An Early Pregnancy HbA_{1c} ≥5.9% (41 mmol/mol) Is Optimal for Detecting Diabetes and Identifies Women at Increased Risk of Adverse Pregnancy Outcomes

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OBJECTIVE

Pregnant women with undiagnosed diabetes are a high-risk group that may benefit from early intervention. Extrapolating from nonpregnancy data, HbA_{1c} ≥6.5% (48 mmol/mol) is recommended to define diabetes in pregnancy. Our aims were to determine the optimal HbA_{1c} threshold for detecting diabetes in early pregnancy as defined by an early oral glucose tolerance test (OGTT) at <20 weeks' gestation and to examine pregnancy outcomes relating to this threshold.

RESEARCH DESIGN AND METHODS

During 2008–2010 in Christchurch, New Zealand, women were offered an HbA_{1c} measurement with their first antenatal bloods. Pregnancy outcome data were collected. A subset completed an early OGTT, and HbA_{1c} performance was assessed using World Health Organization criteria.

RESULTS

HbA_{1c} was measured at a median 47 days' gestation in 16,122 women. Of those invited, 974/4,201 (23%) undertook an early OGTT. In this subset, HbA_{1c} ≥5.9% (41 mmol/mol) captured all 15 cases of diabetes, 7 with HbA_{1c} <6.5% (<48 mmol/mol). This HbA_{1c} threshold was also 98.4% (95% CI 97–99.9%) specific for gestational diabetes mellitus (GDM) before 20 weeks (positive predictive value = 52.9%). In the total cohort, excluding women referred for GDM management, women with HbA_{1c} of 5.9–6.4% (41–46 mmol/mol; *n* = 200) had poorer pregnancy outcomes than those with HbA_{1c} <5.9% (<41 mmol/mol; *n* = 8,174): relative risk (95% CI) of major congenital anomaly was 2.67 (1.28–5.53), preeclampsia was 2.42 (1.34–4.38), shoulder dystocia was 2.47 (1.05–5.85), and perinatal death was 3.96 (1.54–10.16).

CONCLUSIONS

HbA_{1c} measurements were readily performed in contrast to the low uptake of early OGTTs. HbA_{1c} ≥5.9% (≥41 mmol/mol) identified all women with diabetes and a group at significantly increased risk of adverse pregnancy outcomes.

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The prevalence of diabetes in women of childbearing age has dramatically increased (1–3). Unrecognized preexisting diabetes is associated with poor pregnancy outcomes, with increased rates of congenital anomalies and perinatal mortality compared with pregnancies complicated by transient gestational diabetes mellitus (GDM) (4). Excess perinatal mortality and preeclampsia are also seen in pregnancies where GDM is detected early (5,6). Unfortunately, 30–50% of type 2 diabetes cases are undiagnosed (1,7) and in pregnancy may remain unidentified until routine screening for GDM at 24 to 28 weeks' gestation, by which time adverse effects may already be evident.

The International Association of Diabetes and Pregnancy Study Groups (IADPSG) (8), the American Diabetes Association (ADA) (9), and the World Health Organization (WHO) (10) recommend screening for diabetes in pregnancy (also described as "overt" diabetes) at the first antenatal visit; however, the most appropriate test and threshold remain undefined. An HbA_{1c} measurement is an attractive option, as it is easily added to the routine early pregnancy laboratory tests (first antenatal bloods) in the nonfasting patient. It also has advantages over tests of blood glucose relating to preanalytical stability and reproducibility (11). An HbA_{1c} level $\geq$6.5% (48 mmol/mol) is the recommended diagnostic cut point for diabetes in pregnancy (8–10); however, this is based on data in nonpregnant subjects. The optimal HbA_{1c} threshold in pregnancy is likely to be lower since the HbA_{1c} level falls in the first trimester and is 0.5% (5.5 mmol/mol) lower by 14 weeks (12–14). To date, no prospective cohort study has examined the use of an early pregnancy HbA_{1c} measurement as a screening test for undiagnosed preexisting diabetes, as compared with traditional oral glucose tolerance test (OGTT) criteria, or whether there is a useful HbA_{1c} threshold to identify women who are at risk for significant adverse pregnancy outcomes. These women may benefit from intervention prior to routine screening for GDM at 24–28 weeks.

