girls (65% *v* 49%; $P = 0.002$) and the mean gestation time was about 2 weeks shorter (37.3 *v* 39.4 weeks; $P < 0.001$), but there was no significant difference in mean birthweight (Box 1).

Primary and secondary outcomes

The odds for women with type 1 diabetes giving birth to LGA babies was higher than for women without diabetes, after adjustment for BMI and other confounders (adjusted OR [aOR], 7.9; 95% CI, 5.3–11.8). There was no difference in the likelihood of SGA births. Women with type 1 diabetes had a greater likelihood of IOL (aOR, 3.0; 95% CI, 2.0–4.5) and caesarean delivery (aOR, 4.6; 95% CI, 3.1–7.0) than those without diabetes (Box 2). Among those who gave birth to LGA babies, the proportion of women with type 1 diabetes who had caesarean deliveries was greater than for women without diabetes (62% *v* 35%; aOR, 3.0; 95% CI, 1.6–5.4); a significant difference was also found for women who gave birth to non-LGA babies (62% *v* 26%; aOR, 5.1; 95% CI, 2.9–8.9) (data not shown). Women with type 1 diabetes had a higher rate of pre-term births (aOR, 6.7; 95% CI, 4.5–10.0) (Box 2), as well as a higher rate of pre-term caesarean deliveries (39% *v* 11%; aOR, 4.7; 95% CI, 2.8–7.9) (data not shown) but not of pre-term IOL (20% *v* 11%; aOR, 1.9; 95% CI, 0.9–4.0). There was no significant difference in maternal hypertensive complications.

Babies of women with type 1 diabetes were more likely than those of women without diabetes to be admitted to an NICU (aOR, 3.4; 95% CI, 1.8–6.4), and to have hypoglycaemia (aOR, 10.3; 95% CI, 6.8–15.6), jaundice (aOR, 5.1; 95% CI, 3.3–7.7), respiratory distress

1 Demographic and health characteristics of mothers with and without type 1 diabetes, and health characteristics of their neonates

	Women with type 1 diabetes	Women without diabetes	*P*
Number	107	27 075	
Maternal age (years), mean (SD)	29.3 (5.3)	29.4 (5.4)	0.76
Maternal body mass index (kg/m^2) at booking visit, mean (SD)	27.3 (5.0)	25.7 (5.9)	**0.01**
Country of birth			
Australia or New Zealand	95 (89%)	12 806 (47.3%)	**< 0.001**
Europe or Americas	8 (7%)	1850 (6.8%)	0.79
Africa	2 (2%)	1798 (6.6%)	0.05
Asia	2 (2%)	10 620 (39.2%)	**< 0.001**
Parity			0.40
Primiparous	51 (48%)	11 805 (43.6%)	
Parous	56 (52%)	15 269 (56.4%)	
Smoker	24 (22%)	4703 (17.4%)	0.20
Neonate sex			**0.002**
Boy	37 (35%)	13 896 (51.3%)	
Girl	70 (65%)	13 156 (48.6%)	
Gestation at birth (weeks), median (IQR)	37.3 (34.6–38.1)	39.4 (38.4–40.4)	**< 0.001**
Birth weight (g), mean (SD)	3230 (997)	3305 (649)	0.26

(aOR, 2.5; 95% CI, 1.4–4.4) or shoulder dystocia (aOR, 8.2; 95% CI, 3.6–18.7) (Box 2). While there was no difference in the odds of NICU admission for pre-term babies of women with and without type 1 diabetes (aOR, 0.64; 95% CI, 0.29–1.42), they were higher for term babies of women with type 1 diabetes (aOR, 4.3; 95% CI, 1.3–13.8) (data not shown). There was an interaction between type 1 diabetes and gestation time for the likelihood of hypoglycaemia: the odds were higher for term babies of women with type 1 diabetes (aOR, 22; 95% CI, 13–37) than for pre-term babies of women with type 1 diabetes (aOR, 2.9; 95% CI, 1.5–5.3) (data not shown). The odds of an Apgar score under 7 at 5 minutes was not significantly different in the two groups after adjustment for gestation time (Box 2).

There was no difference in the likelihood of congenital malformations, but that of perinatal death was higher for babies of mothers with type 1 diabetes, after adjustment for congenital malformations (aOR, 5.5; 95% CI, 2.4–12.8) (Box 2). There were five stillbirths (5 per 100 live births) to women with type 1 diabetes (three terminations because of malformations, two intra-uterine deaths at 34 and 37 weeks) and two neonatal deaths (2 per 100 live births: one termination, one instance of lung disease in an extremely premature baby). Among women without diabetes, there were 284 stillbirths (1 per 100 live births) and 110 neonatal deaths (0.4 per 100 live births); of these babies, 53 and 34 respectively had malformations.

