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Prediabetes and pregnancy: Early pregnancy HbA_{1c} identifies Australian Aboriginal women with high-risk of gestational diabetes mellitus and adverse perinatal outcomes

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ABSTRACT

Aims: To assess whether early pregnancy HbA_{1c} can predict gestational diabetes mellitus (GDM) and adverse birth outcomes in Australian women.

Methods: Prospective study of 466 women without diabetes, aged ≥16-years at first antenatal presentation. Recruitment was from 27 primary healthcare sites in rural and remote Australia from 9-January 2015 to 31-May 2018. HbA_{1c} was measured with first antenatal investigations (<20-weeks gestation). Primary outcome measure was predictive value of HbA_{1c} for GDM, by routine 75 g oral glucose tolerance test (OGTT; ≥24-weeks gestation), and for large-for-gestational-age (LGA) newborn.

Results: Of 396 (129 Aboriginal) women with routine OGTT, 28.8% had GDM (24.0% Aboriginal). HbA_{1c} ≥5.6% (≥38 mmol/mol) was highly predictive (71.4%, 95% CI; 47.8–88.7%) for GDM in Aboriginal women, and in the total cohort increased risk for LGA newborn (RR 2.04, 95% CI; 1.03–4.01, P = 0.040). There were clear differences between Aboriginal and

Abbreviations: ADIPS, Australasian Diabetes in Pregnancy Society; FLOX, fluoride-oxalate (tube); FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; HbA_{1c}, glycated haemoglobin; IADPSG, International Association of the Diabetes in Pregnancy Study Groups; EDTA, ethylenediamine tetraacetic acid; LGA, large-for-gestational-age; NPV, negative predictive value; OGTT, 75 g oral glucose tolerance test; ORCHID, Optimisation of Rural Clinical and Haematological Indicators for Diabetes in pregnancy (study); PPV, positive predictive value; PG, plasma glucose; RCT, randomized controlled trial; ROC, receiver operating characteristics

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non-Aboriginal women: 16.3% v 5.2% ($P < 0.001$) had elevated HbA_{1c} whereas 12.4% v 29.6% ($P < 0.001$) developed hyperglycemia during pregnancy.
Conclusions: Early pregnancy HbA_{1c} ≥5.6% (≥38 mmol/mol) identifies Aboriginal women with apparent prediabetes and elevated risk of having an LGA newborn. Universal HbA_{1c} at first antenatal presentation could facilitate earlier management of hyperglycemia and improved perinatal outcome in this high-risk population.

1. Introduction

Concomitant with the global rise in type 2 diabetes and prediabetes in women of reproductive age, gestational diabetes mellitus (GDM) is increasing.[1] GDM diagnosed in second or third trimester commonly identifies women with hyperglycemia due to pregnancy induced insulin resistance in the absence of any pre-existing impaired glucose status (*i.e.* 'standard GDM'). However, some women diagnosed with GDM have previously unrecognised prediabetes (impaired glucose status with high-risk for future type 2 diabetes) that could be detected earlier in pregnancy.[2] Prediabetes is associated with both GDM in pregnancy and adverse perinatal outcome in women with polycystic ovarian syndrome and/or undergoing in vitro fertilisation, supporting the importance of early pregnancy screening.[3,4] In the broader population the prevalence of prediabetes going into pregnancy is unclear due to less-than-optimal preconception screening, especially in high-risk Indigenous women.[5–7] To improve birth outcomes recent (2020) Australasian Diabetes in Pregnancy Society (ADIPS) guidelines recommend women with prediabetes (fasting plasma glucose (FPG) 6.1–6.9 mmol/L; or 2-h plasma glucose (PG) 7.8–11.0 mmol/L; or HbA_{1c} 6.0–6.4%, 42–46 mmol/-mol) be managed as having GDM from conception.[8]

The first antenatal visit presents as an opportunity to detect prediabetes, however nonpregnancy thresholds for diagnosis may be inappropriate due to changes in FPG and glycated hemoglobin (HbA_{1c}) throughout pregnancy.[9] FPG drops around 0.4 mmol/L between first and third trimester,[10] and several studies have shown an early FPG ≥5.1 mmol/L has limited accuracy for later GDM.[9] In normoglycemic women HbA_{1c} falls around 0.3–0.8% (4–10 mmol/mol) by second trimester, remaining below pregravid levels throughout gestation.[11–15] An International Association of the Diabetes in Pregnancy Study Groups (IADPSG) working group recently (2016) advised against early diagnosis of GDM by FPG (5.1–6.9 mmol/L), suggesting an early HbA_{1c} ≥5.9% (≥41 mmol/mol) may be preferable.[16] This HbA_{1c} threshold is based on identification of all women with diabetes mellitus in pregnancy by early OGTT (100% sensitivity) and associated two- to three-fold higher risk for adverse pregnancy outcomes, in a New Zealand cohort.[17]

