Early pregnancy HbA_{1c} as the first screening test for gestational diabetes: results from three prospective cohorts

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Summary

Background More than 90% of gestational diabetes cases are estimated to occur in low-income and middle-income countries (LMICs). Most current guidelines recommend an oral glucose tolerance test (OGTT) at 24–28 weeks of gestation. The OGTT is burdensome, especially in LMICs, resulting in a high proportion of women not being screened. We aimed to develop a simple and effective screening strategy for gestational diabetes.

Methods STRiDE, a prospective cohort study, was set up in seven centres in south India and seven centres in western Kenya, and included pregnant women aged 18–50 years of age and at less than 16 weeks of gestation (<20 weeks in Kenya), confirmed by dating ultrasound. We assessed the efficacy of early pregnancy HbA_{1c} (venous and capillary point-of-care), either alone or as part of a composite risk score with age, BMI, and family history of diabetes, in predicting gestational diabetes at 24–28 weeks of gestation, in two LMICs (India and Kenya) and in a UK multi-ethnic population from the PRiDE study. A key secondary outcome was to assess whether an early pregnancy composite risk score can reduce the need for OGTTs. Gestational diabetes was diagnosed using current WHO criteria.

Findings Between Feb 15, 2016, Dec 13, 2019, we enrolled 3070 participants in India and 4104 in Kenya. 4320 participants were included from the PRiDE cohort. Gestational diabetes prevalence by OGTT at 24–28 weeks was 19·2% in India, 3·0% in Kenya, and 14·5% in the UK. Early pregnancy HbA_{1c} was independently associated with incidence of gestational diabetes at 24–28 weeks of gestation. Adjusted risk ratios were 1·60 (95% CI 1·19–2·16) in India, 3·49 (2·8–4·34) in Kenya, and 4·72 (3·82–5·82) in the UK. Composite risk score models that combined venous or point-of-care HbA_{1c} with age, BMI, and family history of diabetes best predicted testing positive for gestational diabetes. A population-specific, two-threshold screening strategy of rule-in and rule-out gestational diabetes using early pregnancy composite risk score could reduce the requirement of OGTTs by 50–64%. For the HbA_{1c}-alone model, the thresholds were 5·4% (rule in) and 4·9% (rule out) in India, 6·0% (rule in) and 5·2% (rule out) in Kenya, and 5·6% (rule in) and 5·2% (rule out) in the UK.

Interpretation Early pregnancy HbA_{1c} offers a simple screening test for gestational diabetes, allowing those at highest risk to receive early intervention and greatly reduce the need for OGTTs. This can also be carried out using point-of-care HbA_{1c} in LMICs.

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Introduction

Gestational diabetes is a major burden for women and maternal care systems all over the world.[1] More than 90% of the global prevalence is estimated to be in low-income and middle-income countries (LMICs), where access to diagnosis and monitoring care remains limited.[2] Although controversy still exists on the method and timing of screening and the thresholds for diagnosis,[3–6] most international and national guidelines recommend using a 75 g oral glucose tolerance test (OGTT) at 24–28 weeks of gestation in a fasted state to diagnose gestational diabetes,[7–9] with an exception of New Zealand criteria, which recommend early pregnancy HbA_{1c} as an initial test.[10] OGTTs are prone to analytical errors and have poor reproducibility.[11] Additionally, OGTTs are difficult to do, especially in LMICs because pregnant women need to travel considerable distances to the laboratory facilities after fasting overnight and then stay for another 2–3 h to complete the test. The evidence for the uptake of OGTTs in LMICs is sparse. Only 20% of health-care providers recommend OGTTs for screening in Nigeria, and the uptake is around 27% in Tanzania.[12,13] Even in high-income countries, 25–70% of women miss OGTT screening.[14,15] Missing gestational diabetes can be associated with a 44% higher risk of stillbirth,[14] although evidence is limited. Thus, a screening strategy that is simple, highly reproducible, and feasible is required, highlighted as a priority by WHO, particularly in LMICs.[16]

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Research in context

Evidence before the study

The oral glucose tolerance test (OGTT) is currently considered the gold-standard approach for screening and diagnosis of gestational diabetes. It is typically conducted at 24–28 weeks of gestation and requires women to attend a facility with appropriate laboratory infrastructure, in a fasting state. This is particularly challenging in rural settings in India, Kenya, and other low-income and middle-income countries (LMICs). In addition, excess fetal adiposity might have occurred by this time. WHO has therefore recommended developing a simple and effective screening strategy in early pregnancy as a priority. Fasting plasma glucose (FPG) and HbA_{1c} have been proposed as alternatives to the OGTT, but FPG has the same issue of fasting and evidence for using HbA_{1c} to diagnose gestational diabetes is sparse. There is some evidence for using HbA_{1c} as a rule-in test for diagnosing gestational diabetes. However, the role of HbA_{1c} has not been prospectively tested for risk stratification in early pregnancy, either on its own or as a composite risk score, with common clinical risk factors. A retrospective study showed it might be of value in a US population. Therefore, the value of using HbA_{1c} needs to be tested in specific populations because the accuracy can vary. We searched PubMed for English-language research articles with the search terms, "gestational diabetes", "GDM", "HbA1c", "risk prediction", "composite risk score" initially on Feb 15, 2015, before grant application and updated on July 15, 2016, before study recruitment.