The aims of this study were to determine the optimal early pregnancy HbA_{1c} threshold to detect diabetes and subsequently to examine whether this threshold identifies women at increased risk of adverse pregnancy outcomes who may potentially benefit from early detection and management.

RESEARCH DESIGN AND METHODS

This prospective cohort study was conducted in Christchurch, New Zealand, between 1 February 2008 and 31 August 2010 in a primary care setting. All women in the Christchurch area were offered HbA_{1c} and random plasma glucose (RPG) testing at the time of their first antenatal bloods. The RPG data are not reported in this paper. We assessed the performance of HbA_{1c} measured at the time of the first antenatal bloods as a screening test for preexisting diabetes and GDM measured by the standard 75 g 2-h OGTT performed before 20 weeks' ($\leq$140 days) gestation. Exclusion criteria for performing an early OGTT were known preexisting diabetes or pregnancy loss. WHO OGTT criteria were applied retrospectively to this cohort to define diabetes (fasting $\geq$126 mg/dL [7.0 mmol/L] or 2 h $\geq$200 mg/dL [11.1 mmol/L]) and GDM (fasting $\geq$92 mg/dL [5.1 mmol/L], 1 h $\geq$180 mg/dl [10.0 mmol/L], or 2 h $\geq$153 mg/dL [8.5 mmol/L]) in the analysis. However, during the study period, women were only referred for management of GDM based on New Zealand OGTT criteria (fasting $\geq$99 mg/dL [5.5 mmol/L] or 2 h $\geq$162 mg/dL [9.0 mmol/L]).

Medical professionals primarily responsible for pregnancy care (general practitioners, midwives, and obstetricians) gained informed consent for testing both HbA_{1c} and RPG at the time of requesting the first antenatal bloods. Our research midwife sought individual consent for the OGTTs after requesting the contact details of potential participants from the medical professionals who had ordered the HbA_{1c} and RPG tests. During the study period, all women received standard antenatal care from a midwife and/or an obstetrician of their choice. All women who did not have an early OGTT or who had an early OGTT that was below the diagnostic threshold for GDM by New Zealand criteria were advised to attend routine screening for GDM at 24–28 weeks' gestation. This involved either a 75 g OGTT or a screening 50 g glucose challenge test followed by a 75 g OGTT if the glucose challenge test was positive (plasma glucose $\geq$140.5 mg/dL [7.8 mmol/L] at 1 h).

Research assistants collecting data were blinded to both the HbA_{1c} and OGTT results. Demographic and pregnancy outcome data were collected from maternity booking forms and electronic and paper hospital records. All data were entered into a central database and were double checked for accuracy. All blood results were received in electronic format from the laboratories. Three independent laboratories were involved in blood sampling and analysis; technicians reporting OGTT results were blinded to the HbA_{1c} results. All laboratories used identical analytical methods and brands of equipment: HbA_{1c} measurements were determined by Variant II high-performance liquid chromatography (Bio-Rad, Hercules, CA), and if an abnormal hemoglobin variant was detected, HbA_{1c} was measured by In2it affinity chromatography radioimmunoassay (Bio-Rad). It was recognized that there may be a 0.02% interlaboratory error at the range of HbA_{1c} levels that we were interested in. Venesection and preanalytical handling of samples were according to the individual laboratory protocol and were not standardized for the study.

Pregnancy outcome analysis was restricted to women who completed their first antenatal blood screen by 20 weeks' ($\leq$140 days) gestation. Women were excluded from the outcome analysis if they had HbA_{1c} $\geq$6.5% ($\geq$48 mmol/mol), received treatment for GDM at any stage in pregnancy, or had a multiple pregnancy. The rationale for these exclusions was that it is well documented that women with preexisting diabetes and HbA_{1c} $\geq$6.5% ($\geq$48 mmol/mol) and women with a multiple pregnancy are at increased risk of adverse pregnancy outcomes, and treatment for GDM could introduce bias by modifying pregnancy outcomes. For the analysis of congenital anomalies, women without delivery data (miscarriage, termination of pregnancy, lost to follow-up/delivered elsewhere) were included; however, these women were excluded from other outcome analyses. Only major congenital anomalies as defined by the National Perinatal Epidemiology and Statistics Unit, University of New South Wales, Australia, were included, which excludes all anomalies associated with chromosomal abnormalities and minor anomalies such as talipes. Preeclampsia was defined by

