Glycemic Targets in the Second and Third Trimester of Pregnancy for Women With Type 1 Diabetes

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OBJECTIVE

To assess the relationship between second and third trimester glycemic control and adverse outcomes in pregnant women with type 1 diabetes, as uncertainty exists about optimum glycemic targets.

RESEARCH DESIGN AND METHODS

Pregnancy outcomes were assessed prospectively in 725 women with type 1 diabetes from the Diabetes and Pre-eclampsia Intervention Trial. HbA_{1c} (A1C) values at 26 and 34 weeks' gestation were categorized into five groups, the lowest, <6.0% (42 mmol/mol), being the reference. Average pre- and postprandial results from an eight-point capillary glucose profile the previous day were categorized into five groups, the lowest (preprandial <5.0 mmol/L and postprandial <6.0 mmol/L) being the reference.

RESULTS

An A1C of 6.0–6.4% (42–47 mmol/mol) at 26 weeks' gestation was associated with a significantly increased risk of large for gestational age (LGA) (odds ratio 1.7 [95% CI 1.0–3.0]) and an A1C of 6.5–6.9% (48–52 mmol/mol) with a significantly increased risk of preterm delivery (odds ratio 2.5 [95% CI 1.3–4.8]), pre-eclampsia (4.3 [1.7–10.8]), need for a neonatal glucose infusion (2.9 [1.5–5.6]), and a composite adverse outcome (3.2 [1.3–8.0]). These risks increased progressively with increasing A1C. Results were similar at 34 weeks' gestation. Glucose data showed less consistent trends, although the risk of a composite adverse outcome increased with preprandial glucose levels between 6.0 and 6.9 mmol/L at 34 weeks (3.3 [1.3–8.0]).

CONCLUSIONS

LGA increased significantly with an A1C ≥6.0 (42 mmol/mol) at 26 and 34 weeks' gestation and with other adverse outcomes with an A1C ≥6.5% (48 mmol/mol). The data suggest that there is clinical utility in regular measurement of A1C during pregnancy.

It is now well established that optimizing glycemic control in pregnant women with type 1 diabetes is associated with improved outcomes (1). However, achieving normoglycemia is not without risks, particularly those associated with maternal hypoglycemia (2).

While there is agreement that poor periconceptual glycemic control increases the risk of congenital malformations (2), much less consensus exists as to the relation of glycemic control later in pregnancy to specific adverse maternal and neonatal

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outcomes. Possible explanations for this lack of consensus include: the small number of randomized controlled or prospective observational cohort trials; the retrospective design of most studies, comparison of women with good and poor outcomes; minimal standardization of maternal and neonatal outcome indicators, including composite outcomes; and comparison of glycemic control in different trimesters of pregnancy using different measures of glycemia such as HbA_{1c} (A1C) and meal-related (pre-, post-, average) measures of glycemic control. In addition, these latter glycemic measures are usually expressed as arbitrary thresholds such as a dichotomy of good or poor control, tertiles of glycemia, or other groupings.

A1C is generally favored as an estimate of glycemic control as it requires one nonfasting blood sample and represents an objective measurement of glycemic control over the preceding 6–8 weeks. However, the literature would suggest that there is a physiological fall in A1C during pregnancy and that A1C is lower in pregnancy than outside of pregnancy. Possible explanations for this include an increasing erythrocyte production rate, reduced glucose affinity, and a shortened erythrocyte life span. This fall requires care with interpretation of results. A systematic review of the relationship between A1C and adverse outcomes (1) reported that an elevated A1C toward the end of the first trimester usually reflects suboptimal control around the time of conception and in the first trimester and has been associated with an increased incidence of congenital malformations and miscarriage (3,4). Some studies in type 1 diabetes reporting A1C values in the second or third trimesters have demonstrated an association between poor control and an increased risk of stillbirth (4,5), fetal macrosomia, or large for gestational age (LGA) (6–10), neonatal intensive care (11), and other adverse outcomes such as preterm delivery (12), pre-eclampsia (13), and composite indicators of adverse outcome (14). Several studies in which women were randomized to either strict or less strict glycemic control were unable to demonstrate an improvement in A1C in the more strictly controlled group (15); however, these studies were small, and, as a consequence, no definite conclusions on the degree of glycemic control necessary to impact on outcomes were reached (16). One nonrandomized study suggested that very tight control was not necessarily required to obtain satisfactory outcomes and was associated with more maternal hypoglycemia (17).