Added value of the study

Our study showed that early pregnancy HbA_{1c}, on its own or as a composite risk score with common risk factors, can be used to predict about 50% of gestational diabetes at 24–28 weeks of gestation. The risk ratios of developing gestational diabetes were different in different populations, highlighting the need for population-specific thresholds. Using two thresholds for rule-in and rule-out gestational diabetes helps with risk stratification in early pregnancy. The need for OGTTs can be reduced by 50–64% in different populations by using venous or point-of-care HbA_{1c}.

Implications of all the available evidence

Our findings can help to improve overall screening rates for gestational diabetes in LMICs and reduce the burden of OGTTs. This can help to redirect the resources required for conducting OGTTs to earlier intervention for women at higher risk. For effective risk stratification, population-specific thresholds are needed. Future randomised controlled trials are required to investigate whether this approach helps to reduce adverse pregnancy outcomes or reduce adverse offspring programming.

Recent studies highlighted that higher fetal adiposity might be present before the diagnosis of gestational diabetes at 24–28 weeks of gestation.[17,18] Even in research settings, diagnosis of gestational diabetes around 28 weeks and subsequent management at best reduces adverse pregnancy and birth outcomes by 50%, and might adversely programme the offspring's adiposity and metabolic risk despite adequate glucose control.[1,19] Therefore, there is a need to change practice towards earlier detection of gestational diabetes especially for those at higher risk of developing adverse outcomes, which can enable early intervention.

The OGTT has been replaced by HbA_{1c} in most high-income countries in non-pregnant adults for the diagnosis of diabetes. HbA_{1c} is highly reproducible and can be carried out at point of care using a finger-prick test.[20] The newer point-of-care HbA_{1c} kits have better validity, are battery operated, and can therefore be carried out even in remote areas in LMICs.[20,21] Previous studies testing HbA_{1c} in early pregnancy have focused mainly on cutoff values above which gestational diabetes is very likely. On the contrary, studies that rule out gestational diabetes based on HbA_{1c} thresholds are sparse and from single centres.[22–24] Although some investigators have tested the usefulness of composite risk prediction models by combining clinical and other biomarkers for predicting gestational diabetes,[25] none have tested the usefulness of a composite risk score, by combining early pregnancy HbA_{1c} with common risk factors such as age, BMI, and family history of diabetes to predict incident gestational diabetes or assessed their utility in reducing the need for OGTT at 24–28 weeks.

We tested whether HbA_{1c} with or without common risk factors in early pregnancy can predict gestational diabetes in two LMIC populations (India and Kenya) and in one high-income, multi-ethnic population (UK). We additionally developed and validated a composite risk factor prediction model to reduce the burden of OGTT in these countries.

Methods

Study design and participants

STRiDE (NCT03005600), a prospective cohort study, was set up in seven centres in south India (Chennai, Hyderabad, and Puducherry) and seven centres in western Kenya (Eldoret).[26] The study design and protocol was approved by respective ethics committees in India and Kenya (appendix p 4). The third cohort from the UK used additional HbA_{1c} data from the PRiDE study (UK-representative population across ten centres).[27] The steering group designed the protocol and oversaw the recruitment and conduct of STRiDE.

In all cohorts, all pregnant women aged 18–50 years of age and at less than 16 weeks of gestation (<20 weeks in Kenya), confirmed by dating ultrasound, were eligible to be included in the study. We excluded women with type 1 or type 2 diabetes, on metformin therapy up to 6 weeks before recruitment for anovulation or infertility, severe

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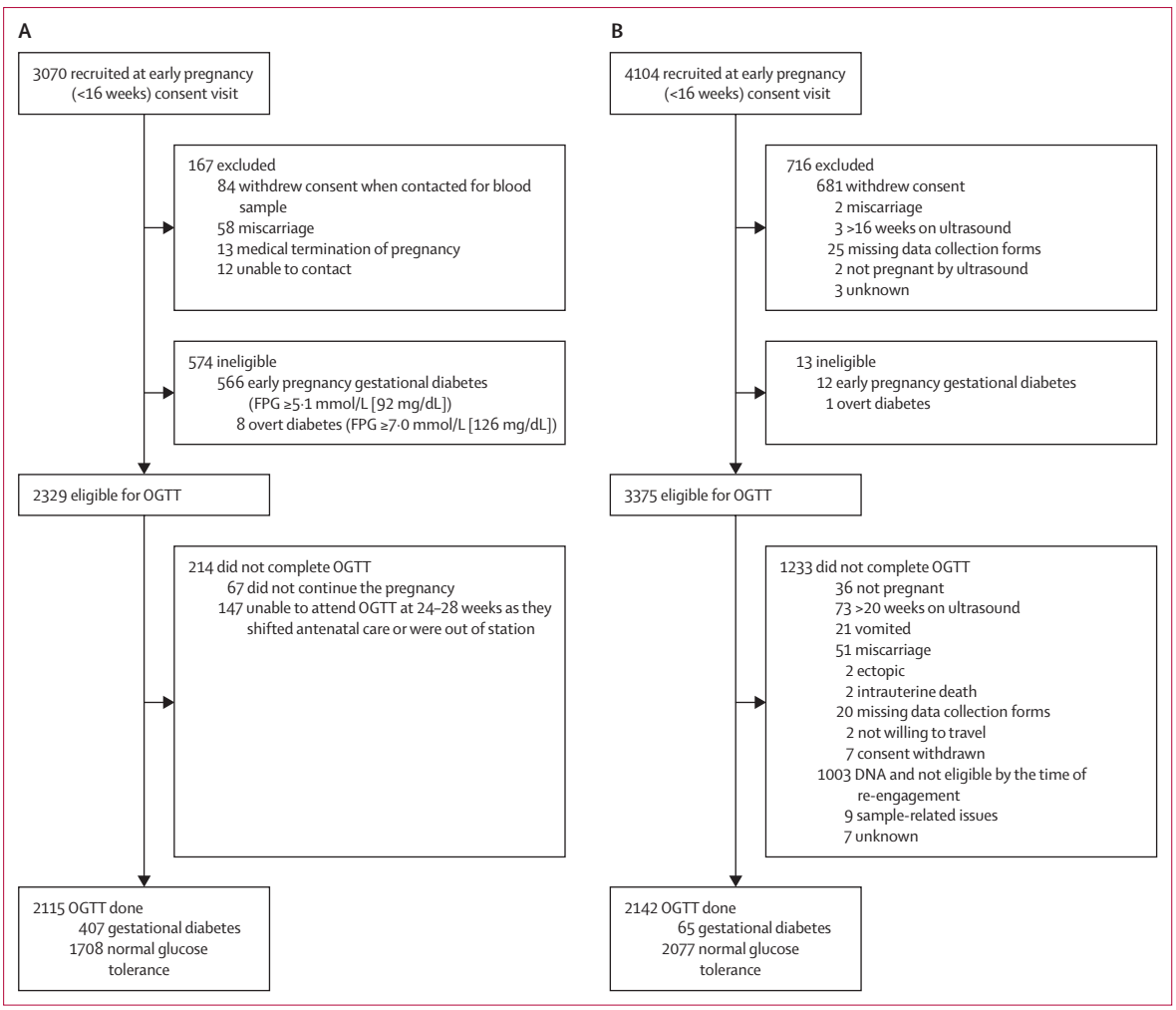