Early HbA_{1c} between 5.4 and 6.0% (36–42 mmol/mol) has demonstrated modest to high specificity (51–100%) with variable positive predictive value (20–100%) for GDM in third trimester.[17–26] The variation in findings may have resulted from significant differences between studies. Threshold selection was either *a priori*, based on nonpregnancy prediabetes criteria,[18–20] or *ad hoc*.[17,21–23,25] GDM prevalence ranged between 6% and 30% using various OGTT protocols.[17–25] Where IADPSG criteria were used, the preanalytical OGTT protocol was not reported,[17–20,22] potentially skewing the GDM incidence due to glycolysis.[28] Early HbA_{1c} screening was either universal,[18–21,24] risk-based,[22,23,25] or done as part of a study,[17,24,26] the latter two potentially biasing the sample.[27] Maximum gestational age at HbA_{1c} ranged between <12- and ≤20-weeks and mean gestational age was between 6.7- and 12.7-weeks (where reported).[18,20,22–24] Most cohorts were derived from populations of mixed ethnicity and differences in background prevalence of prediabetes between ethnic groups were potentially masked by whole cohort analysis. Ethnic variations in early pregnancy HbA_{1c} of up to 0.2% (2.2 mmol/mol) have been reported for women without GDM irrespective of gestational age.[15]

The Optimisation of Rural Clinical and Haematological Indicators for Diabetes in pregnancy (ORCHID) study measured HbA_{1c} at first antenatal presentation in women from rural and remote Australia. The aim for this paper was to identify cut-points for early HbA_{1c} in Aboriginal and non-Aboriginal women that show high specificity for GDM by OGTT (corrected for glycolysis)[28] and increased risk for large-for-gestational-age (LGA).

2. Material and methods

2.1. *Participants*

Pregnant women at first antenatal presentation at a participating site, aged 16 years or older, singleton pregnancy and no documented pre-existing diabetes, were invited to take part. Informed consent was obtained for all participants. Data were collected from 9 January 2015 to 31 May 2018 at 27 sites in the Kimberley, Mid-West, Goldfields, Southwest and Great Southern regions of Western Australia. Aboriginal women were deliberately overrepresented to allow sub-cohort analysis for this high-risk population. Antenatal care providers completed a questionnaire to report baseline maternal characteristics and risk-factors for GDM at first antenatal presentation, including: ethnicity; date of birth (age); height (m); weight (m); body mass index (kg/m^2); parity; antenatal smoking (non-smoker; quit before pregnancy; quit during pregnancy; smoker); personal history of GDM; macrosomia (birthweight >4500 g) in a previous pregnancy; first degree relative with diabetes (type 1, type 2 or GDM); personal history of polycystic ovarian syndrome; and current use of corticosteroid

or antipsychotic medication. Risk-based early screening and management for GDM throughout pregnancy was at the discretion of the antenatal care provider. As per study requirements a HbA_{1c} was requested for all participants irrespective of risk-factor assessment.

2.2. Laboratory testing and diagnostic criteria

At first antenatal investigations an additional venous whole blood sample was collected into an EDTA tube (BD Biosciences, Australia) and transported to the central laboratory for measurement of HbA_{1c} by Tinaquant HbA_{1c} Gen 3 assay (Roche Diagnostics, Australia). Coefficient of variation for the study period was 2%. All HbA_{1c} results were reported to the antenatal care provider.

Local procedures were relied on for collection and measurement of total hemoglobin, ferritin and OGTT. All three analytes were measured in National Association of Testing Authorities, Australia, accredited facilities. Samples for hemoglobin were collected into EDTA tube (BD Biosciences, Australia). Samples for ferritin were collected into serum separator tube (BD Biosciences, Australia). Samples for OGTT were collected into fluoride-oxalate tubes (FLOX; BD Biosciences, Australia), generally stored at room temperature prior to laboratory transport.[28]

Using previously published algorithms,[28] OGTT PG was corrected to predicted results had glycolysis been minimised by following IADPSG recommendations for measuring PG; FLOX tube immediately stored on crushed ice and processed within 1 h.[29] This was done to ensure OGTT results were directly comparable to OGTT from the Hyperglycemia and Adverse Pregnancy Outcomes study from which the IADPSG diagnostic criteria for GDM were derived.

Early HbA_{1c} was defined as measurement before 20-weeks gestation (<140 days) for consistency with other studies.[17,18] Routine OGTT was defined as measurement after 24-weeks gestation (≥168 days); the ADIPS recommended timeframe is between 24- and 28-weeks gestation (168–202 days). Hyperglycemia in pregnancy was classified using ADIPS recommendations for diagnostic criteria, as follows:[30]

Diabetes mellitus in pregnancy: if one or more of the following criteria were met:
Early HbA_{1c} ≥6.5% (48 mmol/mol);
FPG ≥7.0 mmol/L;
2-h PG ≥11.1 mmol/L post 75 g oral glucose load;
Random plasma glucose (RPG) ≥11.1 mmol/L with diabetes symptoms.
GDM: if one or more of the following OGTT criteria were met (following correction for glycolysis, vide supra):
FPG 5.1–6.9 mmol/L;
1-h PG ≥10.0 mmol/L;
2-h PG 8.5–11.0 mmol/L.