the International Society for the Study of Hypertension in Pregnancy criteria (15) as new-onset or worsening hypertension after 20 weeks' gestation and the coexistence of one or more of the following new-onset conditions: proteinuria (PCR >30 mg/mmol), other maternal organ dysfunction, or fetal growth restriction. Perinatal deaths were defined by New Zealand criteria as deaths occurring at ≥20 weeks' gestation or a birth weight of ≥400 g irrespective of gestation up to 28 completed days after birth. Shoulder dystocia was defined as a difficult delivery after birth of the head, requiring maneuvers such as McRoberts maneuver, suprapubic pressure, or intravaginal manipulation. Customized birth weight centiles were calculated using the GROW Bulk Centile Calculator version 6.7 from the Perinatal Institute, Birmingham, U.K., which adjusts for maternal age, parity, height, weight (without limits), and ethnicity as well as for gestational age at delivery and sex.

A biostatistician was involved in study design and performed the analysis. An HbA_{1c} threshold with a sensitivity of at least 90% for detecting diabetes was considered desirable for screening purposes. The sample size was based on achieving 6% precision (CI) around this sensitivity, with 105 abnormal OGTTs before 20 weeks' gestation being required. In order to achieve this, we estimated that 15,000 to 18,000 women required HbA_{1c} measurements based on our annual delivery rate of ~5,000, the 5.6% prevalence of GDM within our population, the assumption that 25–30% of women with GDM had hyperglycemia predating pregnancy (based on New Zealand follow-up data), and allowing for a 50% attrition rate due to both eligibility and selection criteria and due to women declining to participate.

Statistical analysis was performed using the statistical software package SAS version 9.1. The performance of the first-trimester HbA_{1c} test was measured by the gold standard OGTT performed by 20 weeks' (140 days) gestation. This timing limit was imposed in order to remove the confounding effects of pregnancy-induced insulin resistance that occurs beyond this gestation (16,17). Resource constraints prevented us from inviting all women for an early OGTT, thus invitations were limited to women with HbA_{1c} ≥5.6% (38 mmol/mol; mean +1 SD determined after 1 month of testing) or RPG ≥99 mg/dL (5.5 mmol/L) as endorsed by the National Health and Medical Research Foundation of Australia (18), and a consecutive series of 1,000 women with both HbA_{1c} and RPG below these cutoff levels were also invited for an OGTT (this allowed for a small sample of 200 after allowing an attrition rate of 80%). In view of the selection criteria, the sensitivity and specificity analyses were derived by weighting the data and adjusting the variance of the estimates as described by Potthoff et al. (19). CIs for positive predictive values and negative predictive values were derived using the mid-P exact method. Relative risks (RRs) and the associated CIs were calculated using the online statistical software package Open Epi version 2.3.1 (20).

RESULTS

HbA_{1c} testing was performed for 16,122 women over a 31-month period at a median (interquartile range) of 47 (38–62) days' gestation. The mean ± SD HbA_{1c} was 5.3 ± 0.3% (34 ± 3.3 mmol/mol), and 33 (0.2%) women had HbA_{1c} ≥6.5% (48 mmol/mol).