Figure 1: **Study flow**
(A) STRiDE India. (B) STRiDE Kenya. FPG=fasting plasma glucose. OGTT=oral glucose tolerance test.

anaemia (haemoglobin <8 g/L), abnormal haemoglobin or haemoglobinopathies, or any serious medical illness.

In STRiDE, study sites were selected to represent all socioeconomic groups in the respective regions of south India and western Kenya. All women were approached at the booking visit for written informed consent and returned for a fasting or a random visit for a screening venous blood sample (for plasma glucose and HbA_{1c}) and a point-of-care finger-prick test (glucose and HbA_{1c}). Women were excluded from OGTTs if fasting plasma glucose (FPG) or random plasma glucose or HbA_{1c} was in the diabetes range (FPG ≥7·0 mmol/L; random plasma glucose ≥11·1 mmol/L; HbA_{1c} ≥6·5% [≥48 mmol/mol], defined by WHO criteria)[8] or FPG was in the gestational diabetes range (≥5·1 mmol/L and ≤6·9 mmol/L), as defined by the International Association of Diabetes and Pregnancy Study Groups (IADPSG).[28] All other women completed their 75 g OGTT between 24 weeks and 28 weeks. Gestational diabetes was diagnosed by 2010 IADPSG or 2013 WHO criteria. Local guidelines were followed for the management of gestational diabetes.

Objectives

The primary objective of the study was to test whether venous HbA_{1c} on its own or in a composite risk score with age, BMI, and family history of diabetes in early pregnancy accurately identifies women who test positive for gestational diabetes by an OGTT at 24–28 weeks of pregnancy. It is well known that these three are the common risk factors for developing gestational diabetes and are simple to measure and document in most health-care settings. The secondary objectives were to assess whether use of a composite risk score using HbA_{1c} as an initial screening test could reduce the number of OGTTs required for diagnosing gestational diabetes; to assess the role of point-of-care HbA_{1c} compared with venous HbA_{1c}; and to assess the role of other easily measurable risk factors in LMICs such as parity, socioeconomic status (SES), gestational

	Overall (n=2115)	Gestational diabetes (n=407)	No gestational diabetes (n=1708)
Age, years	26·9 (4·1)	27·5 (4·3)	26·7 (4·0)
Height, cm	156·2 (6·2)	156·0 (6·6)	156·3 (6·1)
Weight, kg	59·2 (12·6)	60·2 (13·4)	58·9 (12·3)
BMI, kg/m^2	24·2 (4·6)	24·6 (4·8)	24·1 (4·6)
Nulliparous	1291 (61·0%)	254 (62·4%)	1037 (60·7%)
Family history of diabetes	860 (40·7%)	195 (47·9%)	665 (38·9%)
Systolic blood pressure, mm Hg	102 (10·0)	103·6 (9·8)	101·6 (10·0)
Missing	186	46	140
Diastolic blood pressure, mm Hg	68·6 (8·9)	70 (8·9)	68·3 (8·8)
Missing	186	46	140
Gestational age at recruitment, weeks	10·5 (2·9)	10·0 (2·8)	10·6 (3·0)
Gestational age at OGTT, weeks	25·4 (3·6)	25·4 (3·0)	25·4 (3·7)
Missing	232	62	170
HbA_{1c}			
Point of care, %	5·15% (0·49)	5·22% (0·54)	5·14% (0·48)
Point of care, mmol/mol	32·81 (5·39)	33·60 (5·91)	32·63 (5·25)
Missing	387	85	302
Venous, %	5·08% (0·33)	5·14% (0·37)	5·07% (0·32)
Venous, mmol/mol	32·08 (3·60)	32·70 (4·03)	31·93 (3·48)
Missing	169	40	129

Data are mean (SD), n (%), or n. OGTT=oral glucose tolerance test.

Table 1: **Maternal characteristics in early pregnancy in STRiDE India**

weight gain, and blood pressure for prediction of gestational diabetes. The rationale for using these covariates are presented in detail in the protocol (appendix p 5) and the likely direction of relationships is in the appendix (p 40).