2.3. Birth outcomes

Birth outcomes were recorded from hospital discharge summaries, including gestational age at delivery which was used to confirm gestational age at first presentation. Birthweight centiles were calculated using Global bulk centile calculator, GROW v8.0.1, adjusting for gestational age, maternal height, maternal weight at first antenatal visit, parity, ethnicity and infant sex. LGA newborn was defined as birthweight greater than 90th centile.

2.4. Sample size

The primary outcomes were cut-points for early HbA_{1c} to rule-out (95% sensitivity) and rule-in (90% specificity) the subsequent development of GDM based on routine OGTT. The predicted GDM prevalence of the sample was 25%. Out of a sample size of 600, 150 would have GDM. A sensitivity of 95% would detect 143 women with GDM giving a 95% confidence interval (CI) of 91–98%. A specificity of 90% would correctly classify 405 women with normoglycemia giving a 95% CI of 87–93%.

2.5. Statistical analysis

Study data were collected and managed using secure REDCap electronic data capture tools hosted at The University of WA.[31] All analyses were performed with Stata, version 15 (Statacorp). Differences in characteristics between ethnic groups were compared using χ^2 tests for categorical data, and t-tests for continuous data.

The HbA_{1c} equivalence values for screening for high and low-risk of developing GDM were determined from receiver operating characteristics (ROC) curves, using routine OGTT (corrected for glycolysis). Women with diabetes mellitus in pregnancy or GDM diagnosed and managed before 20-weeks gestation were excluded from ROC analysis. The latter due to a lack of evidence and stakeholder consensus for GDM diagnosed based on early glucose investigations using criteria derived from OGTT ≥24-week gestation.[16] Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) were calculated for each HbA_{1c} measurement, stratified by Aboriginal status.

As a first step, regression models were created using a backwards stepwise approach to identify factors associated with i) routine OGTT completion, ii) early HbA_{1c} in controls (no GDM). Following this, a nested mixed effect regression model with antenatal care sites (n = 27) included as a random effect, was fitted for the screening outcome. Significant control covariates for HbA_{1c} and Aboriginal status (Aboriginal; non-Aboriginal) as a ROC covariate was fitted for the adjusted ROC model.

An unadjusted generalised linear model was also developed for the entire cohort with early HbA_{1c} (irrespective of early glucose investigations and routine OGTT completion but excluding deliveries prior to 30 weeks gestation) and used to calculate risk ratio for LGA by HbA_{1c} category, 95% CI is reported in square brackets. $P < 0.05$ was defined as statistically significant.

2.6. Ethics approval

Ethics approval was obtained from the WA Aboriginal Health Ethics Committee (584), WA Country Health Service Human Research Ethics Committee (RGS2924) and supported by the

Kimberley Aboriginal Health Planning Forum Research Subcommittee.

3. Results

Of 694 participants, 541 presented for antenatal care before 20-weeks gestation and continued study participation (Fig. 1). Most Aboriginal (85.7%, 174/203) and non-Aboriginal (86.4%, 292/338) women had an early HbA_{1c} as per study requirements. Generally, Aboriginal women had HbA_{1c} collected earlier in gestation (at first antenatal visit), whereas half (55.5%, 163/292) of non-Aboriginal women had HbA_{1c} collected at the time of first trimester screening (9.0 ± 3.8 weeks v 11.0 ± 2.8 weeks non-Aboriginal, $P < 0.001$). No participants had HbA_{1c} ≥6.5% (≥48 mmol/mol) and all six who retrospectively met IADPSG revised (2016) criteria (HbA_{1c} ≥5.9%, 41 mmol/mol) were Aboriginal.

Routine OGTT was not required for eleven participants recommended for early management of hyperglycemia based on early glucose investigations (diabetes mellitus in pregnancy (1) and GDM (10)). Of the 455 women eligible for routine OGTT, 396 achieved a definitive OGTT result. Overall, 28.8% had GDM by OGTT; none had diabetes mellitus in pregnancy. Baseline characteristics (Table 1) did not significantly differ from the cohort with early HbA_{1c} measurements (n = 466 with delivery >30-weeks gestation; Supplementary Table 1). Early HbA_{1c}, hemoglobin, ferritin and routine OGTT investigations (corrected for glycolysis) for this sub-cohort (n = 396) are reported in Supplementary Table 2.