2 Maternal and neonatal adverse outcomes for women with and without type 1 diabetes

			Odds ratio (95% CI) Reference category: women without diabetes	
	Women with type 1 diabetes	Women without diabetes	Crude odds ratio	Adjusted odds ratio
Number	107	27 075		
Large for gestational age baby	47 (44%)	2087 (7.7%)	9.4 (6.4–13.8)	**7.9 (5.3–11.8)***
Small for gestational age baby	7 (7%)	3964 (14.7%)	0.41 (0.19–0.88)	0.52 (0.24–1.12)†
Induction of labour	51 (48%)	5738 (21.2%)	3.4 (2.3–5.0)	**3.0 (2.0–4.5)‡**
Caesarean delivery	66 (62%)	7116 (26.3%)	4.5 (3.1–6.7)	**4.6 (3.1–7.0)‡**
Pre-term birth	42 (39%)	2186 (8.1%)	7.4 (5.0–10.9)	**6.7 (4.5–10.0)†**
Gestational hypertension	2 (2%)	527 (2.0%)	0.96 (0.24–3.9)	0.86 (0.21–3.5)§
Pre-eclampsia	5 (5%)	645 (2.4%)	2.0 (0.8–5.0)	1.8 (0.7–4.5)§
Neonatal intensive care unit admission	11 (11%)	727 (2.7%)	4.3 (2.3–8.1)	**3.4 (1.8–6.4)¶**
Hypoglycaemia	41 (38%)	1074 (4.0%)	15.0 (10.1–22.3)	**10.3 (6.8–15.6)****
Jaundice requiring phototherapy	40 (37%)	1737 (6.4%)	8.7 (5.9–12.9)	**5.1 (3.3–7.7)**
Respiratory distress requiring resuscitation	16 (15%)	1039 (3.8%)	4.4 (2.6–7.5)	**2.5 (1.4–4.4)**
Shoulder dystocia††	7 of 41 (17%)	498 of 19 958 (2.5%)	8.1 (3.5–18.2)	**8.2 (3.6–18.7)**
Apgar score under 7 at 5 min††	7 of 40 (17%)	577 of 19 887 (2.9%)	7.1 (3.1–16.1)	2.7 (0.90–8.1)**
Congenital malformation	4 (4%)	996 (3.7%)	1.02 (0.4–2.8)	1.05 (0.39–2.9)
Perinatal death	7 (7%)	394 (1.5%)	4.7 (2.2–10.3)	**4.3 (1.9–9.9)**
Perinatal death, excluding congenital malformation	7 (7%)	307 (1.2%)	6.1 (2.8–13.3)	**5.5 (2.4–12.8)**

All outcomes adjusted for age and body mass index. Additional adjustments: * adjusted for parity, smoking status and country of birth; † adjusted for pre-eclampsia, smoking status and country of birth; ‡ adjusted for parity and pre-eclampsia; § adjusted for parity; ¶ adjusted for smoking status and country of birth; ** adjusted for gestation. †† Reported for vaginal delivery only. ◆

3 Association between maternal body mass index and pregnancy outcomes for 107 women with type 1 diabetes

	Women with type 1 diabetes	Odds ratio (95% CI)	
		Crude odds ratio	Adjusted odds ratio
Body mass index as continuous variable (per 1 kg/m^2 difference in body mass index)			
Large for gestational age baby	47 (44%)	1.06 (0.98–1.14)	1.08 (0.98–1.18)*
Small for gestational age baby	7 (8%)	1.07 (0.93–1.24)	1.06 (0.91–1.22)
Induction of labour	51 (48%)	0.98 (0.91–1.06)	0.99 (0.91–1.07)†
Caesarean delivery	66 (62%)	1.03 (0.95–1.12)	1.03 (0.94–1.12)†
Pre-term birth	42 (39%)	0.98 (0.91–1.06)	0.99 (0.90–1.09)‡
Hypertensive complications††	7 (7%)	1.08 (0.93–1.25)	1.07 (0.93–1.24)
Hypoglycaemia	41 (38%)	1.03 (0.95–1.11)	1.03 (0.92–1.14)§
Jaundice	40 (37%)	1.01 (0.94–1.10)	0.99 (0.88–1.10)§
Shoulder dystocia‡‡	7 (17%)	1.07 (0.92–1.24)	1.10 (0.93–1.29)¶
Congenital malformation	4 (4%)	1.22 (1.01–1.48)	**1.51 (1.03–2.23)****
Perinatal death	7 (7%)	0.77 (0.61–0.98)	0.91 (0.70–1.17)*
Body mass index as categorical variable			
Large for gestational age baby ($n = 47$)			
Normal weight (< 25.0 kg/m^2)	13 (28%)	1.00	1.00
Overweight (25.0–29.9 kg/m^2)	18 (38%)	1.5 (0.6–3.6)	2.7 (0.77–9.2)
Obese (≥ 30.0 kg/m^2)	16 (34%)	2.2 (0.8–5.9)	**3.7 (1.02–13.2)**

