Early pregnancy high normal HbA_{1c}: a high risk group?

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ABSTRACT

AIM: To determine if high normal early pregnancy HbA_{1c} (35–40mmol/mol), in the absence of diabetes, was associated with increased risk of adverse perinatal outcomes compared to normal HbA_{1c} (<35mmol/mol).

METHOD: A retrospective chart review was carried out on all singleton births in the Wellington region from 1 July 2019 to 31 December 2019. Exclusion criteria were participants domiciled outside the Wellington region, HbA_{1c} ≥50mmol/mol, pre-existing diabetes, gestational diabetes in current pregnancy, no HbA_{1c} performed <20 weeks or the first HbA_{1c} was taken at ≥20 weeks. Baseline characteristics, HbA_{1c} and pregnancy outcomes were obtained. The primary outcome was birth weight and was analysed using multiple linear regression.

RESULTS: There were 1,067 participants in the normal HbA_{1c} ($nHbA_{1c}$) group and 186 in the high normal HbA_{1c} ($hnHbA_{1c}$) group. There was no difference in birth weight between $hnHbA_{1c}$ and $nHbA_{1c}$. $hnHbA_{1c}$ had significantly lower odds of post-partum haemorrhage and composite maternal adverse outcomes compared to $nHbA_{1c}$ (OR 0.52, 95% CI 0.35–0.76) and (OR 0.64, 95% CI 0.46–0.89).

CONCLUSION: High normal HbA_{1c} was not associated with increased risk of adverse perinatal outcomes in pregnant people who did not develop gestational diabetes.

HbA_{1c} (glycated haemoglobin) predicts pregnancy-related adverse outcomes in people with pre-diabetes and diabetes.[1–3] Aotearoa New Zealand guidelines recommend measuring HbA_{1c} with the first antenatal blood tests to identify previously undiagnosed diabetes; where HbA_{1c} ≤40mmol/mol is normal, 41–49mmol/mol suggests greater risk and ≥50mmol/mol represents probable undiagnosed diabetes.[1] HbA_{1c} ≥50mmol/mol is diagnostic of diabetes in Aotearoa New Zealand, and those meeting this criteria are referred to secondary services for specialist input during pregnancy.[1] Some people with HbA_{1c} of 41–49mmol/mol are referred, however this is dependent on local guidelines.[4]

People with pre-diabetes and gestational diabetes (GDM) are at increased risk of adverse perinatal outcomes.[2–7] The *Hyperglycemia and Adverse Pregnancy Outcome (HAPO)* study identified increasing risk of perinatal complications with increasing maternal glycaemia below the threshold for diabetes.[5] There is limited literature on pregnancy outcomes in people without diabetes with an early pregnancy HbA_{1c} at the upper limit of normal. In 466 women followed prospectively in Australia, an early pregnancy HbA_{1c} of ≥38 mmol/mol was highly predictive of developing GDM and increased risk for large for gestational age (LGA).[8] In Aotearoa New Zealand, Hughes et al. (2014) demonstrated that women with an early pregnancy HbA_{1c} in the pre-diabetes range (41–46mmol/mol) who were not treated for GDM had increased rates of major congenital anomaly, pre-eclampsia, shoulder dystocia and perinatal death compared to women with normal HbA_{1c}.[2] There is no data in Aotearoa New Zealand for people who have a booking HbA_{1c} of <41mmol/mol.

HbA_{1c} may not be a reliable predictor of glycaemic control at early gestations, falling 4–10mmol/mol by the second trimester.[8,9] Several factors contribute to this fall, including haemodilution and an increase in red cell turnover.[10] Therefore, a person with pre-diabetes based on an HbA_{1c} of 41–49mmol/mol outside of pregnancy, who has already developed a degree of glucose dysregulation, may have a normal HbA_{1c} by the time the first antenatal bloods are taken. This means these people are not identified as higher risk—either at all, or until later in pregnancy.

In Aotearoa New Zealand, routine measurement of early pregnancy HbA_{1c} has enabled identification of previously undiagnosed type 2 diabetes mellitus and more timely interventions. However, when performing screening it is vital to understand the risks associated with "high normal" results of a continuous variable. We hypothesise that women with "high normal" early pregnancy HbA_{1c} may experience higher rates of adverse perinatal outcomes. The aim of this study was to determine whether early pregnancy HbA_{1c} of 35–40mmol/mol in people without either pre-existing diabetes or a later diagnosis of GDM was associated with

an increased risk of adverse perinatal outcomes compared to people with HbA_{1c} <35mmol/mol. The second aim was to establish whether the risk of adverse outcomes increases as HbA_{1c} increases.