Reports that have used self-monitored capillary blood glucose as a measure of glycemic control have tended to compare women with and without adverse outcomes in relation to mean glucose values: either preprandial, postprandial, or combined. Karlsson and Kjellmer (18) reported that increased rates of poor pregnancy outcomes were associated with increasing third trimester mean glucose values. Damm et al. (14) demonstrated that more women had poor outcomes when capillary glucose values were outside the normal range. The Diabetes in Early Pregnancy Study (6) showed an association between increasing birth weight and increasing mean postprandial, but not preprandial, glycemia, a finding reported elsewhere (19), while other studies suggested a relationship with preprandial (20) or mean levels (21). Another approach has been to create arbitrary glycemic thresholds such as good or poor control, and some studies have demonstrated higher neonatal morbidity in the poor glycemic control group (22,23). Furthermore, Mello et al. (24) showed that the risk of LGA was increased with poor glycemic control in the second trimester even if glycemic control was good in the third. Due to the limitations of self-monitoring of glycemic control, Kerssen et al. (25) used continuous glucose monitoring and in a small study showed a relationship between the median 24-h glucose level and LGA. Finally, in a randomized controlled trial, Manderson et al. (26) highlighted the relevance of postprandial glycemia to both maternal and fetal outcomes.

Although these studies have generally demonstrated an association between suboptimal glycemic control and an increased risk of poor pregnancy outcome, they are of limited value in informing clinicians about the optimal glycemic targets required to minimize these risks. In addition, while it is usually possible with treatment to achieve normoglycemia in gestational diabetes and often in type 2 diabetes, this is much more challenging in the pregnant woman with type 1 diabetes and must be constantly balanced against the risks of hypoglycemia. Various guidelines for glycemic control in pregnancy have been proposed. The American Diabetes Association (27) recommends a target A1C $<7\%$ (53 mmol/mol) prior to conception, similar to that recommended in Scotland (28). In the rest of the U.K., the National Institute for Health and Care Excellence (NICE) guidelines (29) recommend a target A1C of $\leq 6.1\%$ (43 mmol/mol) prior to conception, if this can be achieved safely. During pregnancy, the A1C target in the U.S. is 6.0% (307) with monitoring every 1–3 months. In contrast, U.K. NICE guidelines advise against routine measurement of A1C in the second and third trimester (29), apparently because of lack of evidence and physiological changes in pregnancy. With regard to glycemic targets, there is fairly close agreement in the U.S. and U.K. guidelines, with the U.S. advising preprandial values 3.3–5.4 mmol/L (60–99 mg/dL) and peak postprandial values between 5.4 and 7.1 mmol/L (100–129 mg/dL) (30), while the U.K. NICE guidelines recommend preprandial capillary glucose target values between 3.5 and 5.9 mmol/L and 1-h postprandial values <7.8 mmol/L (29). While there is good evidence to support the statement that poor pregnancy outcomes are more likely to be associated with suboptimal glycemic control during pregnancy, there is actually minimal data to inform clinical targets for either A1C or glucose, and so to date, guidelines have been based mainly on expert opinion.

Given this background, the aim of this study was to assess the relationship between glycemic control, as assessed by both A1C and capillary blood glucose profiles in the second and third trimesters of pregnancy, and maternal and neonatal outcomes in a large prospective cohort of women with type 1 diabetes.

RESEARCH DESIGN AND METHODS

The study population comprised 762 women with type 1 diabetes recruited from 25 joint antenatal-metabolic clinics across northern Ireland, northwest England, and Scotland between April 2003 and June 2008 into the Diabetes and Preeclampsia Intervention Trial (DAPIT). DAPIT was a multicenter, randomized, placebo-controlled trial of vitamin C and E

supplementation to prevent pre-eclampsia in pregnant women with type 1 diabetes. As no effect of antioxidant vitamins on the development of pre-eclampsia was demonstrated, the active treatment and placebo groups were combined for analysis (31).

Details of the methodology have been described previously (13,31). In brief, women with type 1 diabetes were recruited between 8 and 22 weeks' gestation and randomized to vitamin C and E supplementation or matched placebo. A total of 762 women were recruited, with 749 women progressing to at least 20 weeks' gestational age. The 725 women who subsequently delivered an infant without a major malformation were included in this analysis. At the first antenatal-metabolic clinic visit, details including ethnicity, parity, years of education, social class, and smoking habits were recorded and BMI and A1C measured. Subsequently, women were reviewed at 26 (± 2) weeks' gestation and at 34 (± 2) weeks' gestation when venous blood samples were obtained for measurement of A1C. The samples were stored at −70°C for transportation to the Nutrition and Metabolism Laboratories, Queen's University Belfast, and batch assayed at the end of the study. A1C (Diazyme Laboratories, Poway, CA) was measured by spectrophotometry using an automated ILab 600 biochemical analyzer. As a National Glycohemoglobin Standardization Program and International Federation for Clinical Chemistry and Laboratory Medicine–certified method, the values reported were aligned with the Diabetes Control and Complications Trial system, with intra- and interassay coefficients of variation <2%. A1C results were arbitrarily grouped by 0.5% intervals from <6.0 (42 mmol/mol) to ≥7.5% (59 mmol/mol), with <6.0% (42 mmol/mol) taken as the reference group. All women were requested to measure their capillary blood glucose on a standardized meter eight times a day (pre- and 1 h postmeals and at bedtime) and to record the values on the day prior to the 26- and 34-week study visit. The mean of the fasting/preprandial values and the mean of the postprandial values were analyzed in relation to 1-mmol/L increments; for preprandial, the range was from <5.0 to ≥8.0 mmol/L and for postprandial, <6.0 to ≥9.0 mmol/L. The lowest group in both cases was taken as the reference.