All variables adjusted for age. Additional adjustments: * adjusted for mean HbA_{1c} level; † adjusted for parity and smoking status; ‡ adjusted for mean HbA_{1c} level and pre-eclampsia; § adjusted for third trimester HbA_{1c} level; ¶ adjusted for gestation; ** adjusted for first trimester HbA_{1c} level. †† Pre-eclampsia and gestational hypertension. ‡‡ Reported for vaginal delivery only. ◆

Subgroup analysis for women with type 1 diabetes

The mean HbA_{1c} level of women with type 1 diabetes during pregnancy was 53 mmol/mol (SD, 13). The median levels were 61 mmol/mol during the first, 52 mmol/mol during the second, and 51 mmol/mol during the third trimester. Nephropathy was documented in 14 women (15%) and retinopathy in 19 (20%), but microvascular complications were not associated with adverse outcomes. When analysed as a continuous variable, increased BMI was associated with increased odds of congenital malformations after adjustment for age and first trimester HbA_{1c} levels (aOR [for kg/m^2 difference in BMI], 1.5; 95% CI, 1.03–2.2). It was not associated with an increased likelihood of the primary outcomes, LGA and SGA babies, nor with increased odds for the secondary outcomes. When BMI was analysed as a categorical variable, however, obese women with type 1 diabetes were more likely to give birth to LGA babies than normal weight women, after adjustment for age and first trimester HbA_{1c} levels (aOR, 3.7; 95% CI, 1.02–13.2) (Box 3).

A one percentage point increase in mean HbA_{1c} level during pregnancy was associated with increased odds of pre-term birth (aOR, 1.9; 95% CI, 1.1–3.0) and perinatal death (aOR, 5.1; 95% CI, 1.5–17.5), but not with other adverse outcomes. Women with a mean HbA_{1c} level of 64 mmol/mol or more were less likely to give birth to LGA babies than those with levels below 53 mmol/mol (aOR, 0.20; 95% CI, 0.05–0.80) (Box 4). Pre-eclampsia and nephropathy were not associated with a change in the odds for LGA births (data not shown). Each one percentage point increase in first trimester HbA_{1c} level was associated with an increasing likelihood of pre-term birth (aOR, 2.5; 95% CI, 1.4–4.3) and perinatal death (aOR, 4.5; 95% CI, 1.1–18.4) and a reduced likelihood of an LGA baby (aOR, 0.62; 95% CI, 0.40–0.97) (Box 4). Second and third trimester HbA_{1c} levels were not correlated with adverse outcomes (data not shown).

Discussion

We compared pregnancy outcomes for women with type 1 diabetes with those for women without diabetes in a large study in a quaternary public health care setting. Mean BMI was greater and the mean duration of gestation shorter for women with type 1 diabetes than for women without diabetes; the likelihood of IOL was three times, of caesarean delivery five times, and of pre-term birth seven times that for women without diabetes. The odds of babies of women with type 1 diabetes being admitted to an NICU were three times those of neonates with mothers without diabetes; the odds of their being LGA and having hypoglycaemia, jaundice, respiratory distress, shoulder dystocia or perinatal death were also increased. In women with type 1 diabetes, obesity was associated with an increased likelihood of macrosomia and congenital malformations in their babies. Higher HbA_{1c} levels were associated with an increasing likelihood of pre-term birth and perinatal death, and reduced odds of an LGA birth.