Method

A retrospective chart review was performed to look at the relationship between early pregnancy HbA_{1c} (<20 weeks gestation) and adverse perinatal outcomes in pregnant people from the Wellington region delivering at Wellington Regional Hospital, Kenepuru Maternity Unit or Paraparaumu Maternity Unit between 1 July 2019 to 31 December 2019. This study was approved by the Health and Disability Ethics Committee of Aotearoa New Zealand.

Baseline characteristics and pregnancy outcomes were obtained from the Capital and Coast District Health Board (CCDHB) Patient Information Management System database. HbA_{1c} results from Wellington Southern Community Laboratory were collected. HbA_{1c} was quantified using Bio-Rad Variant D-100 Ion Exchange High-performance Liquid Chromatography (HPLC). D-100 has shown reliable analytical performance with good precision and linearity and a CV of <1%.[11] Singleton pregnancies with HbA_{1c} <50mmol/mol at <20 weeks gestation were included. Exclusion criteria were pre-existing diabetes mellitus, developing GDM in the current pregnancy, missing BMI, no HbA_{1c} at <20 weeks gestation or the first HbA_{1c} was taken at ≥20 weeks gestation.

Participants were divided into groups: HbA_{1c} <35mmol/mol, ("$nHbA_{1c}$"), HbA_{1c} 35–40mmol/mol, ("$hnHbA_{1c}$") and HbA_{1c} 41–49mmol/mol ("pre-diabetes").

The primary outcome was birth weight (g). An equally important outcome was customised birth weight centiles, which were calculated using the GROW Bulk Centile Calculator version 6.7.8.3 (Perinatal Institute, Birmingham, UK), which adjusts for maternal height, weight, ethnicity, parity, sex and gestational age at delivery. LGA was defined as >90th customised centile, and small for gestational age (SGA) was defined as <10th customised centile. Secondary outcomes were mode of delivery: normal vaginal delivery, caesarean delivery, assisted vaginal delivery; shoulder dystocia; perineal tears (third and fourth degree); post-partum haemorrhage (PPH) (estimated blood loss >500ml at delivery); induction of labour; pre-term delivery (<37 weeks); neonatal hypoglycaemia requiring treatment, Neonatal Intensive Care Unit (NICU) admission requiring respiratory support; NICU admission in days and perinatal death. Perinatal death was defined according to the Perinatal and Maternal Mortality Review Committee as foetal death occurring >20 weeks gestation, or ≥400g birth weight, and included neonatal deaths occurring up to 28 days of life.[12]

Power calculations were performed prior to data collection. It was estimated that a sample size of 1,400 was achievable in the study timeframe, which would have at least 80% power to compare HbA_{1c} groups with respect to birth weight (assuming a difference of 150g, SD=580), and adverse outcomes (assuming a difference of 10% vs 20%), testing at the 5% significance level.

Baseline characteristics and adverse outcomes are presented as mean (Standard Deviation) or median (range), and n (percent) as appropriate. The $nHbA_{1c}$ and $hnHbA_{1c}$ groups were compared with respect to age (independent-samples *t*-Test), BMI (Wilcoxon Rank-Sum Test with continuity correction), ethnicity and parity (Pearson's Chi-squared test of independence). Dichotomous adverse outcomes were analysed using binomial logistic regression and birth weight was analysed with multiple linear regression. All analyses for adverse outcomes were tested for differences between the $nHbA_{1c}$ and $hnHbA_{1c}$ groups, adjusting for age, BMI and ethnicity. In addition, a further analysis was performed for vaginal birth and post-postpartum haemorrhage that controlled for parity. There were few observed events for the adverse events of shoulder dystocia and perinatal death recorded, so no analyses were run. Maternal and neonatal composite adverse outcomes were created separately. Composite outcomes were used that included clinically important outcomes; for neonatal this included birth weight >4,000g, LGA, SGA, shoulder dystocia, pre-term delivery (<37 weeks), admission to NICU, hypoglycaemia requiring treatment and perinatal death. For maternal this included delivery via caesarean section, perineal tears (third and fourth degree), PPH, induction of labour, pre-term delivery (<37 weeks). Secondary analyses were conducted with BMI as the only predictor. No correction for multiple comparisons was applied, p-values less than 0.05 were considered statistically significant and data were analysed in R version 4.2.0 for Windows (Vienna, Austria).