Maternal and neonatal outcomes were as previously specified (31), but only a selection has been analyzed in this study. Pre-eclampsia was defined as gestational hypertension and proteinuria in accordance with the International Society for the Study of Hypertension in Pregnancy (32). Birth weight centiles were calculated using customized birth weight charts (33) and those >90th centile classified as LGA. Admission to a neonatal unit was defined as either high dependency or intensive care (levels 2 and 3), with these levels of care being rigorously defined. Neonatal hypoglycemia was defined by the need for an intravenous glucose infusion and neonatal hyperbilirubinemia by the need for phototherapy. In addition, cesarean delivery and gestation at delivery were also considered. As serious adverse outcomes are rare, a composite outcome variable composed of several individual adverse end points was also included. Unfortunately, no such standardized outcome exists in the literature and neither was one specified in the DAPIT study. The composite outcome used in this study was adapted from that used in the Australian Carbohydrate Intolerance Study in Pregnant Women (34) (namely perinatal death, shoulder dystocia, fractures, or nerve palsy), with the addition of admission to the neonatal intensive care unit for level 2 or 3 care.

The West Midlands Multicentre Research Ethics Committee provided ethical approval (MREC 02/7/016). The DAPIT study was registered as an International Standard Randomized Controlled Trial, ISRCTN27214045.

Statistical Analysis

Comparisons of outcomes in groups defined by A1C levels or by averaged capillary blood glucose levels at 26 or 34 weeks were performed using the χ^2 test for trend in contingency tables. Logistic regression was used to estimate the odds of outcomes in each group relative to the group with lowest A1C or averaged glucose values, with results expressed as odds ratios (ORs) with 95% CIs. This was done both before and after adjustment for potentially confounding variables (age, BMI, ethnicity, diabetes duration, parity, current smoking, years of education, social class, plasma ascorbate, and serum α-tocopherol at randomization, microalbuminuria before pregnancy, vitamin treatment group, and center). All statistical analyses were performed using SPSS software, version 20 (IBM Corp., Armonk, NY).

RESULTS

Maternal characteristics and glycemic control are shown in Table 1. Further characteristics have previously been described in detail (31).

A1C results were available for 576 (79%) and 505 (70%) participants at 26 and 34 weeks' gestation, respectively. Maternal and neonatal outcomes by A1C groups are described in Tables 2 and 3, showing both the unadjusted and adjusted rates allowing for specific confounders. With higher values of A1C, there were increasing risks of pre-eclampsia, preterm delivery, LGA, neonatal hypoglycemia requiring a glucose infusion, hyperbilirubinemia requiring phototherapy, and a composite adverse outcome. The less common outcomes of birth weight <10th centile (rate 3%) and Apgar score at 5 min <7 (rate 2%) were also investigated and no significant relationship found. Ethnicity had no effects on outcomes. Allowing for A1C values in the first or early second trimester of pregnancy had a slight modifying effect on the degree of significance of some of the outcomes, but the trends remained (Supplementary Tables 1 and 2).

The A1C measurements at 26 and 34 weeks were strongly correlated ($r = 0.8$), resulting in the associations between A1C at 34 weeks and adverse outcomes, adjusted for A1C at 26 weeks, being weakened and in many cases nonsignificant; a similar finding occurred with analysis of A1C at 26 weeks adjusting for A1C at 34 weeks (data not shown). However, the 41 women with A1C ≥6.5% (48 mmol/mol) in the second trimester, but <6.5% (48 mmol/mol) in the third, had significantly fewer LGA babies ($P = 0.033$), with a trend toward fewer adverse composite outcomes ($P = 0.065$) and cases of preterm delivery ($P = 0.064$) compared with those women whose A1C remained ≥6.5% (48 mmol/mol) in both trimesters ($n = 191$). However, the number of subjects was small, and the data need to be interpreted with caution.

Comparison of the women with and without A1C measurements at 26 and 34 weeks showed some differences

Table 1—Maternal characteristics and glycemic control in 725 participants

Age (years), mean (SD)	29.6 (5.6)
BMI (kg/m^2), mean (SD)*	27.4 (4.7)
Diabetes duration (years), mean (SD)	14.5 (8.2)
Primiparous, *n* (%)	361 (49.8)
Smoker, *n* (%)	139 (19.2)
Social class: head of household in professional or managerial/technical occupation, *n* (%)†	297 (46.0)
Nonwhite ethnicity, *n* (%)	26 (3.6)
Education (years), mean (SD)	14.0 (2.8)
A1C [% (mmol/mol)], mean (SD)‡	
First antenatal visit	7.8 (1.4)/62 (15)
26 weeks' gestation	6.7 (0.8)/50 (9)
34 weeks' gestation	6.6 (0.7)/48 (7)
Mean fasting/preprandial capillary glucose (mmol/L), mean (SD)§	
26 weeks' gestation	6.4 (1.8)
34 weeks' gestation	6.0 (1.7)
Mean 1-h postprandial capillary glucose (mmol/L), mean (SD)‖	
26 weeks' gestation	7.5 (2.4)
34 weeks' gestation	7.2 (2.3)