OGTTs were performed before 20 weeks' (≤140 days) gestation by 974/4,201 women (23.2% of those invited) at a median (interquartile range) of 99 (84–113) days' gestation. The distribution of women who performed an early OGTT within the whole cohort can be seen in Fig. 1. The OGTT criteria for diabetes were met in 15 women, median HbA_{1c} 6.5% (48 mmol/mol), range 5.9–8.9% (41 to 74 mmol/mol); the lowest quartile had HbA_{1c} ≤6.1% (43 mmol/mol). OGTT criteria for GDM (excluding those meeting diabetes criteria) were met in 170 women before 20 weeks' gestation, median HbA_{1c} 5.8% (40 mmol/mol), range 4.8–7.3% (29 to 56 mmol/mol). Women with higher HbA_{1c} results were more likely to perform an early OGTT, ranging from 2.8% of those with HbA_{1c}<5.6% (<38 mmol/mol) to 57.6% of those with HbA_{1c} ≥6.5% (≥48 mmol/mol); therefore the sensitivity and specificity analyses were performed on weighted data. Receiver-operated curves are shown in Supplementary Fig. 1, and the sensitivity and specificity data for various HbA_{1c} cut-off points are shown in Supplementary Tables 2 and 3. The optimal HbA_{1c} screening threshold for detecting diabetes was ≥5.9% (41 mmol/mol), and this was met by 2.9% of the total cohort; sensitivity 100% (95% CI 91.8–100), specificity 97.4% (95% CI 95.5–99.2), positive predictive value 18.8% (95% CI 15.7–22.4), negative predictive value 100 (95% CI 100–100) (weighted data for diabetes around an HbA_{1c} threshold of 5.9% [41 mmol/mol] was 98.6 HbA_{1c} ≥5.9% and positive OGTT, 15,707.1 HbA_{1c} <5.9% and negative OGTT, 425.4 HbA_{1c} ≥5.9% and negative OGTT, and 0 HbA_{1c} <5.9% and positive OGTT). This HbA_{1c} threshold was also highly specific, 98.4% (95% CI 97.0–99.9), but less sensitive, 18.8% (95% CI 6.6–31.1), for early GDM, positive predictive value 52.9% (95% CI 48.6–57.1) and negative predictive value 92.8% (95% CI 92.4–93.2) (weighted data for GDM around an HbA_{1c} threshold of 5.9% [41 mmol/mol] was 277.1 HbA_{1c} ≥5.9% and positive OGTT, 15,305.3 HbA_{1c} <5.9% and negative OGTT, 247.0 HbA_{1c} ≥5.9% and negative OGTT, and 1,192.8 HbA_{1c} <5.9% and positive OGTT). HbA_{1c} <4.8% (29 mmol/mol) excluded early GDM.

An early pregnancy OGTT was performed by 173 women with HbA_{1c} ≥5.9% (41 mmol/mol). The OGTT was abnormal in 88 (50.9%), of whom 15 (8.7%) met diabetes criteria, and 10 of the 88 women subsequently miscarried. Of the 85 women with a normal early OGTT, 3 miscarried and 73 had a second OGTT after 24 weeks' gestation, of which 40/73 (54.8%) met GDM criteria. In total, 128 (74.0%) women with early HbA_{1c} ≥5.9% (41 mmol/mol) who performed an OGTT met GDM criteria at some stage in their pregnancy, and 18 (10.4%) of these women met diabetes criteria.

Postnatal OGTTs were only offered to women who had been referred for GDM management (by New Zealand criteria). In women with HbA_{1c} 5.9–6.4% (41–46 mmol/mol), 73/78 completed a postnatal OGTT, and 34 (46.6%) were abnormal, 10 (13.7%) had diabetes, 24 (32.9%) had impaired glucose tolerance (IGT), and a further 8 (11.0%) met the ADA criteria for impaired fasting glucose (100–109 mg/dL or 5.6–6.0 mmol/L). Of the 29 women with HbA_{1c} ≥6.5% (≥48 mmol/mol) before 20 weeks' gestation, 25 (86.2%) had a postnatal OGTT, 20 (80%) had diabetes, and 5 (20%) had IGT. All four women with HbA_{1c} ≥6.5% (≥48 mmol/mol) measured after 20 weeks'