Statistical analysis

We planned to recruit 3400 women in India and 4000 women in Kenya in early pregnancy, anticipating 320 women in India and 120 women in Kenya to be diagnosed with gestational diabetes at 24–28 weeks. It is generally accepted that for each risk factor included in a model, at least ten observations with positive outcomes are needed for logistic regression analysis.[29] The detailed assumptions on sample size calculations, handling of missing data (multivariate imputation by chained equations algorithm [20 imputations]), and statistical analysis plan are presented in the protocol (appendix p 10).

We did two sets of analyses. First, Poisson regression models with the outcome being presence or absence of gestational diabetes based on the OGTT result were fitted to determine how HbA_{1c} (model 1a) and age, BMI, and family history of diabetes predicted gestational diabetes. Model 1b tested the association of early pregnancy age, BMI, and family history diabetes, adjusted for each other. Then model 2 tested and reported the adjusted risk ratio (RR) of HbA_{1c}, for gestational diabetes diagnosis, adjusted for age, BMI, and family history of diabetes. Additional analyses using waist-to-height ratio were presented instead of BMI to assess the potential role of waist circumference. Model 3 included other variables that were associated with gestational diabetes in our dataset (gestational age, parity, SES, and systolic and diastolic blood pressure). The unadjusted RRs were determined to select the covariates adjusted in this model (appendix p 16). The Akaike information criterion (AIC) was used to compare the composite risk prediction models (models 1a, 1b, 2, and 3).[29] The model is considered better when the AIC value is lower by more than 3.[29]

Second, receiver operating characteristic (ROC) curves were used to identify the single best composite risk factor threshold for prediction of gestational diabetes. To evaluate performance of the prediction models (model development), the area under the ROC curve (AUC) was calculated. Validation was carried out by using bootstrapping with 1000 iterations in all three cohorts.[30] We estimated and report the optimism-corrected AUC values for all models.

In the absence of a single best threshold, the two-threshold approach was used to rule in women who will develop gestational diabetes and rule out those who will not develop gestational diabetes at different levels of sensitivity and specificity, which results in a similar burden of gestational diabetes compared with the OGTT-based approach. These analyses were repeated in the PRiDE cohort. The proportion of OGTTs that can be avoided by this rule-in and rule-out two-threshold approach in each of the models was calculated. All analyses were done in R (version 4.3.2).

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Feb 15, 2016, Dec 13, 2019, we enrolled 7174 participants (3070 in India and 4104 in Kenya). After excluding early pregnancy type 2 diabetes and gestational diabetes at booking, 407 (19·2%) women in India and 65 (3·0%) women in Kenya had gestational diabetes based on OGTTs (figure 1). Baseline characteristics of participants with and without gestational diabetes are shown in tables 1 and 2. Participants were well represented across the SES categories and representative of the regions studied (appendix p 41). In both India and Kenya, women who missed OGTTs were younger and had lower BMI than those who underwent OGTTs (appendix pp 17–18). Early pregnancy venous and point-of-care HbA_{1c} values were fairly normally distributed (figure 2). Mean venous HbA_{1c} was marginally higher in Kenya than in India, but the point-of-care HbA_{1c} values were similar (tables 1, 2; figure 2). The UK PRiDE study cohort (n=4320; 565 [14·5%] with gestational diabetes)

participant flow, HbA_{1c} distribution, and baseline characteristics are shown in the appendix pp 19–20, 42–43).

The adjusted RRs for HbA_{1c} were 1·60 (95% CI 1·19–2·16) in India, 3·49 (2·8–4·34) in Kenya, and 4·72 (3·82–5·82) in the UK. The composite risk score model with HbA_{1c}, age, BMI, and family history of diabetes (model 2) had the best AICs in all populations (table 3). Notably, HbA_{1c}, on its own, had better AIC than model 1b in Kenya, but the opposite was seen in India. Compared with the STRiDE cohorts, the RRs in the PRiDE cohort were higher, but similar to STRiDE, had best AIC value for model 2 (table 3). Addition of other contributing risk factors such as SES, parity, gestational age at recruitment, and blood pressure significantly improved the AIC values in India and Kenya (appendix p 21). The predictive ability to diagnose gestational diabetes improved marginally when BMI was replaced with waist-to-height ratio in India but not in Kenya or the UK (appendix p 22). Similarly, replacing BMI with height and mid-upper arm circumference in Kenya did not improve predictive ability further (appendix p 22). The appendix (p 44) shows the RRs of gestational diabetes by HbA_{1c} category. Inclusion of women with early gestational diabetes in the Indian cohort (those who had FPG ≥5·1 mmol/L in early pregnancy) changed the RR to 1·78 (95% CI 1·5–2·2) for model 1a, and 1·51 (1·2–1·9) for model 2.