Results

Between 1 July 2019 and 31 December 2019

there were 1,514 singleton births in the Wellington region (Figure 1). Of these, 261 were excluded from analysis, 1,067 recorded $nHbA_{1c}$ (<35mmol/mol) and 186 recorded $hnHbA_{1c}$ (HbA_{1c} 35–40mmol/mol). One person had an HbA_{1c} in the 41–49mmol/mol range, so this group was not made. Seven people had no BMI recorded and were excluded. The mean HbA_{1c} of those who developed GDM (and were excluded) was 34.7mmol/mol (SD=6.8).

Baseline characteristics are presented in Table 1. Participants in the $hnHbA_{1c}$ group had a higher BMI (25.4kg/m^2 vs 24.4kg/m^2, p=0.023), were more likely to be Pacific peoples, Indian or Other Asian ethnicity compared to participants in the $nHbA_{1c}$ group (p <0.05) and multiparous (65.6% $hnHbA_{1c}$ vs 52.6% $nHbA_{1c}$, p=0.001).

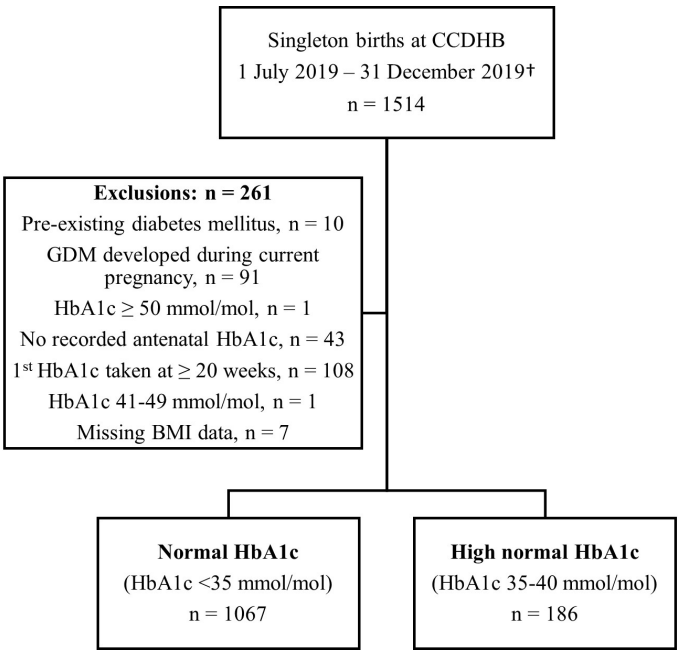
Perinatal outcomes are presented in Table 2. There was no difference in birth weight between $hnHbA_{1c}$ and $nHbA_{1c}$ groups. There was no significant relationship between pregnancy outcomes, including birth weight, and HbA_{1c} as a continuous variable. Participants with $hnHbA_{1c}$ had significantly higher odds of experiencing a normal vaginal delivery than those with $nHbA_{1c}$ (OR 1.4, 95% CI 1.01–1.97), adjusting for age, BMI and ethnicity. However, after controlling for parity, $hnHbA_{1c}$ was no longer significantly associated with a normal vaginal delivery (OR 1.33, 95% CI 0.89–1.97).

Participants with $hnHbA_{1c}$ had significantly lower odds of experiencing a PPH compared to participants with $nHbA_{1c}$ (OR 0.52, 95% CI 0.35–0.76). After controlling for parity, there was little change (OR 0.56, 95% CI 0.38–0.82). Of the people who had a PPH, 5% in the $hnHbA_{1c}$ group had a blood loss of >2,000ml compared to 1.5% of people in the $nHbA_{1c}$ group. No significant differences were found in other pregnancy outcomes, including neonatal outcomes. Five perinatal deaths occurred in the $nHbA_{1c}$ group—two stillbirths and three neonatal deaths—and none in the $hnHbA_{1c}$ group.

A statistically significant difference between the $hnHbA_{1c}$ group and the $nHbA_{1c}$ group was found in the risk of composite maternal adverse perinatal outcomes (OR 0.64, 95% CI 0.46–0.89), and remained significant after adjusting for parity (OR 0.64, 95% CI 0.45–0.91).