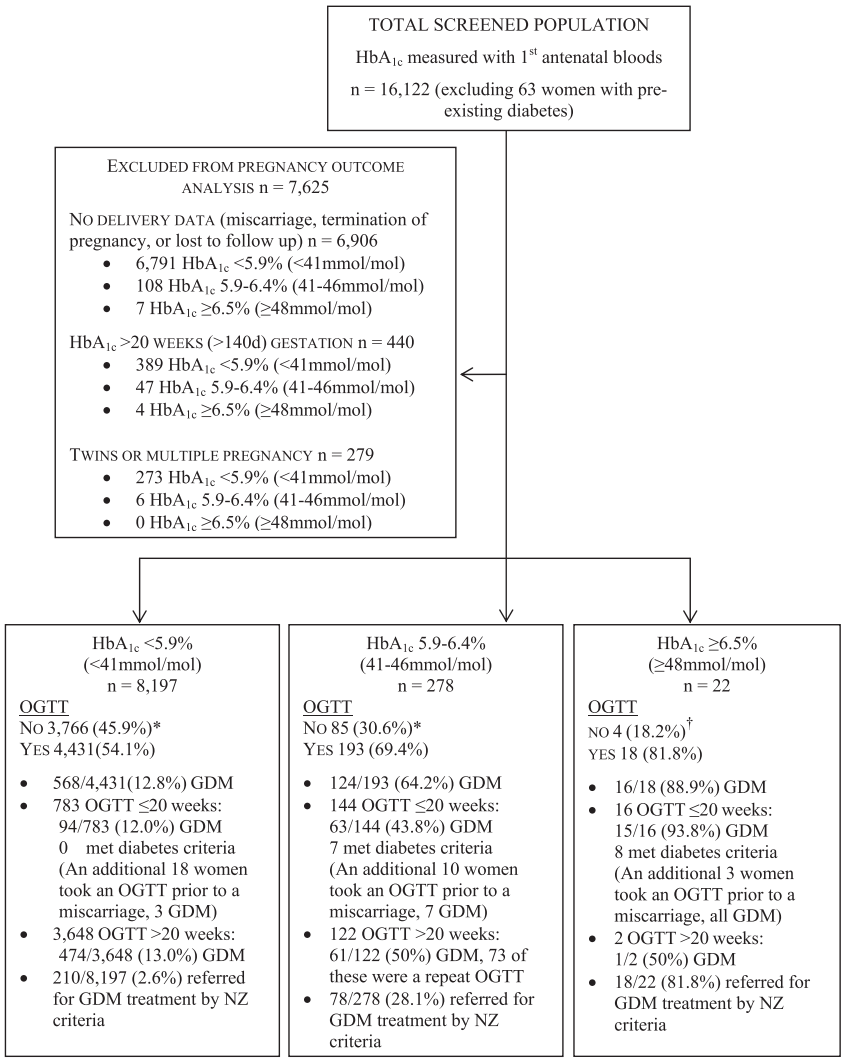

Figure 1—Flow diagram of recruitment and screening outcomes. The WHO (and IADPSG) OGTT criteria were used to define hyperglycemia (GDM and diabetes) in pregnancy, and ≤20 weeks includes up to 140 days' gestation. *Either performed a glucose challenge test (nonfasting 50 g glucose load) that was normal or had no follow-up. †Two were referred directly to antenatal diabetes clinic, and two had no follow-up. NZ, New Zealand.

gestation had diabetes confirmed postpartum. Of the 15 women who met WHO OGTT criteria for diabetes in pregnancy, 11 (73.3%) showed persistent diabetes on a postnatal OGTT while 4 (26.7%) met the criteria for IGT. Pregnancy outcome data were analyzed in the total cohort to examine whether an HbA_{1c} threshold of ≥5.9% (41 mmol/mol) measured before 20 weeks' gestation was associated with increased pregnancy risks (Tables 1 and 2). Women treated for GDM in pregnancy were excluded as a potential cofounding factor. Women with HbA_{1c} ≥5.9% (≥41 mmol/mol) compared with women who had HbA_{1c} <5.9% (<41 mmol/mol) had a greater than a 2-fold increased RR of preeclampsia, shoulder dystocia, and major congenital anomaly; a greater than 3-fold increased RR of perinatal death; and a greater than 1.5-fold increased risk of delivery before 37 weeks' gestation. Ten of the 16 premature deliveries were spontaneous, 8 following premature rupture of membranes. Of the six iatrogenic deliveries, two were for preeclampsia and four were for fetal concerns, with three subsequent perinatal deaths and one hypoxic ischemic encephalopathy. There were four perinatal deaths to women with HbA_{1c} 5.9–6.4% (41–46 mmol/mol) who had routine pregnancy care. One was an intrauterine fetal death at 21 weeks' gestation of a fetus with a univentricular heart and normal karyotype. The second was at 23 weeks' gestation in a woman who presented with spontaneous rupture of membranes and chorioamnionitis, going on to deliver a female infant weighing 510 g who died at 4 days of age. There was no evidence of cervical incompetence, and the woman had a subsequent pregnancy where GDM, requiring medication, was diagnosed and she delivered at term. The third was a stillbirth in a woman who presented in spontaneous labor at 39 weeks and delivered a previously unrecognized severely growth restricted-infant weighing 1,734 g. All these women were nonsmokers, normotensive, and not obese (BMI range 23.6 to 26.5). The fourth death occurred at 32 weeks' gestation in association with fetal thrombocytopenia and hemorrhagic hydrocephalus; anti-HPA1A antibodies were subsequently found. After excluding the fourth loss, given that it cannot be plausibly connected with dysglycemia, the RR of perinatal death in women with a booking HbA_{1c} 5.9–6.4% (41–46 mmol/mol) remained significantly elevated: RR 3.03 (95% CI 1.01–9.72).