Despite higher prevalence of additional risk-factors for hyperglycemia in pregnancy than non-Aboriginal women (Table 1), Aboriginal women were less likely to complete a routine OGTT (74.8% v 93.7% non-Aboriginal, P <0.001) and less than half completed testing within the recommended timeframe (47.4% v 85.9% non-Aboriginal, P <0.001). There

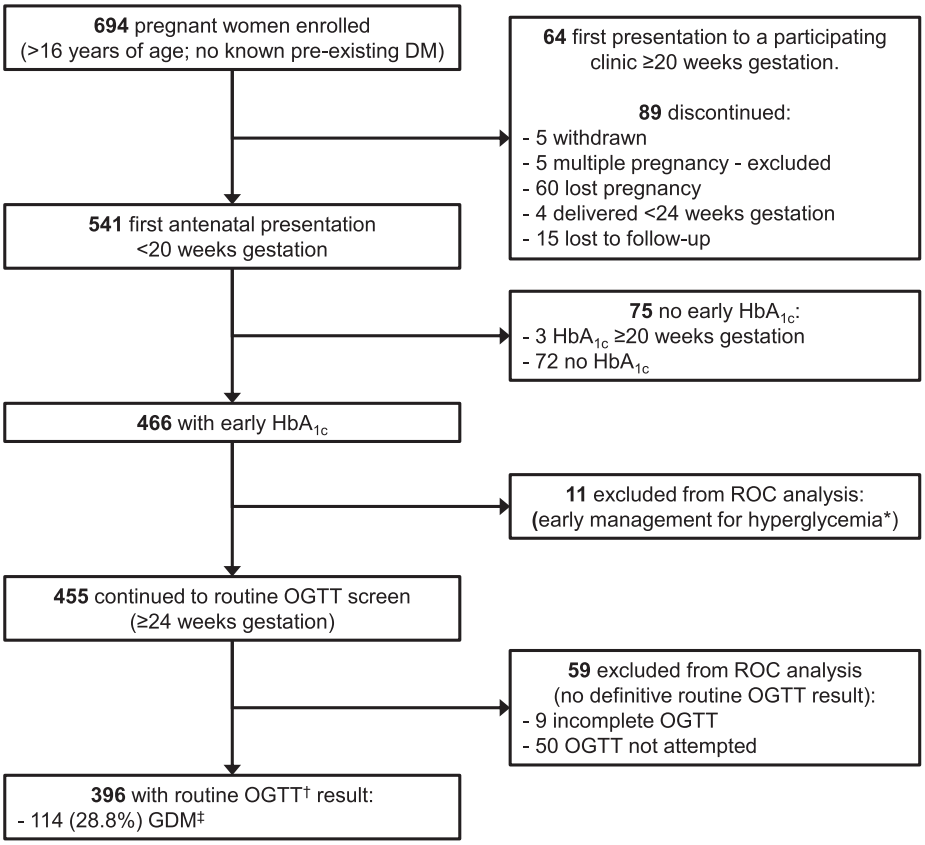

Fig. 1 – Flow chart for prospective ORCHID cohort participation and completion of early and routine screening for hyperglycemia in pregnancy. ORCHID = Optimisation of Rural Clinical and Haematological Indicators for Diabetes in pregnancy study; OGTT = 75 g oral glucose tolerance test; GDM = gestational diabetes mellitus. Hyperglycemia in pregnancy classified using Australasian Diabetes in Pregnancy Society (ADIPS) diagnostic criteria: diabetes mellitus in pregnancy if one or more of the following criteria are met: HbA_{1c} ≥6.5% (≥48 mmol/mol); fasting plasma glucose (FPG) ≥7.0 mmol/L; 2-h plasma glucose (PG) ≥11.1 mmol/L following 75 g glucose load; random PG ≥11.1 mmol/L with diabetes symptoms; and GDM if one or more of the following OGTT criteria are met: FPG 5.1–6.9 mmol/L; 1-h PG ≥10.0 mmol/L; 2-h PG 8.5–11.0 mmol/L. *Early screening for hyperglycemia by glucose investigation based on risk-factor assessment and local clinical judgement, as per ADIPS guidelines; †Routine OGTT PG corrected to predicted results had glycolysis been minimised according to International Association for the Diabetes and Pregnancy Study Groups (IADPSG) recommendations: fluoride-oxalate (FLOX) tube immediately stored on crushed ice and processed within 1 h; correction by $FLOX^{ICE}$ algorithm.[28] ‡Two women with GDM based on definitive FPG results from incomplete OGTT.

Table 1 – Maternal characteristics and prevalence of risk-factors for hyperglycemia in pregnancy in 396 ORCHID participants with early HbA_{1c} and routine OGTT, stratified by Aboriginal status.

	Aboriginal (N = 129)	non-Aboriginal* (N = 267)	P-value
Maternal characteristic			
Age (years)	26.2 ± 5.4	30.5 ± 5.2	<0.001
BMI at first antenatal presentation (kg/m^2)	28.7 ± 7.4	25.9 ± 5.6	<0.001
Parity (prior delivery ≥20-weeks) ≥1 at enrolment	90 (69.8%)	184 (68.9%)	0.863
Any antenatal smoking	52 (40.3%)	31 (11.6%)	<0.001
Length of gestation at first presentation (weeks)	8.5 ± 3.7	8.1 ± 2.9	0.179
Risk-factor for hyperglycemia in pregnancy†			
Age ≥ 40 years	2 (1.5%)	4 (1.5%)	0.968
Obesity (BMI ≥ 30.0 kg/m^2)	48 (37.2%)	54 (20.2%)	<0.001
Previous GDM‡	15 (16.7%)	18 (9.8%)	0.100
Previous macrosomia (birthweight > 4500 g)‡	7 (7.8%)	8 (4.4%)	0.241
Family history of diabetes	60 (46.5%)	58 (21.7%)	<0.001
Polycystic ovarian syndrome	2 (1.6%)	22 (8.2%)	0.009
Use of corticosteroid or antipsychotic medication	3 (2.3%)	2 (0.8%)	0.190
Total number of risk-factors excluding ethnicity:			<0.001
No risk-factors	57 (44.2%)	176 (65.9%)	
One risk-factor	59 (45.7%)	69 (25.8%)	
Two or more risk-factors	13 (10.1%)	22 (8.2%)	