A secondary analysis was performed looking at BMI only as a predictor of adverse perinatal outcomes. Increasing BMI was associated with an increased likelihood of macrosomia (birth weight >4,000g) (OR 1.06, 95% CI 1.04–1.09), caesarean section compared to normal vaginal delivery (OR 1.02, 1.01–1.04), PPH (OR 1.03, 1.01–1.05) and induction of labour (OR 1.04, 1.02–1.06). Maternal and neonatal composite adverse outcomes were

Figure 1: Flow diagram of study protocol.



†Births at Wellington Regional Hospital, Kenepuru Maternity Unit or Paraparaumu Maternity Unit. Only people who domiciled to the Wellington region (CCDHB) were included.

Table 1: Baseline characteristics of participants based on early pregnancy HbA_{1c} group, excluding pre-existing diabetes and GDM in current pregnancy.

		Normal HbA_{1c} (HbA_{1c} <35mmol/mol) n = 1,067	**High normal HbA_{1c} (HbA_{1c} 35–40mmol/mol) n = 186**	**p-value**
Age, years	mean (SD)	32.1 (5.4)	32.4 (5.2)	.3929
BMI, kg/m^2	median (range)	24.4 (16.9–68.1)	25.4 (14.5–59.9)	.0263
Ethnicity	NZ European, n (%)	492 (46.1%)	55 (29.6%)	<.0001
	Māori, n (%)	125 (11.7%)	28 (15.1%)	
	Pacific peoples, n (%)	91 (8.5%)	27 (14.5%)	
	Indian, n (%)	50 (4.7%)	18 (9.7%)	
	Other Asian, n (%)	125 (11.7%)	33 (17.7%)	
	Other, n (%)	184 (17.2%)	25 (13.4%)	
Parity	Primiparous, n (%)	506 (47.4%)	64 (34.4%)	.0013
	Multiparous, n (%)	561 (52.6%)	122 (65.6%)	

Table 2: Perinatal outcomes using odds ratios comparing early pregnancy HbA_{1c} group: high normal HbA_{1c} vs normal HbA_{1c}, excluding pre-existing diabetes and GDM in current pregnancy.

Outcomes	**Normal HbA_{1c} (HbA_{1c} <35mmol/mol) n = 1,067**	**High normal HbA_{1c} (HbA_{1c} 35–40mmol/mol) n = 186**	**p-value[†]**	**Odds ratio (95% CI)[†]**
Birth weight (g)				
Mean (SD)[‡]	3,459.6 (582.1)	3,417.3 (578.8)	.6933	
Customised birth centiles				
Large for gestational age (>90th centile), n (%)	140 (13.1%)	23 (12.4%)	.7775[§]	0.934 (0.570, 1.470)[§]
Small for gestational age (<10th centile), n (%)	86 (8.1%)	23 (12.4%)	.0565[§]	1.610 (0.968, 2.584)[§]
Neonatal composite adverse outcomes,[¶] n (%)	414 (38.8%)	83 (44.6%)	.1837	1.244 (0.900, 1.713)
Maternal composite adverse outcomes,[#] n (%)	647 (60.6%)	98 (52.7%)	.0074	0.640 (0.462, 0.888)*

Table 2 (continued): Perinatal outcomes using odds ratios comparing early pregnancy HbA_{1c} group: high normal HbA_{1c} vs normal HbA_{1c}, excluding pre-existing diabetes and GDM in current pregnancy.

Components of composite outcomes			
Mode of delivery			
Normal vaginal delivery (NVD), n (%)	600 (56.2%)	118 (63.4%)*	
Caesarean section (CS)			
Total caesarean section, n (%)	362 (33.9%)	58 (31.2%)	
Emergency caesarean section, n (%)	235 (22.0%)	37 (19.9%)	
Forceps or ventouse delivery, n (%)	105 (9.8%)	10 (5.4%)	
Shoulder dystocia, n (%)	1 (0.1%)	0 (0%)	
Perineal tears (third and fourth degree), n (%)	44 (4.1%)	8 (4.3%)	
Post-postpartum haemorrhage (PPH), n (%)	342 (32.1%)	40 (21.5%)*	
Induction of labour, n (%)	235 (22.0%)	30 (16.1%)	
Pre-term delivery, <37 weeks, n (%)	63 (5.9%)	15 (8.1%)	
NICU admission, n (%)	160 (15.0%)	28 (15.1%)	
NICU admission in days, mean (SD)	12.3 (21.6)	13.6 (21.1)	
NICU requiring respiratory support, n (%)	89 (8.3%)	14 (7.5%)	
Hypoglycaemia requiring treatment, n (%)	70 (6.6%)	16 (8.6%)	
Perinatal death, n (%)	5 (0.5%)	0 (0%)	