*Based on *n* = 708 results. †Based on *n* = 646 results. ‡Based on *n* = 698/576/505 results at first antenatal visit/26 weeks' gestation/34 weeks' gestation. §Based on *n* = 610/546 results at 26 weeks' gestation/34 weeks' gestation. ‖Based on *n* = 484/447 results at 26 weeks' gestation/34 weeks' gestation.

with regard to maternal age in that the women with missing data were ~1 year younger (although of similar BMI, diabetes duration, and total daily dose of insulin), and they were also recruited ~1 week later. In addition, at 34 weeks, there were significantly more nulliparous women with missing data, but there was no difference at 26 weeks.

Average pre- and postprandial capillary blood glucose results were available for 610 (84%)/484 (67%) and 546 (75%)/447 (62%) participants at 26 and 34 weeks, respectively. The maternal and neonatal outcomes according to capillary blood glucose categories are shown in Table 4 and Supplementary Tables 3–5. Significant linear trends were demonstrated for LGA with preprandial glycemia at both 26 ($P < 0.001$) and 34 ($P < 0.05$) weeks' gestation. For postprandial glycemia, significant trends for LGA were again demonstrated at 26 ($P < 0.03$) and 34 ($P < 0.02$) weeks' gestation. No other significant trends were demonstrated for postprandial glycemia (Supplementary Tables 4 and 5). However, increasing preprandial glycemia was also associated with significantly increasing rates of preterm delivery at both 26 weeks (OR 2.0 [95% CI 1.1–3.7] when glucose 7.0–7.9 mmol/L) and 34 weeks (OR 2.4 [95% CI 1.2–5.0] when glucose ≥8.0 mmol/L) (Table 4 and Supplementary Table 3). Other significant associations with preprandial glycemia at 34 weeks were also demonstrated (Table 4).

CONCLUSIONS

This large, prospective study of women with type 1 diabetes has demonstrated a relationship between increasing A1C categories during the second and third trimesters of pregnancy and a series of relevant, rigorously defined adverse maternal and neonatal outcomes including a composite neonatal outcome. Unlike previous data, this study gives a much clearer picture of the A1C and capillary glucose targets that should be aimed for to minimize the risk of adverse outcomes.

While a randomized controlled trial is a gold standard for looking at the association between varying degrees of glycemic control and adverse pregnancy outcomes, such a design is impractical and most likely unethical. Previous studies have been too small (16,17) to examine the main outcomes included in the current study, and thus, only a large prospective observational study would appear feasible. Although the primary outcome of the DAPIT trial was preeclampsia, prospective documentation of other prespecified outcomes, together with A1C measurements in each trimester, permitted utilization of this valuable cohort of subjects with type 1 diabetes to examine the important question of the relationship between glycemic control in later pregnancy and maternal and neonatal outcomes. However, given the rarity of outcomes such as perinatal death and birth trauma, prior to data analysis, we considered it necessary to derive a composite adverse neonatal outcome that we defined as that used in the Australian Carbohydrate Intolerance Study in Pregnant Women (34), combined with need for admission to level 2 or 3 neonatal intensive care as defined in the DAPIT trial. Prior to data analysis, A1C and blood glucose categories were also agreed.

The association of increasing A1C in early pregnancy and the risk of miscarriage and congenital anomalies is well established (35). However, while a number of studies have shown an association between deteriorating glycemic control and an increased risk of adverse outcomes, few have data relating specific A1C target values later in pregnancy with adverse outcomes, and some national guidelines question the clinical utility of A1C measurements outside the first trimester. Indeed, in the U.K., the current NICE guidelines suggest that A1C should not be measured in the second and third trimester (29), presumably on the basis of lack of evidence to support its measurement and concern regarding interpretation of the result given the physiological fall in A1C during pregnancy. The current study has clearly demonstrated an increased risk of adverse outcomes in later pregnancy with increasing A1C values. Tennant et al. (5) showed an increasing rate of stillbirths and neonatal deaths with increasing maternal A1C. However, our data have the advantage of being collected prospectively and include the examination of a wide range of maternal and neonatal outcomes by specific target ranges of A1C and pre- and postprandial capillary blood glucose measurements. In addition, unlike most previous studies, pregnancies complicated by a major congenital anomaly were excluded to focus on adverse outcomes associated with glycemic control in the second and third trimester. Data were available for 79% of the women at 26 weeks and 70% at 34 weeks, the latter reduction being partly due to preterm delivery. However, while there