Data are mean ± standard deviation for continuous variables. For categorical variables, data are number (%) of ethnic group. Two-sided t-test P-value reported for comparison between groups for continuous data. Pearson Chi-square test P-value reported for comparison between groups for categorical data. ORCHID = Optimisation of Rural Clinical and Haematological Indicators for Diabetes in pregnancy study; GDM = gestational diabetes mellitus. Data include 396 participants with early HbA_{1c} (<20-weeks gestation) and routine 75 g oral glucose tolerance test (OGTT ≥24-weeks gestation).

*The non-Aboriginal group was predominantly Caucasian (89.1%, 238/267), with the remainder of high-risk ethnicity (Asian 4.1%, 11/267; Maori 3.0%, 8/267; Pacific Islander 1.9%, 5/367; Middle Eastern 1.1%, 3/267; Indigenous African 0.8%, 2/267).

† Risk-factors for hyperglycemia in pregnancy according to Australasian Diabetes in Pregnancy Society guidelines (2014).

‡ Denominator excludes nulliparous women.

was no association between early HbA_{1c} result (or any other maternal characteristic) and routine OGTT completion.

ROC curves stratified by Aboriginal status are shown in Fig. 2. Sensitivity, specificity and predictive values for each HbA_{1c} measurement are provided in Supplementary Tables 3 and 4. An early HbA_{1c} ≥5.6% (≥38 mmol/mol) was the optimal cut-point to identify women with GDM by OGTT with *a priori* >90% specificity for both ethnic groups. Overall, this cut-point had moderate predictive value for GDM (54.3% [36.6–71.2]) but had higher sensitivity (48.4% v 4.8%) and PPV (71.4% v 28.6%) for GDM in Aboriginal participants compared to non-Aboriginal women (Table 2).

In the cohort with an early HbA_{1c} who delivered after 30-weeks gestation (n = 466), threefold more Aboriginal women (14.9% v 5.5%, P = 0.001) had HbA_{1c} ≥5.6% (≥38 mmol/mol) compared to non-Aboriginal women. Furthermore, women above this threshold had twofold (RR 2.04) risk for LGA newborn compared to women below the threshold and without GDM (includes all ethnicities, 54 managed for hyperglycemia in pregnancy, and 59 missing routine OGTT; Table 3). One in five (7/36) women with early HbA_{1c} 5.6–5.8% (38-40 mmol/mol) and one in three (2/6) women with early HbA_{1c} ≥5.9% (≥41 mmol/mol) had an LGA newborn. After excluding women with elevated early HbA_{1c} levels (16.3% Aboriginal women, 5.2% non-Aboriginal women in the ROC sub-cohort), only 12.4% of Aboriginal women with OGTT developed hyperglycemia in pregnancy (GDM diagnosed by routine OGTT) compared to 29.6% of non-Aboriginal women (P < 0.001). LGA incidence in this group of women was similar to women with early HbA_{1c} ≥5.6% (18.9% v 21.4%, P = 0.736; Table 3).

HbA_{1c} <5.0% (<31 mmol/mol) met the *a priori* 95% sensitivity to exclude GDM in 7.9% (21/267) of non-Aboriginal women with NPV of 81.0% [58.1–94.6]. Early HbA_{1c} did not appear useful for excluding GDM in Aboriginal participants (HbA_{1c} <4.9% (<30 mmol/mol), 0.8% (1/129) of participants, sensitivity 96.8% [83.3–99.9%], NPV 0.0% [0.0–97.5]).

4. Discussion

Our study showed that an HbA_{1c} cut-point of ≥5.6% (≥38 mmol/mol) early in pregnancy could identify 15% of Aboriginal women who had elevated risk of having an LGA newborn (21%), and that this result could be obtained significantly earlier than using a routine OGTT. The twofold increased risk for LGA newborn compared to women below this threshold was comparable to the twofold LGA risk in Chinese women with impaired glucose tolerance recognised prior to pregnancy (OR 2.13),[3] and the LGA risk in a mixed New Zealand cohort (RR 1.6).[17] The Chinese study is the evidence base for ADIPS recommendations for treatment of women with pregestational prediabetes as having GDM from conception.[8] The New Zealand study formed the clinical basis for the IADPSG recommendation for GDM diagnosis by early HbA_{1c} ≥5.9% (≥41 mmol/mol).[16]

Due to this increased risk for adverse perinatal outcome some experts suggest women with early HbA_{1c} in the prediabetes range should be labelled as having 'early' GDM or