ROC curves were plotted to identify a threshold for gestational diabetes diagnosis. Bootstrap-based optimism-corrected AUCs were calculated for each of the above models to evaluate their predictive performances. This did not reveal a single threshold that would be suitable (neither by HbA_{1c} alone nor with other risk factors), although the AUC for model 2 in Kenya was moderate at 77·2% (appendix pp 45–47). Addition of FPG into model 2 in India and Kenya only marginally improved the AUC (appendix p 48). We tested the two-threshold approach for both ruling in and ruling out gestational diabetes with thresholds in each population chosen to ensure gestational diabetes prevalence was similar to, or lower than the ones based on the OGTT approach. This was to ensure that the overall burden of gestational diabetes did not increase in respective countries. The exact sensitivity and specificities are shown in table 4. The proportions of OGTT that can be avoided by this method using HbA_{1c} alone (model 1a) were 42·0% in India, 50·4% in Kenya, and 47·9% in the UK. In model 2, these proportions improved to 49·8% in India, 64·0% in Kenya, and 54·7% in the UK (table 4). The mean baseline age, BMI, blood pressure, and family history of diabetes were highest in women who were ruled in to have gestational diabetes (highest-risk group), lowest in the ruled-out category (lowest-risk group) and were in between in the middle-risk group. Detailed characteristics of the relevant risk factors and key outcomes are shown in the appendix (pp 23–25). Across all three populations, of 199 women who were false negative (lowest risk group) by this approach, 181 (91%) had only one abnormal glucose value (appendix p 26) with lower mean glucose values than the rest of the women with gestational diabetes (appendix p 27). Their median glucose values were also only marginally higher than the gestational diabetes diagnostic thresholds (appendix p 28). In addition, the median glucose values were marginally lower to any one of the diagnostic thresholds in the false positives. The observed outcomes were similar or higher in this group than in women who were diagnosed by OGTTs alone (appendix p 29). The positive predictive values and negative predictive values of the proposed two-threshold approach for the three populations are shown in the appendix (p 30).

When point-of-care HbA_{1c} was used instead of the venous HbA_{1c}, the performance of the models was similar (appendix p 31) and for the two-threshold approach, proportions of OGTTs that can be avoided were also similar (52·5% in India and 63·6% in Kenya; appendix p 32). The appendix (pp 33–34) shows the proportions of OGTTs that could be avoided if different rule-in and rule-out thresholds (80%, 85%, 90%, and 95%) are used to aid local decision making based on resource availability. The adjusted RRs of the various models against NICE diagnostic thresholds were marginally higher (appendix

	Overall (n=2142)	Gestational diabetes (n=65)	No gestational diabetes (n=2077)
Age, years	26·2 (5·0)	28·5 (6·0)	26·2 (5·0)
Height, cm	161·2 (6·9)	160·6 (6·5)	161·2 (6·9)
Missing	361	15	346
Weight, kg	63·7 (12·0)	72·3 (13·3)	63·4 (11·9)
BMI, kg/m²	24·5 (4·5)	28·6 (5·4)	24·4 (4·4)
Missing	363	15	348
Nulliparous	1063/2141 (49·6%)	19 (29·2%)	1044/2076 (50·3%)
Family history of diabetes	310/2131 (14·5%)	15/64 (23·4%)	295/2067 (14·3%)
Systolic blood pressure, mm Hg	113·5 (12·4)	119·7 (13·3)	113·3 (12·3)
Missing	91	3	88
Diastolic blood pressure, mm Hg	70·2 (9·1)	74·6 (9·2)	70·0 (9·0)
Missing	92	3	89
Gestational age at recruitment, weeks	15·5 (3·1)	15·6 (3·2)	15·5 (3·1)
Missing	76	5	71
Gestational age at OGTT, weeks	25·5 (2·5)	25·9 (2·2)	25·5 (2·5)
Missing	138	8	130
HbA_{1c}			
Point of care, %	5·13% (0·56)	5·59% (0·86)	5·11% (0·54)
Point of care, mmol/mol	32·55 (6·07)	37·59 (9·44)	32·4 (5·88)
Missing	25	2	23
Venous, %	5·23% (0·44)	5·66% (0·74)	5·21% (0·42)
Venous, mmol/mol	33·64 (4·82)	38·35 (8·14)	33·49 (4·60)
Missing	31	0	31

Data are mean (SD), n (%), or n. OGTT=oral glucose tolerance test.