Obstetric decisions about the mode of birth are largely driven by hospital protocol. We observed high rates of IOL and caesarean deliveries among women with type 1 diabetes, comparable with those reported in the United Kingdom[14] and New Zealand,[15] but higher than those in Nordic countries,[10,12] where the reported mean BMI of women was lower. The difference in the proportions of pre-term births to women with and without type 1 diabetes (39% *v* 8%) was greater than reported in a recent systematic review (25% *v* 6%).[6] While similar rates were reported in Denmark (41.7% *v* 6%),[5] a much lower rate among women with type 1 diabetes was reported in Sweden (21% *v* 5%).[12] Further, women in our study who gave birth before term were more likely to require a caesarean delivery. These differences may reflect the higher risk status of our cohort, given its higher proportion of overweight women, as the hospital protocol recommends earlier delivery for women at risk of adverse outcomes.

Neonatal outcomes were less than optimal for babies of women with type 1 diabetes. We found the likelihood of an LGA baby was eight times that for women without diabetes, and that it was independent of obesity, confirming the findings of an earlier study.[12] Excess gestational weight gain[16] and dyslipidaemia[17] were associated with increased odds of giving birth to an LGA child, and this requires further study. Increased rates of hypoglycaemia, jaundice, respiratory distress and shoulder dystocia have similarly been associated with LGA births to mothers with type 1 diabetes.[18] The odds of babies of women with type 1 diabetes being admitted to an NICU were three times those of other neonates; this compares favourably with the greater than 5-fold likelihood of admission reported by other Australian investigators,[8] and may be related to our policy of routine special care nursery observation of such babies. LGA births and related adverse outcomes remain

4 Association between maternal HbA_{1c} levels across gestation and pregnancy outcomes for 107 women with type 1 diabetes

	Women with type 1 diabetes	Odds ratio (95% CI)	
		Crude odds ratio	Adjusted odds ratio
HbA_{1c} level as continuous variable			
Large for gestational age baby	47 (44%)	0.75 (0.51–1.1)	0.74 (0.48–1.1)
Small for gestational age baby	7 (8%)	0.99 (0.47–2.1)	1.1 (0.49–2.5)
Induction of labour	51 (48%)	0.93 (0.65–1.3)	0.93 (0.61–1.4)*
Caesarean delivery	66 (62%)	0.97 (0.67–1.4)	1.1 (0.76–1.7)†
Pre-term birth	42 (39%)	2.0 (1.3–3.2)	**1.9 (1.1–3.0)†**
Hypertensive complications§	7 (7%)	0.70 (0.28–1.7)	0.72 (0.27–1.9)
Hypoglycaemia	41 (38%)	0.94 (0.65–1.4)	0.93 (0.63–1.4)
Jaundice	40 (37%)	1.06 (0.74–1.5)	0.69 (0.41–1.2)‡
Shoulder dystocia¶	7 (17%)	1.01 (0.54–1.9)	1.5 (0.52–4.1)‡
Congenital malformation	4 (4%)	1.3 (0.64–2.7)	2.0 (0.60–6.8)‡
Perinatal death	7 (7%)	3.8 (1.4–10.3)	**5.1 (1.5–17.5)**
First trimester HbA_{1c} level as continuous variable (per one percentage point difference in HbA_{1c} level)			
Large for gestational age baby	47 (44%)	0.61 (0.41–0.93)	**0.62 (0.40–0.97)**
Pre-term birth	42 (39%)	2.3 (1.4–3.8)	**2.5 (1.4–4.3)**
Perinatal death	7 (7%)	2.5 (1.2–5.1)	**4.5 (1.1–18.4)**
HbA_{1c} level as categorical variable			
Large for gestational age baby ($n = 47$)			
< 53 mmol/L	23 (52%)	1	1
53–63 mmol/L	18 (41%)	1.3 (0.51–3.1)	1.05 (0.41–2.7)
≥ 64 mmol/L	2 (7%)	0.20 (0.05–0.76)	**0.20 (0.05–0.80)**

All variables adjusted for age and body mass index. Additional adjustments: * adjusted for smoking status; † adjusted for parity; ‡ adjusted for gestation. § Pre-eclampsia and gestational hypertension. ¶ Reported for vaginal delivery only. ◆

problems despite the modern management of pregnant women with type 1 diabetes, highlighting the importance of active monitoring.

The harmful effects of obesity in the general obstetric population are recognised. Scandinavian research identified that type 1 diabetes and obesity are synergistic risk factors for maternal and neonatal complications, with diabetes the stronger risk factor.[11] The study found increased rates of congenital malformation in obese women with type 1 diabetes, but the authors did not examine glycaemic control.[11] We found that maternal obesity in women with type 1 diabetes, after adjustment for glycaemic control, was associated with a nearly 4-fold likelihood of LGA births; further, each 1 kg/m^2 increase in BMI was associated with a 50% increase in the likelihood of congenital malformations after adjustment for age and first trimester HbA_{1c} levels. Optimal reproductive health therefore requires strategies for assisting women with type 1 diabetes to avoid excess weight prior to conception.