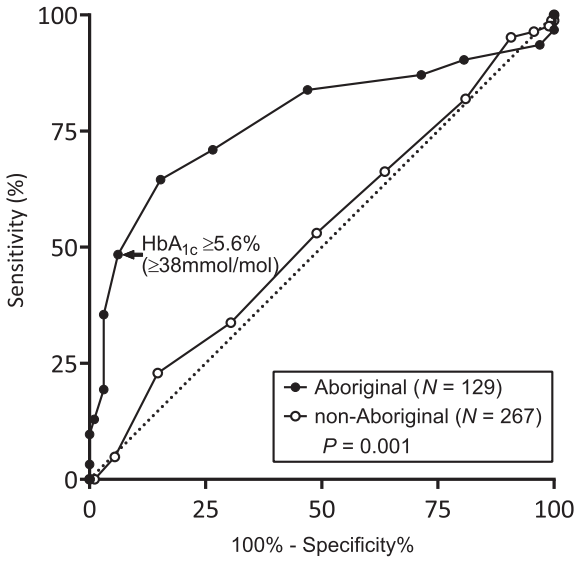

Fig. 2 – Performance of early HbA1c for detecting gestational diabetes mellitus (GDM) at ≥24-weeks gestation, after correction for glycolysis, in 396 ORCHID participants, stratified by Aboriginal status. Receiver operating characteristic curve of early HbA_{1c} for GDM diagnosed by routine 75 g oral glucose tolerance test (OGTT). Data include 396 participants with results for early HbA_{1c} (<20-weeks gestation) and routine OGTT (≥24-weeks gestation). OGTT plasma glucose (PG) corrected to predicted results had glycolysis been minimised according to International Association for the Diabetes and Pregnancy Study Groups (IADPSG) recommendations: fluoride-oxalate (FLOX) tube immediately stored on crushed ice and processed within 1 h; correction by $FLOX^{ICE}$ algorithm.[28] GDM diagnosed by Australasian Diabetes in Pregnancy Society (2014) endorsed IADPSG diagnostic criteria: one or more routine OGTT PG meeting the following thresholds: FPG 5.1–6.9 mmol/L; 1-h PG ≥10.0 mmol/L; 2-h PG 8.5–11.0 mmol/L. Includes two participants with GDM by incomplete OGTT.

'pregestational prediabetes' (*i.e.* they had hyperglycemia before pregnancy). This would then distinguish them from women with 'standard' GDM,[11,32] which develops after 20-weeks gestation due to pregnancy induced insulin resistance.[33,34] Further supporting evidence for referring to women in the ORCHID cohort as having pregestational prediabetes is the range of lower limits for HbA_{1c} used internationally to diagnose prediabetes in the nonpregnant population (≥5.7 to ≥6.0%, ≥39 to ≥42 mmol/mol),[35,36] the ~ 0.5% (~6 mmol/mol) drop in HbA_{1c} by second trimester,[11] the estimated high levels of prediabetes in young Aboriginal people from Northern Australia (12–28%),[5] and less than optimal preconception screening coverage.[6]

Differentiation of women with 'pregestational prediabetes' (16.3% of Aboriginal women in our cohort with HbA_{1c} ≥5.6%, 38 mmol/mol) from those who develop GDM in the second half of pregnancy (12.4% of Aboriginal women in our cohort) may be clinically relevant. A review of several small studies in women referred for self-monitoring of blood glucose based on elevated early HbA_{1c} showed pharmaceutical intervention is often required prior to 24-weeks gestation in women with HbA_{1c} 5.7–5.9% (39–41 mmol/mol).[11] Larger randomized controlled trials (RCT) are necessary to determine if this translates into improved perinatal outcome whilst avoiding small-for-gestational-age newborn. For Aboriginal women, their families and their communities, a co-designed, culturally appropriate intervention to manage hyperglycemia in early pregnancy is essential. An RCT specifically for Aboriginal women would then be required to assess the clinical benefit of management of those with HbA_{1c} ≥5.6% (≥38 mmol/mol) given the significant differences between ethnic groups in our study, including lower OGTT uptake.

In the current study the optimal HbA_{1c} threshold to predict abnormal routine OGTT was the same between ethnic groups. However, most (71.4%) Aboriginal women with an early HbA_{1c} ≥5.6% (≥38 mmol/mol) went on to have an abnormal routine OGTT compared to only 28.6% of non-Aboriginal women. Despite the lower HbA_{1c} threshold this PPV of 71.4% was also higher than other studies using IADPSG criteria (HbA_{1c} ≥5.7%, 39 mmol/mol, PPV 29–48%;[19,20,22] HbA_{1c} ≥5.9%, 41 mmol/mol, PPV 50%).[17] Notably the preanalytical OGTT protocol was not described in these papers, which can impact GDM incidence and consequently PPV.[29] However, the high underlying prevalence of prediabetes is the most likely explanation for the high PPV observed in Aboriginal women from our study compared to non-Aboriginal women. The overall PPV was lower (54%) in our cohort when analysed as a whole group and it is possible that differences in PPV between ethnic-groups with variable prevalence of prediabetes were masked in whole group analysis of other study cohorts.