†Adjusting for age, ethnicity and BMI.
‡Box Cox transformation applied, lambda = 1.92.
§Not adjusted for ethnicity or BMI as these are adjusted for within the GROW Calculator.
¶Neonatal composite adverse outcomes: birth weight more than 4,000g, large for gestational age, small for gestational age, shoulder dystocia, pre-term delivery (<37 weeks), admission to NICU, hypoglycaemia requiring treatment and perinatal death.
#Maternal composite adverse outcomes: caesarean section, perineal tears (third and fourth degree), post-postpartum haemorrhage, induction of labour and pre-term delivery (<37 weeks).
*Statistically significant difference. P-value = 0.05 for NVD and 0.01 for PPH.

significantly increased with increasing BMI.

Of the 91 people who developed GDM, and were excluded, 86.5% had an HbA_{1c} <41mmol/mol and 13.5% had an HbA_{1c} ≥41mmol/mol. In those who had an HbA_{1c} ≥41mmol/mol (n = 12/1,514) (excluding those with pre-existing diabetes), 91.7% went on to develop GDM (11 of 12). Of all the people with high normal HbA_{1c} (35–40mmol/mol), before excluding for GDM, 13.8% went on to develop GDM (30 of 218).

Discussion

This retrospective review demonstrated that pregnant people with an early pregnancy high normal HbA_{1c}, without pre-existing diabetes or later development of GDM, have no difference in birth weight compared to people with normal HbA_{1c}. Those in the hnHbA_{1c} group did not have an increased risk of adverse perinatal outcomes and were less likely to have a PPH or experience adverse composite outcomes, even after controlling for parity. Increasing BMI, irrespective of HbA_{1c}, significantly increased the odds of macrosomia, caesarean section, PPH and induction of labour.

There were proportionally more Indian and Pacific peoples in the high normal HbA_{1c} group compared to the normal HbA_{1c} group. These ethnicities have the highest rates of gestational diabetes and type 2 diabetes in Aotearoa New Zealand.[13,14] This may be clinically relevant, and future research could explore whether people of these ethnicities should be screened or managed at a lower HbA_{1c} threshold.

People with high normal HbA_{1c} were less likely to have a PPH compared to those with normal HbA_{1c}. The high normal group had more multiparous people and were more likely to experience a vaginal birth, which could have influenced these results. Risk factors identified from previous pregnancies may have resulted in increased use of active management of the third stage of labour, thereby reducing the risk of PPH.

We excluded participants who later developed GDM in order to report on perinatal outcomes independent of any treatment potentially received. Our findings are in keeping with those of Immanuel et al. (2020), who reported that early pregnancy HbA_{1c} ≥39mmol/mol in obese European women did not predict adverse pregnancy outcomes.[15] Likewise, a recent retrospective cohort study showed no increased risk of adverse outcomes in women with early pregnancy HbA_{1c} 38.8–46.4mmol/mol.[16] In contrast, Capula et al. (2013) demonstrated that HbA_{1c} is a strong predictor of negative outcomes in women with GDM, with HbA_{1c} >34mmol/mol associated with a two-fold increased risk of pregnancy-related hypertension, LGA and neonatal morbidity compared to HbA_{1c} <34mmol/mol.[17] Poor pregnancy outcomes related to HbA_{1c} independent of GDM, such as macrosomia, have been reported elsewhere with HbA_{1c} ≥41mmol/mol[18] and HbA_{1c} ≥39mmol/mol.[19] Our findings that BMI predicts adverse outcomes are significant in this study and are concordant with international literature.[20–22] Of concern, more people are conceiving with an increased BMI, which, independent of dysglycaemia, increases risk of both maternal and neonatal adverse outcomes.[20–22]