Table 2: **Maternal characteristics in early pregnancy in STRiDE Kenya**

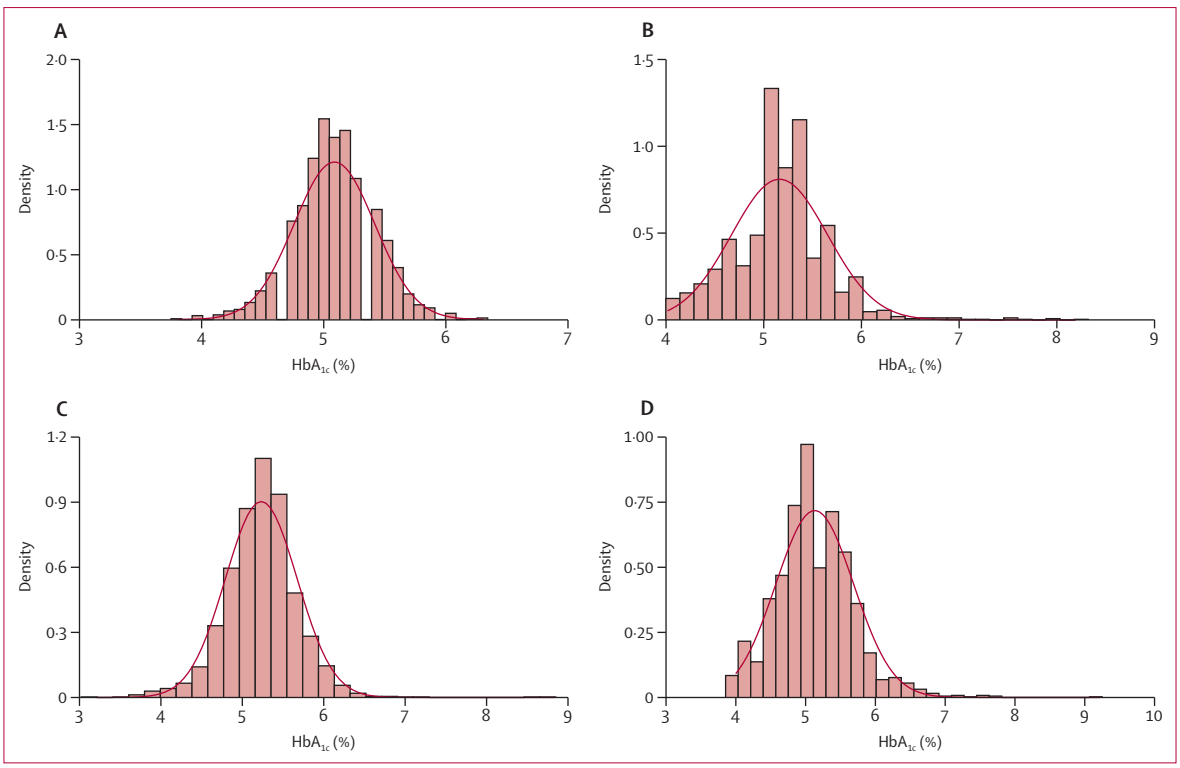

Figure 2: **Distributions of early pregnancy venous (A) and point-of-care (B) HbA_{1c} in STRiDE India participants and distributions of early pregnancy venous (C) and point-of-care (D) HbA_{1c} in STRiDE Kenya participants**

p 35), and the proportions of OGTTs avoided were similar (appendix p 36). Point-of-care HbA_{1c} was not available for the UK cohort. Although haemoglobin concentrations were tested to rule out severe anaemia, the actual haemoglobin concentration was not documented in India and in a significant proportion of participants in Kenya. Hence, ethnicity-specific subgroup analysis was carried out with haemoglobin and HbA_{1c}, and addition of haemoglobin as a covariate to the composite risk score model 2. The effect sizes were significant but very small and did not change the adjusted RRs of HbA_{1c} for gestational diabetes. Notably, this association was seen mainly in women without anaemia (appendix p 37). Missing variable percentages, sensitivity analysis of the multiple imputations, and the composite risk score are reported in the appendix (pp 10, 38–39).

Discussion

Our study tested the validity of early pregnancy HbA_{1c} in two LMICs and one high-income population and its association with the diagnosis of gestational diabetes at 24–28 weeks of gestation. Early pregnancy HbA_{1c} on its own, or in combination with commonly used risk factors such as age, BMI, and family history of diabetes, identified about 50% of women who had gestational diabetes in late pregnancy. Using a two-threshold approach, we were able to stratify women into three categories at early pregnancy: those at highest risk (rule-in gestational diabetes), lowest risk (rule-out gestational diabetes) and medium risk (requires an OGTT at 24–28 weeks). It is estimated that this strategy can reduce the need for conducting OGTTs by 50% to 64% in different populations. Women who were ruled in had significantly older age, BMI, and other risk factors, including blood pressure, suggesting that these women were potentially at highest metabolic risk and could benefit from early intervention. They also seemed to have a higher number of adverse outcomes. Point-of-care HbA_{1c} can also be used, which can reduce the need for OGTTs by similar proportions. These findings were cross-validated using modern validation methods and tested in a multi-ethnic cohort in the UK, suggesting that this approach could be useful for other populations. Our approach also provides evidence for countries to modify the thresholds for needing an OGTT based on the resources available.

Screening for gestational diabetes is difficult using OGTT, especially in LMICs, where the biggest burden of gestational diabetes is currently estimated to occur. To compound the issue, LMICs have poor screening rates.[2] Findings from a trial in the USA showed that screening uptake is higher (66% *vs* 92%) when a two-step strategy is used (50 g glucose challenge as the initial test),[4] as women are likely to accept simpler initial screening in a non-fasted state, followed by a cumbersome test such as the OGTT, if necessary. Our approach could improve screening rates further, especially by using point-of-care

	STRiDE India (n=2115)		STRiDE Kenya (n=2142)		PRiDE UK (n=4320)	
	RR (95% CI)	AIC score	RR (95% CI)	AIC score	RR (95% CI)	AIC score
Model 1a	..	2061·5	..	532·1	..	3358·5
HbA_{1c} alone (per %)	1·60 (1·19–2·16)	..	3·49 (2·8–4·34)	..	4·72 (3·82–5·82)	..
HbA_{1c} alone (per 0·1%)	1·05 (1·02–1·09)	..	1·13 (1·11–1·16)	..	1·17 (1·14–1·19)	..
Model 1b*	..	2058·5	..	551·7	..	3476·4
Age (per year)	1·03 (1·01–1·06)	..	1·05 (1·00–1·10)	..	1·06 (1·04–1·07)	..
BMI (per unit)	1·00 (0·98–1·02)	..	1·11 (1·07–1·14)	..	1·05 (1·04–1·06)	..
Family history of diabetes (yes or no)	1·29 (1·08–1·54)	..	1·58 (0·91–2·75)	..	1·11 (0·95–1·29)	..
Model 2†	..	2052·5	..	519·0	..	3289·2
(Model 1a + 1b; per %)	1·46 (1·07–1·98)	..	2·72 (2·15–3·43)	..	3·92 (3·17–4·86)	..
per 0·1 %	1·04 (1·01–1·07)	..	1·1 (1·08–1·13)	..	1·15 (1·12–1·17)	..