Excluded from the outcome analysis were 78 women with HbA_{1c} 5.9–6.4% (41–46 mmol/mol) referred for GDM management. Compared with women who were not treated for GDM, those treated had higher HbA_{1c} and BMI measurements and fewer were European: mean ± SD HbA_{1c} 6.0 ± 0.1% (42 ± 1.1 mmol/mol) vs. 6.1 ± 0.2% (43 ± 2.2 mmol/mol), $P < 0.001$; BMI 28.9 ± 7.4 vs. 32.8 ± 7.6 kg/m^2, $P < 0.001$; European 63.5 vs. 53.8%, $P < 0.01$. The mean age was not significantly different: 31.5 ± 6.3 vs. 32.5 ± 5.9 years, $P = 0.23$. The women treated for GDM had similarly high rates of major congenital anomaly 3 (3.8%), shoulder dystocia 2 (2.6%), and preeclampsia 9 (11.5%), but there were no perinatal deaths in this group. When women treated for GDM were included in the pregnancy outcome analysis (78 with HbA_{1c} 5.9–6.4% [41 mmol/mol-46 mmol/mol] and 187 with HbA_{1c} <5.9% [<41 mmol/mol]), the higher risk of adverse pregnancy outcome in the group with HbA_{1c} 5.9–6.4% (41–46 mmol/mol) remained; major congenital anomaly RR 2.76 (95% CI 1.51–5.04), preeclampsia RR 3.04 (1.97–4.70), and shoulder dystocia 2.48 (1.21–5.10), but perinatal death RR 2.24 (0.75–6.69) no longer reached significance after excluding the fourth death.

Table 1—Patient information stratified according to HbA_{1c} measurement at ≤20 weeks' (140 days') gestation, excluding women treated for GDM

	HbA_{1c} 5.9–6.4% (41–46 mmol/mol) *n* = 200 *n* (%)	HbA_{1c} <5.9% (<41 mmol/mol) *n* = 7,987 *n* (%)	*P* value
Age, years, mean (SD)	31.5 (6.3)	30.3 (5.9)	<0.01
BMI kg/m^2	*n* = 155	*n* = 1,391	
Mean (SD)	28.9 (7.4)	25.9 (5.7)	<0.001
Median (range)	27.5 (17.5–48.3)	24.5 (21.9–57.53)	
Ethnicity			<0.001
NZ European	127 (63.5)	6,288 (78.7)	
Māori	20 (10)	586 (7.3)	
Pacific Islander	10 (5)	204 (2.6)	
Other	43 (21.5)*	895 (11.2)	
Unknown	0	14 (0.2)	

*36 (18%) Asian.

CONCLUSIONS

We determined that HbA_{1c} ≥5.9% (41 mmol/mol) identified all women with diabetes in the subgroup of our population who completed an OGTT before 20 weeks' (≤140 days') gestation. A threshold ≥6.5% (48 mmol/mol) would have missed almost half of these women and is therefore too high for screening purposes. In this subgroup, 74% of women with an early pregnancy HbA_{1c} ≥5.9% (41 mmol/mol) had an abnormal OGTT at some stage in their pregnancy, with over two-thirds of these being identified before 20 weeks' gestation. Moreover, in the total cohort, we found that an early pregnancy HbA_{1c} measurement of 5.9–6.4% (41–46 mmol/mol) was associated with an increased risk of adverse pregnancy outcomes, including major congenital anomaly, preeclampsia, shoulder dystocia, and perinatal death. Our pragmatic study has demonstrated the feasibility of routine screening with HbA_{1c} in early pregnancy. HbA_{1c} testing is easy, reproducible, and reflects the mean blood glucose levels over a period of time (11).