Type 1 diabetes is associated with an increased risk of congenital malformations and perinatal death, which may result from poor glycaemic control during conception and the first trimester of pregnancy.[6,9] A systematic review reported a 2-fold risk of congenital malformations and an approximately 4-fold risk of perinatal death in women with type 1 diabetes compared with women without diabetes.[6] We similarly found that the odds of perinatal death for babies of women with type 1 diabetes were four times those of other neonates, but there were no differences in the rates of congenital malformations. The women in our study had reasonable glycaemic control, and elevated HbA_{1c} levels during the entire pregnancy and during the first trimester were associated with an increased incidence of perinatal death, but HbA_{1c} levels were not predictive of congenital malformations after 20 weeks' gestation. Comparisons with existing literature are difficult because of the differing periods during which congenital malformations were monitored.

The association between glycaemic control and other neonatal morbidity is less evident. A retrospective study of women with pre-existing diabetes found no association between first trimester HbA_{1c} levels and adverse maternal or fetal outcomes.[7] More recently, a prospective trial of women with type 1 diabetes in the UK found that HbA_{1c} levels of 42–46 mmol/mol at 26 weeks' gestation were associated with LGA births, and HbA_{1c} levels of 48–52 mmol/mol were associated with preterm birth, pre-eclampsia and a need for neonatal glucose infusion.[19] In our cohort, there was a continuous relationship between glycaemic control throughout gestation and during the first trimester with rates of preterm birth and perinatal death, underscoring the importance of optimal pre-conception and early antenatal glycaemic control.

Higher first trimester HbA_{1c} levels were also associated with a reduced likelihood of an LGA birth. This is possibly related to closer monitoring of and earlier intervention in women with poor glycaemic control. Third trimester HbA_{1c} levels were not linked with neonatal hypoglycaemia, jaundice or respiratory distress in our diabetes group. It is notable that another study found no relationship between HbA_{1c} levels during pregnancy and neonatal hypoglycaemia or macrosomia, although maternal glucose levels during labour were negatively correlated with those of the neonate.[20] We recommend intensified management in order to optimise maternal HbA_{1c} levels, but acknowledge the limitations of this approach during pregnancy.[1] Glucose level variability may be more informative when making decisions, especially later in gestation, and this question should be investigated further.

Limitations to our study include the absence of data on preconception glycaemic control, diabetes duration, and gestational weight gain. As we only analysed births from 20 weeks' gestation, we may have under-represented the proportion of pregnancies with congenital malformations that did not continue beyond 20 weeks. Odds estimates are less precise for some of the rarer outcomes, and we cannot exclude an unrecognised type 2 error. The non-matched study design may have reduced the efficiency of the study and our ability to control for known confounders. Further, the large number of women in the non-diabetes group may have led to deflation of *P* values; that is, the statistical significance of between-group differences may have been exaggerated by the disparate sizes of the two groups. Strengths of our study include the fact that the large number of participants enabled us to address key gaps in our knowledge, with a broad range of standardised outcomes. Attention to confounders such as obesity and glycaemic control, unlike many previous investigations, improves the generalisability of our results.

Conclusion

We have addressed gaps in the literature by investigating a contemporary cohort of women with type 1 diabetes receiving multidisciplinary care, taking both BMI and glycaemic control into consideration. We found that type 1 diabetes in pregnant women, including those with reasonable glycaemic control, was associated with an increased likelihood of adverse obstetric and neonatal outcomes even when optimally managed in a quaternary setting. Increased HbA_{1c} levels, even after correcting for maternal BMI, do not fully account for the increased frequency of adverse outcomes for women with type 1 diabetes. The higher BMI of pregnant women with type 1 diabetes was associated with a higher incidence of LGA births, independent of glycaemic control, highlighting the importance of controlling both weight and hyperglycaemia in these women. Further research could provide insights into how best to optimise pre-conception and antenatal care for women with type 1 diabetes in order to minimise the associated risks.

Acknowledgements: Helena Teede, Jacqueline Boyle and Barbora de Courten are National Health and Medical Research Council (NHMRC) postdoctoral fellows; Sophia Zoungas is a National Heart Foundation postdoctoral fellow. Sally Abell holds an NHMRC postgraduate scholarship.

Competing interests: No relevant disclosures.