AIC=Akaike information criterion. RR=risk ratio. *Care should be taken to interpret the adjusted RR of model 1b as they are adjusted for each other variable in the model. †Model 2 adjusted RR of HbA_{1c} adjusted for age, BMI, and family history of diabetes. Adjusted RRs for both 1% and 0·1% increment of HbA_{1c} are reported to aid comparison. The 0·1% increment adjusted RR values are 1% increment adjusted RR values to the power 0·1.

Table 3: **Adjusted risk ratio and AIC scores of simple and composite risk score models using venous HbA_{1c} for gestational diabetes at 24–28 weeks**

HbA_{1c} as the initial screening test, in real-life and rural settings that have no laboratory facilities for conducting OGTTs.

A recent systematic review of studies that was mainly conducted in high-income countries at the time of diagnosis of gestational diabetes concluded that although a venous HbA_{1c} threshold of 5·7% can diagnose gestational diabetes, a two-threshold, rule-in, rule-out approach might be better.[31] Our findings extend this observation to early pregnancy in three different populations, the validity of the composite risk score, and the potential value of point-of-care HbA_{1c}. However, our rule-in approach can result in higher false positives than an OGTT-based gestational diabetes diagnosis, which can result in higher anxiety, higher cost (monitoring), and higher caesarean sections rates. Conversely, the uptake might be higher for the easier HbA_{1c} test than the OGTT, and therefore the proportion of gestational diabetes diagnoses missed (because of not getting tested) could be less, which can result in less net harm.[14] A balanced approach is advised until the usefulness is proven or unproven in a randomised controlled trial. In addition, the thresholds for risk stratification in early pregnancy can be modified (eg, by using higher rule-in thresholds for gestational diabetes) to ensure that only women with the highest risk are offered treatment, especially in LMICs with low prevalence rates.

The STRiDE cohorts used a universal screening strategy in India and Kenya, whereas the PRiDE cohort had selective screening based on NICE guidelines, highlighting that a HbA_{1c}-based approach can be useful, even in countries that have a selective screening strategy by using simple clinical factors. Although HbA_{1c} thresholds across the populations are similar, the differences in adjusted RRs underscore the need for population-specific thresholds to achieve the best results, similar to the HAPO substudy results for adverse pregnancy outcomes.[32] Our proposed HbA_{1c} first model also addresses the increasing issue of undiagnosed type 2 diabetes before pregnancy, which often goes undetected until 24–28 weeks of gestation. The cost savings or cost-effectiveness of the proposed approach for screening and pregnancy outcomes will require additional analyses, which are beyond the remit of this paper.

Recent studies have shown that the diagnosis of gestational diabetes improves outcomes irrespective of the diagnostic thresholds used during OGTTs.[3,4] The TOBOGM study showed that earlier diagnosis might improve short-term neonatal outcomes, but also highlighted the challenges and reproducibility of the OGTT.[6] Using HbA_{1c} in early pregnancy during the COVID-19 pandemic has identified a higher-risk population than that identified by OGTTs at 24–28 weeks.[33] This is confirmed by our observation in three populations. A second test with an OGTT in a smaller proportion of pregnant women with medium risk offers a significant reduction in health-care resource use, which could then be used on earlier management of the highest-risk population. We recommend that HbA_{1c} should be tested between 10–12 weeks of pregnancy and that HbA_{1c} should not be used instead of OGTTs at 24–28 weeks. Whether our two-step approach with a population-specific composite risk score in early pregnancy results in overall improvement in pregnancy and long-term outcomes will require additional randomised controlled trials. Such studies should be carefully designed to compare current practices in local populations, including non-fasting OGTTs. Nevertheless, we believe that our findings pave a way for reducing the need for OGTTs during pregnancy and offer an alternative, more patient-friendly approach.

Our study provides other novel observations. It highlights the huge variations in the prevalence of gestational diabetes in two LMICs and large differences in metabolic risk factors across LMICs. Despite the lower prevalence in Kenya, the mean HbA_{1c} values were higher than in the Indian population, further supporting the importance of population-specific thresholds. Variations in HbA_{1c} among

	Threshold scores*	Actual sensitivity	Actual specificity	Percentage of OGTTs avoided	Total percentage of OGTTs avoided
STRiDE in India (n=2115)					
Model 1a	..	..	..	..	42·0%
Rule-out threshold	4·9%	80·6%	22·7%	22·0%	..
Rule-in threshold	5·4%	28·6%	82·0%	19·9%	..
Model 1b	..	..	..	..	45·7%
Rule-out threshold	0·150	80·1%	24·7%	23·8%	..
Rule-in threshold	0·224	29·5%	80·0%	21·9%	..
Model 2	..	..	..	..	49·8%
Rule-out threshold	0·164	80·1%	28·5%	26·9%	..
Rule-in threshold	0·229	35·4%	80·0%	22·9%	..
STRiDE Kenya (n=2142)					
Model 1a	..	..	..	..	50·4%
Rule-out threshold	5·2%	80·0%	46·1%	45·3%	..
Rule-in threshold	6·0%	21·5%	96·9%	5·1%	..
Model 1b	..	..	..	..	49·5%
Rule-out threshold	0·020	79·6%	47·2%	45·7%	..
Rule-in threshold	0·086	22·4%	96·8%	3·8%	..
Model 2	..	..	..	..	64·0%
Rule-out threshold	0·022	79·6%	61·1%	60·0%	..
Rule-in threshold	0·100	28·6%	96·8%	3·9%	..
PRiDE UK (n=4320)					
Model 1a	..	..	..	..	47·9%
Rule-out threshold	5·2%	79·5%	38·5%	35·8%	..
Rule-in threshold	5·6%	23·8%	90·8%	12·0%	..
Model 1b	..	..	..	..	45·9%
Rule-out threshold	0·113	79·9%	36·5%	34·1%	..
Rule-in threshold	0·218	21·9%	89·9%	11·8%	..
Model 2	..	..	..	..	54·7%
Rule-out threshold	0·107	80·0%	45·0%	41·4%	..
Rule-in threshold	0·237	33·1%	90·0%	13·4%	..