Table 2—Pregnancy outcomes stratified according to HbA_{1c} measurement at ≤20 weeks' (140 days') gestation, excluding women treated for GDM

	HbA_{1c} 5.9–6.4% (41–46 mmol/mol) *n* = 200 *n* (%)	HbA_{1c} <5.9% (<41 mmol/mol) *n* = 7,987 *n* (%)	RR (95% CI)
Delivery gestation			
<37 weeks	16 (8.0)	392 (4.9)	1.66 (1.01–2.74)*
<32 weeks	3 (1.5)	71 (0.9)	1.67 (0.55–5.10)
Induction of labor	35 (17.5)	1,016 (12.7)	1.44 (1.01–2.06)*
Caesarean delivery			
Total	65 (32.5)	2,428 (30.4)	1.10 (0.82–1.47)
Emergency	33 (16.5)	1,529 (19.1)	0.84 (0.58–1.21)
Major congenital anomalies		*n* = 7,992	
	7 (3.5)	103 (1.3)	2.67 (1.28–5.53)*
Preeclampsia	11 (5.5)	181 (2.3)	2.42 (1.34–4.38)*
Perinatal death	4 (2.0)	38 (0.5)	3.96 (1.54–10.16)*
Shoulder dystocia	5 (2.5)	79 (1.0)	2.47 (1.05–5.85)*
Birth weight	*n* = 199		
Mean (SD)	3,480.2 (597.0)	3,483.8 (571.0)	*P* = 0.93
>4,000 g	34 (17.1)	1,240 (15.5)	1.12 (0.78–1.61)
Population birth weight centiles†	*n* = 199		
Small for gestational age	22 (11.1)	1,202 (15.1)	0.71 (0.46–1.10)
Large for gestational age	26 (13.1)	655 (8.2)	1.66 (1.11–2.48)*
Customized birth weight centiles‡	*n* = 199		
Small for gestational age	23 (11.6)	1,173 (14.7)	0.76 (0.50–1.17)
Large for gestational age	21 (10.1)	641 (8.0)	1.34 (0.86–2.09)

Small for gestational age <10th centile; large for gestational age >90th centile. *Significant difference. †Adjusted for gestational age at delivery and sex of baby. ‡Adjusted for ethnicity, maternal height and weight, parity, gestational age at delivery, and sex of baby. Missing height or weight data defaulted to the population median of 165 cm and 65 kg, respectively.

Our study was designed to examine how the early HbA_{1c} measurement related to a pregnancy diagnosis of diabetes by OGTT and whether it defined a higher-risk population that may benefit from earlier intervention. It was not designed to predict the postnatal diagnosis of diabetes. However, in the subgroup of women who were referred for diabetes treatment during pregnancy and had postnatal follow-up, the OGTT was abnormal in all women with HbA_{1c} ≥6.5% (48 mmol/mol) and in 46.6% (57.6% by ADA criteria) of women with HbA_{1c} 5.9–6.4% (41–46 mmol/mol). We do not know if the untreated women had a different risk of abnormal glucose tolerance after pregnancy, but our data suggest that women with HbA_{1c} ≥ 5.9% are in a high-risk subgroup for diabetes and glucose intolerance postpartum, and ongoing follow-up is important.

In support of our proposed early pregnancy HbA_{1c} threshold of ≥5.9% (41 mmol/mol), the reported upper limit of normal for a first-trimester HbA_{1c} in other populations with diverse ethnic backgrounds ranges from 5.5 to 5.7% (37–39 mmol/mol) (13,14,21,22). Two other studies have also reported a first-trimester HbA_{1c} measurement as a predictor of GDM. HbA_{1c} ≥6.0% (42 mmol/mol) was 100% predictive of GDM in a study in Indian women (23), and a North American study found that all those with HbA_{1c} ≥6.1% (43 mmol/mol) developed GDM (24). In women with preexisting diabetes, early pregnancy HbA_{1c} directly correlates with pregnancy outcome (25–27). Our study cannot determine if the increased pregnancy risks in women with HbA_{1c} 5.9–6.4% (41–46 mmol/mol) are independently related to elevated HbA_{1c} levels and dysglycemia. Outcome frequencies were too low to adjust for potential confounding