Table 2—Adverse pregnancy outcomes by A1C category at 26 weeks' gestation

	A1C at 26 weeks					
	<6.0% (<42 mmol/mol) (*n* = 101)	6.0–6.4% (42–47 mmol/mol) (*n* = 176)	6.5–6.9% (48–52 mmol/mol) (*n* = 128)	7.0–7.4% (53–58 mmol/mol) (*n* = 98)	7.5+% (59+ mmol/mol) (*n* = 73)	*P* value for trend
Pre-eclampsia						
No. (%)	8/101 (8)	23/176 (13)	29/128 (23)	24/98 (24)	17/73 (23)	
OR (95% CI)	1.0 (Reference)	1.7 (0.8–4.1)	3.4‡ (1.5–7.8)	3.8‡ (1.6–8.9)	3.5‡ (1.4–8.7)	<0.001
OR (95% CI)*	1.0 (Reference)	2.0 (0.8–4.9)	4.3‡ (1.7–10.8)	4.6‡ (1.8–12.0)	5.1‡ (1.9–14.1)	<0.001
LGA (>90th centile)						
No. (%)	36/99 (36)	88/175 (50)	73/128 (57)	60/98 (61)	46/73 (63)	
OR (95% CI)	1.0 (Reference)	1.8† (1.1–2.9)	2.3‡ (1.4–4.0)	2.8§ (1.6–4.9)	3.0§ (1.6–5.6)	<0.001
OR (95% CI)*	1.0 (Reference)	1.7† (1.0–3.0)	2.5‡ (1.4–4.5)	3.2§ (1.7–6.1)	3.7§ (1.8–7.5)	<0.001
Cesarean section delivery						
No. (%)	67/101 (66)	125/176 (71)	85/128 (66)	76/98 (78)	46/73 (63)	
OR (95% CI)	1.0 (Reference)	1.2 (0.7–2.1)	1.0 (0.6–1.7)	1.8 (0.9–3.3)	0.9 (0.5–1.6)	0.90
OR (95% CI)*	1.0 (Reference)	1.1 (0.6–2.0)	1.1 (0.6–2.0)	2.0 (1.0–3.9)	1.0 (0.5–1.9)	0.48
Neonatal hypoglycemia requiring glucose infusion						
No. (%)	20/99 (20)	42/170 (25)	49/124 (40)	39/95 (41)	30/70 (43)	
OR (95% CI)	1.0 (Reference)	1.3 (0.7–2.4)	2.6‡ (1.4–4.7)	2.8‡ (1.5–5.2)	3.0‡ (1.5–5.9)	<0.001
OR (95% CI)*	1.0 (Reference)	1.5 (0.8–2.9)	2.9‡ (1.5–5.6)	3.5§ (1.7–7.2)	3.8§ (1.7–8.2)	<0.001
Hyperbilirubinemia requiring phototherapy						
No. (%)	13/99 (13)	25/173 (14)	26/127 (20)	28/96 (29)	20/71 (28)	
OR (95% CI)	1.0 (Reference)	1.1 (0.5–2.3)	1.7 (0.8–3.5)	2.7‡ (1.3–5.7)	2.6† (1.2–5.7)	<0.001
OR (95% CI)*	1.0 (Reference)	1.4 (0.6–2.9)	2.1 (0.9–4.5)	3.7‡ (1.7–8.3)	3.8‡ (1.6–8.9)	<0.001
Delivery before 37 weeks						
No. (%)	21/101 (21)	51/176 (29)	48/128 (38)	50/98 (51)	33/73 (45)	
OR (95% CI)	1.0 (Reference)	1.6 (0.9–2.8)	2.3‡ (1.3–4.2)	4.0§ (2.1–7.4)	3.1§ (1.6–6.1)	<0.001
OR (95% CI)*	1.0 (Reference)	1.6 (0.8–2.9)	2.5‡ (1.3–4.8)	5.1§ (2.6–10.2)	3.8§ (1.8–8.0)	<0.001
Composite adverse neonatal outcome						
No. (%)	8/101 (8)	21/176 (12)	25/128 (20)	27/98 (28)	16/73 (22)	
OR (95% CI)	1.0 (Reference)	1.6 (0.7–3.7)	2.8† (1.2–6.6)	4.4§ (1.9–10.3)	3.3† (1.3–8.1)	<0.001
OR (95% CI)*	1.0 (Reference)	1.6 (0.7–4.1)	3.2‡ (1.3–8.0)	6.7§ (2.6–17.0)	4.4‡ (1.6–12.3)	<0.001

*Adjusted for age, BMI, years of education, social class, ethnicity, parity, current smoking, duration of diabetes, microalbuminuria before pregnancy, vitamin treatment group, and center. †$P < 0.05$, ‡$P < 0.01$, §$P < 0.001$.

were some differences in the characteristics of the women with and without readings, it seems unlikely that these differences would have significant clinical implications.