The relationship between perinatal outcomes and maternal glycaemia, and the associated role of HbA_{1c}, has been explored. The HAPO study demonstrated an increased risk of adverse pregnancy outcomes with increasing maternal glycaemia,[5] and in a sub-group of women, increasing HbA_{1c} was associated with increased LGA and primary caesarean section.[3] Bozkurt et al. (2020) observed beta cell dysfunction and glucose dysregulation when early pregnancy HbA_{1c} was ≥39mmol/mol and was associated with greater risk for LGA.[23] Comparably, women with pre-pregnancy impaired glucose tolerance had a two-fold increased risk of LGA, demonstrated by Wei et al. (2017).[24]

Together with the HAPO studies, this evidence supports our hypothesis that women with a degree of glucose dysregulation, below the diagnostic criteria for diabetes, are at increased risk of adverse pregnancy outcomes, including large for gestational age. Although HbA_{1c} is a useful tool to identify people with undiagnosed pre-existing diabetes, it may be that an alternative assessment for early dysglycaemia is required to reduce adverse perinatal outcomes, or as in the studies reported here, an HbA_{1c} closer to the pre-diabetes range is required to identify dysglycaemia, which influences perinatal outcomes.

Importantly, some have suggested people who receive treatment for hyperglycaemia or diabetes in early pregnancy have improved outcomes compared to those that do not.[25] The TOBOGM Research Group has recently found that early treatment of GDM before 20 weeks gestation improves composite neonatal outcomes, though conversely, treatment did not improve maternal outcomes.[25] Also of note, Rowan (2022) demonstrated early treatment of a first antenatal HbA_{1c} of 41–46 mmol/mol reduces the likelihood of LGA, pre-eclampsia and pre-term birth.[26] In contrast, the GEMS Study demonstrated that a lower diagnostic threshold for GDM (fasting plasma glucose level of ≥5.1mmol/l, 1-hour level of ≥10.0mmol/l, or a 2-hour level of ≥8.5mmol/l) did not improve pregnancy outcomes, but leads to an increased consumption of healthcare services.[27] However, their sub-group analysis showed that women who were treated for "milder" GDM based on the lower glycaemic criteria had a reduced risk of LGA and pre-eclampsia compared to women with similar

glucose test results who received no treatment.[27]

This study has reliably captured HbA_{1c} for every person who had early pregnancy blood tests during the study time period. All samples were analysed in the same laboratory, reducing potential analytical error. As testing early pregnancy HbA_{1c} is routine in Aotearoa New Zealand, no additional investigations were required. Moreover, utilising HbA_{1c}, as opposed to glucose measures, avoids pre-analytical glucose errors. The study was undertaken within the same locality; therefore, management of each person's pregnancy followed the same guidelines.

Limitations include the short time period (6 months) and the smaller than expected sample size. The difference in birth weight was much smaller than expected, only 42.3g, so we did not have sufficient power to detect the expected difference of 150g. This difference is unlikely to be clinically meaningful; therefore, a larger sample size is required to identify a difference of this magnitude. Seven people had no BMI recorded and were excluded, further reducing sample size. One person had an HbA_{1c} of 15mmol/mol due to a history of hereditary spherocytosis, so this HbA_{1c} does not accurately reflect glucose status. It is possible that there were other participants with undiagnosed haemoglobinopathies that may have influenced their HbA_{1c} results. Additionally, pre-eclampsia is an important adverse outcome associated with hyperglycaemia in pregnancy but was not included as a secondary outcome. There was an unexpectedly low number of participants recorded as having pre-eclampsia, suggesting the data may be incomplete.

In conclusion, there is no evidence of a difference in outcomes of birth weight, neonatal or maternal outcomes in pregnant people who have an early pregnancy high normal HbA_{1c} or normal HbA_{1c}. HbA_{1c}, early in pregnancy, identifies those with pre-diabetes or undiagnosed diabetes, allowing appropriate management of these higher risk groups. There is no evidence that HbA_{1c} can be used to stratify risk outside of this range. However, given the continuous nature of an HbA_{1c} measure, and the pregnancy effects on the HbA_{1c} analysis, it is possible that these diagnostic cut points are not accurate in pregnancy. Further exploration of the appropriate use of HbA_{1c} in early pregnancy is important if Aotearoa New Zealand is to continue using it as a screening tool.

COMPETING INTERESTS
The authors report no conflict of interest. This study was approved by the Health and Disability Ethics Committee of New Zealand.
LW received payment for statistical consulting hours to her institution from Capital and Coast District Health Board.

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URL
https://nzmj.org.nz/journal/vol-137-no-1604/early-pregnancy-high-normal-hba1c-a-high-risk-group

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