The differences in sensitivity for GDM (48.4% v 4.8% non-Aboriginal) between the two ethnic groups appear to reflect differences in the aetiology: hyperglycemia present before pregnancy (pregestational prediabetes) versus 'standard' GDM. Whilst the crude (not age-standardised) GDM incidence (28.8%) was similar between groups, significantly more Aboriginal women had an early HbA_{1c} ≥5.6%, ≥38 mmol/mol compared to non-Aboriginal women (16.3% v 5.2%). Nearly all (95%) GDM diagnoses in non-Aboriginal women were in women with early HbA_{1c} <5.6% (<38 mmol/mol) suggesting these women were normoglycemic at conception and developed glucose intolerance in the second half of pregnancy, that is 'standard' GDM. These data suggest that early HbA_{1c} is not effective in identifying women who are at risk of developing 'standard' GDM.

Despite amenability to OGTT at recruitment, many Aboriginal women either did not complete an OGTT or delayed testing until well into the third trimester. By contrast, uptake of early HbA_{1c} was high. Potentially, following a co-design process, an early HbA_{1c} measurement could be used to triage Aboriginal women for further screening and reduce the OGTT testing burden in Aboriginal pregnancies (by 15% in our cohort with early HbA_{1c}). Women with HbA_{1c} ≥5.9% (≥41 mmol/mol) could be managed as having GDM from conception (3.5% in our cohort). Targeted healthy lifestyle advice could be provided early in pregnancy for women with HbA_{1c} 5.6–5.8% (38–40 mmol/mol) with self-monitoring of blood glucose initiated between 20- and 24-weeks gestation, on average 5–9 weeks earlier than routine OGTT completion (11.4%

Table 2 – Sensitivity, specificity, predictive values and classification by early HbA_{1c} ≥ 5.6% for gestational diabetes mellitus (GDM) at ≥ 24-weeks gestation after correction for glycolysis, stratified by Aboriginal status.

	Aboriginal (N = 129)	non-Aboriginal (N = 267)	P-value
n with GDM by OGTT	31 (24.0%)	83 (31.1%)	0.146
n with HbA_{1c} ≥5.6%	21 (16.3%)	14 (5.2%)	<0.001
n with HbA_{1c} ≥5.6% & GDM by OGTT	15 (11.7%)	4 (1.5%)	<0.001
Sensitivity (95% CI, %)	48.4 (30.2–66.9)	4.8 (1.3–11.9)	
Adjusted sensitivity (95% CI, %)*	52.2 (37.2–67.2)	18.2 (10.6–25.8)	
Specificity (95% CI, %)	93.9 (87.2–97.7)	94.6 (90.2–97.4)	
Positive predictive value (95% CI, %)	71.4 (47.8–88.7)	28.6 (8.4–58.1%)	
Negative predictive value (95% CI, %)	85.2 (77.1–91.3)	68.8 (62.7–74.4)	
Correctly classified (%)	83.0	66.7	

N = denominator, total number in ethnic group; *n* = numerator, number with criteria; CI = confidence interval. HbA_{1c} 5.6% is equivalent to 38 mmol/mol by International Federation of Clinical Chemistry (IFCC) units. Data include 396 participants with early HbA_{1c} (<20-weeks gestation) and routine 75 g oral glucose tolerance test (OGTT, ≥24-weeks gestation). OGTT plasma glucose (PG) corrected to predicted results, had glycolysis been minimised according to International Association for the Diabetes and Pregnancy Study Groups (IADPSG) recommendations: fluoride-oxalate (FLOX) tube immediately stored on crushed ice and processed within 1 h; correction by $FLOX^{ICE}$ algorithm.[28] GDM diagnosed by Australasian Diabetes in Pregnancy Society (2014) endorsed IADPSG diagnostic criteria: one or more routine OGTT PG meeting the following thresholds: Fasting PG 5.1–6.9 mmol/L; 1-h PG ≥ 10.0 mmol/L; 2-h PG 8.5–11.0 mmol/L. Includes two participants with GDM by incomplete OGTT.

*Model adjustment for covariates with independent association with HbA_{1c} in women without GDM (maternal hemoglobin as a continuous variable, obesity (not-obese; obese) and age (<40 years; ≥40 years)). Model predicted sensitivity for GDM reported at the 90% specificity point.

Table 3 – Risk for large-for-gestational-age (LGA) newborn stratified by early HbA_{1c} and routine OGTT status in 466 women with early HbA_{1c}.