We found a striking linear relationship between A1C categories and the composite adverse neonatal outcome, and even for A1C 6.5–6.9% (48–52 mmol/mol), the risk was significantly increased at 26 and 34 weeks' gestation. Macrosomia is a commonly reported outcome that has previously been associated with increasing A1C (6–10), and we have shown a clear association with the strict definition of birth weight >90th centile (LGA) using customized birth weight charts. There was a linear trend with increasing A1C and a significant increase in LGA even for the A1C category 6.0–6.4% (42–47 mmol/mol) both at 26 and 34 weeks' gestation. Neonatal hypoglycemia is an indicator of maternal antenatal glycemic control, but is difficult to standardize because of differing definitions and sampling times. Accordingly, we used a more robust measure, namely treatment with an intravenous glucose infusion, and found a linear increase in neonatal hypoglycemia with increasing A1C, a significant increase being present for A1C between 6.5 and 6.9% (48–52 mmol/mol). Similar relationships were demonstrated with preterm delivery. Hyperbilirubinemia, a recognized neonatal complication of the baby born to a mother with diabetes and not reported in other studies, also showed a linear trend with increasing maternal A1C, although significance was not apparent until A1C ≥7.0% (53 mmol/mol). A previous analysis of the DAPIT cohort showed an increasing risk of pre-eclampsia with increasing A1C (13), and further analysis in this study showed a significant increased risk with A1C ≥6.5% (48 mmol/mol) at 26 and 34 weeks' gestation. Furthermore, we found that the relationships between the adverse outcomes and A1C values in the second and third trimesters persisted even after controlling for A1C in the first or early second trimester. Increasing A1C values had no apparent impact on cesarean section rates, perhaps not surprising given the many factors that contribute to this outcome.

Our study indicates the clinical use of regular A1C measurements throughout pregnancy in predicting whether a

Table 3—Adverse pregnancy outcomes by A1C category at 34 weeks' gestation

	A1C at 34 weeks					
	<6.0% (<42 mmol/mol) (*n* = 98)	6.0–6.4% (42–47 mmol/mol) (*n* = 165)	6.5–6.9% (48–52 mmol/mol) (*n* = 136)	7.0–7.4% (53–58 mmol/mol) (*n* = 66)	7.5+ % (59+ mmol/mol) (*n* = 40)	*P* value for trend
Pre-eclampsia						
No. (%)	8/98 (8)	23/165 (14)	19/136 (14)	12/66 (18)	11/40 (28)	
OR (95% CI)	1.0 (Reference)	1.8 (0.8–4.3)	1.8 (0.8–4.4)	2.5 (1.0–6.5)	4.4‡ (1.6–11.6)	0.005
OR (95% CI)*	1.0 (Reference)	2.4 (0.9–6.3)	3.0† (1.1–7.9)	5.3‡ (1.7–16.9)	6.8‡ (2.1–22.8)	<0.001
LGA (>90th centile)						
No. (%)	33/98 (34)	77/165 (47)	91/136 (67)	44/65 (68)	21/40 (53)	
OR (95% CI)	1.0 (Reference)	1.7† (1.0–2.9)	4.0§ (2.3–6.9)	4.1§ (2.1–8.0)	2.2† (1.0–4.6)	<0.001
OR (95% CI)*	1.0 (Reference)	1.9† (1.1–3.3)	4.6§ (2.5–8.5)	5.6§ (2.6–12.0)	2.9† (1.3–6.7)	<0.001
Cesarean section delivery						
No. (%)	62/98 (63)	107/165 (65)	99/136 (73)	51/66 (77)	23/40 (58)	
OR (95% CI)	1.0 (Reference)	1.1 (0.6–1.8)	1.6 (0.9–2.7)	2.0 (1.0–4.0)	0.8 (0.4–1.8)	0.35
OR (95% CI)*	1.0 (Reference)	0.9 (0.5–1.7)	1.7 (0.9–3.2)	2.4† (1.1–5.4)	0.7 (0.3–1.7)	0.26
Neonatal hypoglycemia requiring glucose infusion						
No. (%)	18/97 (19)	39/158 (25)	45/133 (34)	25/64 (39)	17/38 (45)	
OR (95% CI)	1.0 (Reference)	1.4 (0.8–2.7)	2.2† (1.2–4.2)	2.8‡ (1.4–5.8)	3.6‡ (1.6–8.1)	<0.001
OR (95% CI)*	1.0 (Reference)	1.7 (0.9–3.5)	2.8‡ (1.4–5.8)	4.1‡ (1.8–9.8)	4.8‡ (1.9–12.4)	<0.001
Hyperbilirubinemia requiring phototherapy						
No. (%)	11/98 (11)	24/162 (15)	17/134 (13)	16/65 (25)	13/39 (33)	
OR (95% CI)	1.0 (Reference)	1.4 (0.6–2.9)	1.1 (0.5–2.6)	2.6† (1.1–6.0)	4.0‡ (1.6–9.9)	0.002
OR (95% CI)*	1.0 (Reference)	1.7 (0.7–3.9)	1.3 (0.5–3.3)	3.0† (1.1–7.9)	5.4‡ (1.9–15.5)	0.002
Delivery before 37 weeks						
No. (%)	17/98 (17)	38/165 (23)	48/136 (35)	27/66 (41)	16/40 (40)	
OR (95% CI)	1.0 (Reference)	1.4 (0.8–2.7)	2.6‡ (1.4–4.9)	3.3‡ (1.6–6.8)	3.2‡ (1.4–7.2)	<0.001
OR (95% CI)*	1.0 (Reference)	1.4 (0.7–2.9)	3.0‡ (1.5–6.1)	4.2§ (1.8–9.7)	4.0‡ (1.6–10.4)	<0.001
Composite adverse neonatal outcome						
No. (%)	7/98 (7)	14/165 (8)	20/136 (15)	13/66 (20)	12/40 (30)	
OR (95% CI)	1.0 (Reference)	1.2 (0.5–3.1)	2.2 (0.9–5.5)	3.2‡ (1.2–8.5)	5.6‡ (2.0–15.5)	<0.001
OR (95% CI)*	1.0 (Reference)	1.4 (0.5–4.0)	2.7 (1.0–7.5)	5.5‡ (1.7–17.6)	9.4§ (2.8–31.2)	<0.001