factors; in addition, a large amount of BMI data were missing in the group with lower HbA_{1c} levels. Also, the risk of perinatal death is an outcome that requires cautious interpretation, as it is a rare outcome. Although perinatal death has been shown to be associated with preexisting diabetes, its relationship with lesser degrees of hyperglycemia is not so clear (28–30). Despite these cautions, $HbA_{1c} \geq 5.9\%$ (≥ 41 mmol/mol) was a marker for elevated pregnancy risk, and this threshold may be clinically useful to identify women who may benefit from early referral and increased monitoring in pregnancy. The risks associated with early HbA_{1c} 5.9–6.4% (41–46 mmol/mol) may in fact be underestimated, as 78 of the 278 women in this group were referred for GDM management and therefore not included in the outcomes analysis. This group of 78 women had a higher mean HbA_{1c} and BMI than the group analyzed, and we do not know if outcomes would have been worse if they had not been treated.

There are several other limitations to our study. One is the low uptake of OGTTs before 20 weeks' gestation, although this does emphasize the comparative ease of screening with an HbA_{1c} measurement. Women declining the OGTT cited similar reasons: lack of time, nausea, or not wanting to complete two OGTTs in pregnancy (pre–20 weeks and again routinely at 24–28 weeks). A small proportion of women with an HbA_{1c} measurement $<5.6\%$ took an early OGTT, which means that we may have underestimated the risk of GDM in this group. Secondly, this study was in a relatively low-risk predominantly Caucasian population, and it would be of interest to see how this HbA_{1c} threshold performs in other more diverse populations. Thirdly, we used WHO/IADPSG GDM criteria to define GDM before 20 weeks' gestation, and the usefulness of these criteria in early pregnancy remains unclear. In particular, fasting glucose decreases in pregnancy, and a proportion of women who have an elevated fasting glucose in the first trimester may have a normal later pregnancy OGTT (31,32). However, in our study, the majority of early pregnancy OGTTs were performed between 12 and 20 weeks' gestation, after the initial fall in fasting blood glucose, making it more likely that an abnormal OGTT was a true positive (16,17). Finally, we used the OGTT as the gold standard for diagnosis when it has known limitations, being subject to preanalytical error due to variation in sample handling and having reproducibility issues (33,34). It may be that HbA_{1c} is a more relevant marker in early pregnancy for detecting women whose fetuses are being exposed to significant hyperglycemia. HbA_{1c} measurements are more reproducible than measures of blood glucose, although the use of HbA_{1c} also has issues with variability in measurement that may be important in women with levels close to the threshold we propose. A recent study from Auckland, New Zealand (35), examined women who were referred to a diabetes clinic with $HbA_{1c} \geq 5.9\%$ (41 mmol/mol) and a normal OGTT (by New Zealand criteria). In those referred before 24 weeks' gestation, over 90% required pharmacotherapy (metformin and/or insulin) in addition to lifestyle advice. The authors concluded that early pregnancy $HbA_{1c} \geq 5.9\%$ (41 mmol/mol) was a clinically relevant marker of hyperglycemia without the need for a subsequent confirmatory OGTT. This could mean that we may have underestimated the predictive value of $HbA_{1c} \geq 5.9\%$ in our population.

Further studies could verify our results, particularly across different ethnic groups, as others have shown an interethnic variability in HbA_{1c} levels (36). The impact of early detection and treatment on both maternal and fetal outcomes, as well as the cost-effectiveness of this approach, also need to be examined. In New Zealand, HbA_{1c} measurement costs one-third less than an OGTT, and costs would be even lower if the test was added routinely to the first antenatal screen. Thus an HbA_{1c} measurement is likely to be a more cost-effective screening approach than an early pregnancy OGTT, as well as being a more acceptable test to women in early pregnancy. We consider HbA_{1c} to be a useful addition to the first-antenatal blood screen and that $HbA_{1c} \geq 5.9\%$ (41 mmol/mol) warrants referral for further assessment due to the associated increased risk of adverse pregnancy outcomes.

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Author Contributions. R.C.E.H. conceived and designed the study, recruited participants, collected data, did basic data analysis, and drafted the paper, figures, and tables. M.P.M. conceived and designed the study and recruited participants. J.E.G. collected data. K.M. analyzed the data. J.R. conceived and designed the study. All authors met authorship requirements, actively participated in revising the paper, contributed to the discussion, and gave approval of the final version. R.C.E.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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