Received 15 Apr 2016, accepted 9 June 2016. ■

1 American Diabetes Association. Standards of medical care in diabetes — 2015. *Diabetes Care* 2015; 38 Suppl 1.

2 Australian Institute of Health and Welfare. Diabetes in pregnancy: its impact on Australian women and their babies (AIHW Cat. No. CVD 52; Diabetes Series No. 14). Canberra: AIHW, 2010. http://www.aihw.gov.au/publication-detail/?id=6442472448 (accessed Oct 2015).

3 Diabetes care and research in Europe: the Saint Vincent declaration 1989. *Diabet Med* 1990; 7: 360.

4 The Diabetes Control and Complications Trial Research Group. Pregnancy outcomes in the Diabetes Control and Complications Trial. *Am J Obstet Gynecol* 1996; 174: 1343-1353.

5 Jensen DM, Damm P, Moelsted-Pedersen L, et al. Outcomes in type 1 diabetic pregnancies: a nationwide, population-based study. *Diabetes Care*. 2004; 27: 2819-2823.

6 Colstrup M, Mathiesen ER, Damm P, et al. Pregnancy in women with type 1 diabetes: have the goals of St. Vincent declaration been met concerning foetal and neonatal complications? *J Maternal Fetal Neonatal Med* 2013; 26: 1682-1686.

7 Starikov RS, Inman K, Chien EK, et al. Can hemoglobin A_{1c} in early pregnancy predict adverse pregnancy outcomes in diabetic patients? *J Diabetes Complications* 2014; 28: 203-207.

8 Shand AW, Bell JC, McElduff A, et al. Outcomes of pregnancies in women with pre-gestational diabetes mellitus and gestational diabetes mellitus; a population-based study in New South Wales, Australia, 1998—2002. *Diabet Med* 2008; 25: 708-715.

9 Nielsen GL, Møller M, Sørensen HT. HbA_{1c} in early diabetic pregnancy and pregnancy outcomes: a Danish population-based cohort study of 573 pregnancies in women with type 1 diabetes. *Diabetes Care* 2006; 29: 2612-2616.

10 Evers IM, de Valk HW, Visser GH. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. *BMJ* 2004; 328: 915.

11 Persson M, Pasupathy D, Hanson U, et al. Pre-pregnancy body mass index and the risk of adverse outcome in type 1 diabetic pregnancies: a population-based cohort study. *BMJ Open* 2012; 2: e000601.

12 Persson M, Norman M, Hanson U. Obstetric and perinatal outcomes in type 1 diabetic pregnancies: a large, population-based study. *Diabetes Care* 2009; 32: 2005-2009.

13 Dobbins TA, Sullivan EA, Roberts CL, Simpson JM. Australian national birthweight percentiles by sex and gestational age, 1998—2007. *Med J Aust* 2012; 197: 291-294. https://www.mja.com.au/journal/2012/197/5/australian-national-birthweight-percentiles-sex-and-gestational-age-1998-2007

14 Murphy HR, Steel SA, Roland JM, et al. Obstetric and perinatal outcomes in pregnancies complicated by type 1 and type 2 diabetes: influences of glycaemic control, obesity and social disadvantage. *Diabet Med* 2011; 28: 1060-1067.

15 Cundy T, Morgan J, O'Beirne C, et al. Obstetric interventions for women with type 1 or type 2 diabetes. *Int J Gynaecol Obstet* 2013; 123: 50-53.

16 Scifres CM, Feghali MN, Althouse AD, et al. Effect of excess gestational weight gain on pregnancy outcomes in women with type 1 diabetes. *Obstet Gynecol* 2014; 123: 1295-1302.

17 Barrett HL, Dekker Nitert M, McIntyre HD, Callaway LK. Normalizing metabolism in diabetic pregnancy: is it time to target lipids? *Diabetes Care* 2014; 37: 1484-1493.

18 Gizzo S, Patrelli TS, Rossanese M, et al. An update on diabetic women obstetrical outcomes linked to preconception and pregnancy glycemic profile: a systematic literature review. *ScientificWorldJournal* 2013; 2013: 254901.

19 Maresh MJ, Holmes VA, Patterson CC, et al. Glycemic targets in the second and third trimester of pregnancy for women with type 1 diabetes. *Diabetes Care* 2015; 38: 34-42.

20 Taylor R, Lee C, Kyne-Grzebalski D, et al. Clinical outcomes of pregnancy in women with type 1 diabetes. *Obstet Gynecol* 2002; 99: 537-541. ■