*Adjusted for age, BMI, years of education, social class, ethnicity, parity, current smoking, duration of diabetes, microalbuminuria before pregnancy, vitamin treatment group, and center. †$P < 0.05$, ‡$P < 0.01$, §$P < 0.001$.

woman is at an increased risk of an adverse outcome. While measurement of A1C does not necessarily motivate behavior change, our data do suggest that A1C values ≥6.5% (48 mmol/mol) identify women at increased risk of adverse outcomes. This was shown particularly at 26 weeks, but less so at 34 weeks. Clinically, these findings would support regular measurement of A1C every 1–3 months throughout pregnancy as advised in the U.S. (30). Our data show that for some outcomes such as LGA, the risk is already present when the A1C is ≥6.0% (42 mmol/mol), but such values may not be achievable in routine practice because of hypoglycemia, and targets must be realistic and individualized. However, the data indicate that those women with A1C values in the second trimester ≥6.5% (48 mmol/mol) need to be counseled about the increased risk of adverse outcomes. The risks of stillbirth are present throughout the third trimester (36), and if A1C is ≥6.5% (48 mmol/mol), such women require intensive supervision by experienced clinicians. This may include more frequent clinic visits and, in some women, even a short period of hospitalization. Careful evaluation for evidence of fetal overgrowth or growth restriction on routine monthly ultrasound scans is indicated in these women (37). In the U.S., more detailed fetal assessment including biophysical profile testing, cardiotocography, and Doppler umbilical artery velocimetry has been advised for most patients from ~32 weeks (38), although the benefits of such detailed assessments remain unclear.

However, it is pre- and postprandial monitoring, rather than monthly A1C results, that provide immediate feedback on glucose excursions and guide insulin adjustment. This study has allowed investigation of the effect of varying degrees of glycemia in the second and third trimester on specific maternal and neonatal outcomes. Self-reported measurements have limitations and in this study pertained to one particular day in the second and third trimester. Furthermore, data were not available for a significant number of women, with only 62% of women having postprandial results. While there were some differences in the characteristics of women with and without readings,

Table 4—Adverse pregnancy outcomes by average preprandial glucose category at 34 weeks' gestation