Glycemic status	Proportion with LGA (*n*/*N*)	RR [95% CI], P-value
Early HbA_{1c} <5.6%, no OGTT	7.9% (5/63)	0.75 [0.30–1.88], 0.544
Early HbA_{1c} <5.6%, no GDM by OGTT	10.5% (28/266)	1.0
Early HbA_{1c} <5.6%, GDM by OGTT	18.9% (18/95)	1.80 [1.04–3.10], 0.034
Early HbA_{1c} ≥5.6%*	21.4% (9/42)	2.04 [1.03–4.01], 0.040

OGTT = 75 g oral glucose tolerance test; *n* = numerator, number with LGA newborn; *N* = denominator, total number in glycemic status group; RR = relative risk; CI = confidence interval; GDM = gestational diabetes mellitus. HbA_{1c} 5.6% is equivalent to 38 mmol/mol by International Federation of Clinical Chemistry (IFCC) units. Data include 466 participants with early HbA_{1c} (<20-weeks gestation) who delivered after 30-weeks gestation; as the aim of this analysis was to assess the ability of an early HbA_{1c} to identify risk for LGA, 70 women without routine OGTT were included (including 11 women with hyperglycemia identified by early glucose investigations (HbA_{1c} <5.6% (9); HbA_{1c} ≥5.6% (2)). Routine (≥24-weeks gestation) OGTT plasma glucose (PG) corrected to predicted results had glycolysis been minimised according to International Association for the Diabetes and Pregnancy Study Groups (IADPSG) recommendations: fluoride-oxalate (FLOX) tube immediately stored on crushed ice and processed within 1 h; correction by $FLOX^{ICE}$ algorithm.[28] GDM diagnosed by Australasian Diabetes in Pregnancy Society (2014) endorsed IADPSG diagnostic criteria: one or more routine OGTT PG meeting the following thresholds: FPG 5.1–6.9 mmol/L; 1-h PG ≥10.0 mmol/L; 2-h PG 8.5–11.0 mmol/L. Birthweight centiles were calculated using Global bulk centile calculator, GROW v8.0.1, adjusting for gestational age, maternal height, maternal weight at first antenatal visit, parity, ethnicity and infant sex. Risk for LGA newborn calculated relative to group with HbA_{1c} <5.6% without GDM by routine OGTT.

*Early HbA_{1c} ≥5.6% group includes: 7 women with no routine OGTT (4 LGA); 16 women with no GDM by routine OGTT (0 LGA); and 19 women with GDM by routine OGTT (5 LGA).

in our cohort). An OGTT could continue to be offered after 24-weeks gestation for the remaining women with early HbA_{1c} <5.6% (<38 mmol/mol). Investigation of more acceptable screening strategies is required to improve detection of 'standard' GDM in this group.

There are several limitations of the current study. LGA outcome frequency and the proportion of women with HbA_{1c} ≥5.6% (≥38 mmol/mol) was too small to allow adjustment for potential confounding factors, therefore we could not determine an independent association between increased LGA and HbA_{1c} ≥5.6% (≥38 mmol/mol). Completion of OGTT in Aboriginal women was low; however, as there were no documented differences between those who did and did not complete OGTT it is unlikely that OGTT screening outcomes would have differed significantly. OGTT were corrected to predicted result to account for preanalytical glycolysis providing more accurate glucose results.[28] We also cannot assert that our cohort is representative of the underlying population; prevalence of anaemia was low compared to reports of up to 50% in remote Aboriginal women.[37] Maternal hemoglobin status, BMI and age may be relevant when interpreting HbA_{1c} measurements that are close to suggested thresholds. To validate our findings, we are currently auditing screening outcomes (approximately 1200 Aboriginal pregnancies from 2018 to 2021) in regional sites that have implemented both universal early HbA_{1c} and are using

fluoride-citrate collection tubes to immediately stabilise glucose in OGTT samples.

Due to high patient acceptability, a universal HbA_{1c} at first antenatal presentation for Aboriginal women and other women at high-risk of unrecognised pregestational prediabetes could lead to more comprehensive screening coverage and earlier management of hyperglycemia to reduce adverse perinatal outcome. In line with the 2013–2020 World Health Organization global action plan for prevention and control of noncommunicable diseases,[38] preconception care guidelines for general practitioners need to be updated to clearly stipulate screening for diabetes and prediabetes in high-risk women of child-bearing age to optimise pregnancy outcomes.

CRediT authorship contribution statement

Emma L. Jamieson: Data curation, Formal analysis, Funding acquisition, Investigation, Project administration, Resources, Writing - original draft, Writing - review & editing. **Erica P. Spry:** Investigation, Project administration, Resources, Writing - review & editing. **Andrew B. Kirke:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing - review & editing. **Emma Griffiths:** Conceptualization, Investigation, Methodology, Writing - review & editing. **Cynthia Porter:** Investigation, Writing - review & editing. **Carly Roxburgh:** Conceptualization, Investigation, Methodology, Writing - review & editing. **Sally Singleton:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing - review & editing. **Kylie Sterry:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing - review & editing. **David N. Atkinson:** Conceptualization, Funding acquisition, Methodology, Writing - review & editing. **Julia V. Marley:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Statement of Originality and Authorship

Guarantor

All authors (E. Jamieson, E. Spry, A. Kirke, E. Griffiths, C. Porter, C. Roxburgh, S. Singleton, K. Sterry, D. Atkinson and J. Marley) certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

Prior publication in abstract form

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2021.108868.

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