	Preprandial average glucose at 34 weeks					
	<5.0 mmol/L (*n* = 158)	5.0–5.9 mmol/L (*n* = 176)	6.0–6.9 mmol/L (*n* = 90)	7.0–7.9 mmol/L (*n* = 64)	8.0+ mmol/L (*n* = 58)	*P* value for trend
Pre-eclampsia						
No. (%)	20/158 (13)	25/176 (14)	15/90 (17)	11/64 (17)	9/58 (15.5)	
OR (95% CI)	1.0 (Reference)	1.1 (0.6–2.1)	1.4 (0.7–2.9)	1.4 (0.6–3.2)	1.3 (0.5–3.0)	0.37
OR (95% CI)*	1.0 (Reference)	1.0 (0.5–2.0)	1.2 (0.5–2.6)	1.3 (0.5–3.3)	1.3 (0.5–3.3)	0.44
LGA (>90th centile)						
No. (%)	74/158 (47)	96/175 (55)	49/90 (54)	33/64 (52)	37/58 (64)	
OR (95% CI)	1.0 (Reference)	1.4 (0.9–2.1)	1.4 (0.8–2.3)	1.2 (0.7–2.2)	2.0† (1.1–3.7)	0.07
OR (95% CI)*	1.0 (Reference)	1.4 (0.9–2.2)	1.4 (0.8–2.4)	1.1 (0.6–2.1)	2.5‡ (1.2–5.0)	0.05
Cesarean section delivery						
No. (%)	103/158 (65)	118/176 (67)	61/90 (68)	42/64 (66)	45/58 (78)	
OR (95% CI)	1.0 (Reference)	1.1 (0.7–1.7)	1.1 (0.6–1.9)	1.0 (0.6–1.9)	1.8 (0.9–3.7)	0.19
OR (95% CI)*	1.0 (Reference)	0.9 (0.6–1.5)	1.0 (0.6–1.9)	0.9 (0.5–1.8)	1.5 (0.7–3.1)	0.45
Neonatal hypoglycemia requiring glucose infusion						
No. (%)	33/155 (21)	47/173 (27)	26/86 (30)	22/63 (35)	20/55 (36)	
OR (95% CI)	1.0 (Reference)	1.4 (0.8–2.3)	1.6 (0.9–2.9)	2.0† (1.0–3.8)	2.1† (1.9–4.1)	0.009
OR (95% CI)*	1.0 (Reference)	1.4 (0.8–2.5)	1.7 (0.9–3.4)	1.9 (0.9–3.9)	1.9 (0.9–4.0)	0.04
Hyperbilirubinemia requiring phototherapy						
No. (%)	14/157 (9)	30/175 (17)	14/87 (16)	12/64 (19)	11/57 (19)	
OR (95% CI)	1.0 (Reference)	2.1† (1.1–4.2)	2.0 (0.9–4.3)	2.4† (1.0–5.4)	2.4† (1.0–5.8)	0.04
OR (95% CI)*	1.0 (Reference)	2.1† (1.0–4.3)	2.0 (0.9–4.7)	2.8† (1.1–6.9)	2.9† (1.1–7.4)	0.02
Delivery before 37 weeks						
No. (%)	31/158 (20)	55/176 (31)	25/90 (28)	19/64 (30)	22/58 (38)	
OR (95% CI)	1.0 (Reference)	1.9† (1.1–3.1)	1.6 (0.9–2.9)	1.7 (0.9–3.4)	2.5‡ (1.3–4.8)	0.02
OR (95% CI)*	1.0 (Reference)	1.6 (0.9–2.7)	1.5 (0.8–2.9)	1.6 (0.8–3.2)	2.4† (1.2–5.0)	0.03
Composite adverse neonatal outcome						
No. (%)	11/158 (7)	23/176 (13)	15/90 (17)	9/64 (14)	13/58 (22)	
OR (95% CI)	1.0 (Reference)	2.0 (0.9–4.3)	2.7† (1.2–6.1)	2.2 (0.9–5.6)	3.9‡ (1.6–9.2)	0.003
OR (95% CI)*	1.0 (Reference)	1.9 (0.8–4.2)	3.3‡ (1.3–8.0)	2.6 (1.0–7.2)	5.6§ (2.1–14.5)	<0.001

*Adjusted for age, BMI, years of education, social class, ethnicity, parity, current smoking, duration of diabetes, microalbuminuria before pregnancy, vitamin treatment group, and center. †$P < 0.05$, ‡$P < 0.01$, §$P < 0.001$.

it seems unlikely that these differences would have significant clinical implications. We are unaware of other similar large studies, and it is probable that none will be forthcoming until large multicenter studies using continuous glucose monitoring are reported, although one small study revealed an association with LGA (25). While the relationship between glucose data and adverse outcomes does not show such a clear trend as with A1C, there was an increased linear risk of LGA with both pre- and postprandial glucose concentrations. This is in accord with previous studies that have shown relationships with preprandial glycemia (20), postprandial glycemia (7,19) and mean glucose levels (21,24,25). In the current study, a number of neonatal adverse outcomes were significantly related to preprandial rather than postprandial values, particularly at the 34 weeks' gestation time point. These included the composite adverse neonatal outcome, neonatal hypoglycemia requiring a glucose infusion, hyperbilirubinemia requiring phototherapy, and preterm delivery. We are not aware of other studies that have reported an association between these outcomes and worsening preprandial glycemic control. These results suggest that glycemic control during fasting and preprandial periods may be more relevant to adverse outcomes than the shorter postprandial periods of hyperglycemia. However, defining targets, even for preprandial glycemia, in which there were a number of significant associations is difficult, but our findings would support the current guideline target of <5.5 mmol/L (30) or <6.0 mmol/L (29) if achievable without excessive hypoglycemia. Support for this also comes from the finding that even in the reference group (<5.0 mmol/L), the risks of adverse outcomes are higher than would be anticipated in a normal population.

In summary, the current study has shown a continuous relationship between multiple maternal and neonatal adverse outcomes and increasing A1C values in the second and third trimester of pregnancy in women with type 1 diabetes. These adverse outcomes were significantly associated with A1C of ≥6.5% (48 mmol/mol) and LGA with an A1C ≥6.0% (42 mmol/mol). We feel that women should be advised to aim for target values of <6.5% (48 mmol/mol) and ideally <6.0% (42 mmol/mol), if this is possible without excessive hypoglycemia. If this goal is not achieved, additional surveillance by experienced clinicians is indicated.

While capillary blood glucose data were generally concordant with the A1C results, it was not possible to define a clear target range. However, third trimester preprandial glucose values between 6.0 and 6.9 mmol/L were associated with an increased risk of an adverse composite neonatal outcome, which supports the current American Diabetes Association and NICE guidelines of $<$5.5 and $<$6.0 mmol/L, respectively (27,29). Finally, our data suggest that the current U.K. NICE recommendation not to measure A1C in later pregnancy needs review.

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