OGTT=oral glucose tolerance test. Model 1a tested the performance of HbA_{1c} alone. Model 1b tested the performance of age, BMI, and family history of diabetes. Model 2 tested the performance of HbA_{1c}, age, BMI, and family history of diabetes. *The threshold scores are simple (model 1a) and composite risk scores (model 1b and 2) that were estimated using equations in the appendix (p 39). Women below the rule-out threshold will be at low risk of developing gestational diabetes (and hence will not require an OGTT); those who were above the rule-in threshold will be at high risk of developing gestational diabetes (and hence identified and managed as gestational diabetes from early pregnancy); and those who were in between will be medium risk and recommended to have an OGTT. The characteristics of these three groups of women are described in detail in the appendix (pp 23–25).

Table 4: **Proportion of OGTTs avoided using rule-out and rule-in approach at population-specific sensitivity and specificity thresholds using venous HbA_{1c}**

different ethnic groups have been observed in non-pregnant populations.[34,35] Data from the PRiDE cohort revealed that even in countries that use selective screening, use of HbA_{1c} might help to avoid 55% of OGTTs. The model performances were marginally better for NICE diagnostic thresholds. Although our data suggest that OGTTs can be avoided in a significant proportion of women with the lowest risk based on early pregnancy factors, these women should still be closely followed up, and further glucose testing should be considered if there are any clinical concerns.

Our study has the following strengths. It is the largest study to date in two LMIC populations of women early in pregnancy. The cohorts were representative of local populations in terms of age, BMI, and SES. We used a universal screening strategy and prospectively tested the value of both venous and point-of-care HbA_{1c} to develop a population-specific strategy for screening gestational diabetes. No studies have assessed the role of a composite risk score in these populations. Our models were cross-validated using a bootstrapping approach, and similar findings from a third cohort of multi-ethnic women in the UK support our conclusions. Our study also adds data on the population differences in diabetes risk. The adjusted RRs were much lower even after including the women with early gestational diabetes in the Indian cohort. Lower muscle mass or β-cell dysfunction might explain some of these population differences, as highlighted recently by the differences in type 2 diabetes clusters in Indians compared with White people.[36]

However, there were also key limitations. Our study excluded women with severe anaemia and haemoglobinopathies, which tend to be prevalent in LMICs. Subgroup analysis showed that lower haemoglobin had a negligible effect on HbA_{1c} in women with mild-to-moderate anaemia, similar to a study in a Chinese population.[37] Whereas OGTT attendance in the Indian cohort was more than 90%, it was only around 65% in Kenya. This was despite raising awareness of the importance of gestational diabetes in the communities, at the early pregnancy visit, and a follow-up phone call, and providing reimbursement for lost wages and the transport costs for attending an OGTT. This further emphasises the challenges of conducting OGTTs and the need for a simpler test in LMICs, especially in real-life settings. Continuous glucose monitoring also offers another potential solution, pending results of our recently completed study.[38] A significant proportion of women (about 20%) were diagnosed as having gestational diabetes in early pregnancy based on IADPSG criteria, using fasting glucose in India. Our main analyses excluded these women, which explains the lower adjusted RR observed in India, and including these women increased the adjusted RR, but it was still lower than those observed in Kenya and the UK. However, this enabled us to test the association of early pregnancy HbA_{1c} with milder hyperglycaemia at 24–28 weeks. It is also possible that only using FPG to exclude gestational diabetes in early pregnancy might misclassify some women, but there is also no clear consensus on OGTT thresholds in early pregnancy based on current evidence.[6] Currently, point-of-care HbA_{1c} is not widely used in LMICs, partly due to higher cost.

In conclusion, our study showed that HbA_{1c} can be used for gestational diabetes screening in early pregnancy, followed by selective OGTTs for women at 24–28 weeks of pregnancy at medium risk. Use of point-of-care HbA_{1c} provides the opportunity for women to be screened at

home and in remote settings, which might further improve the rates of screening. This can result in better outcomes in pregnancy, as most adverse outcomes happen in women at high risk who do not get screened. Whether this pathway approach can prevent adverse metabolic programming of the offspring will require future randomised controlled trials that are co-designed with women with lived experience.

Contributors

PS conceived the idea, designed the study, and developed this further with NW, NS, VM, UR, SS, and SP, and was responsible for securing the grants (STRiDE and PRiDE). VM and SP were responsible for the conduct of STRiDE in India and Kenya. MD and RMA were responsible for the day-to-day running in India, and ACD and WKK led this in Kenya. UR, TS, DP, and SDK led the obstetric side in India. ZA completed all the PRiDE HbA_{1c} analysis. WH, CS, SH, NS, VK, and JNH led study recruitment and coordinated site activities in each centre. YGW and GA conducted the analysis with input from NS. All authors contributed to the drafting and revision of the manuscript, and approved the final version, and PS had final responsibility for the decision to submit for publication. PS, VM, and SP vouch for the accuracy and completeness of the data and for the adherence of the study protocol.

Declaration of interests

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Data sharing

Individual participant data that underlie the results reported in this article will be available from 9 months to 36 months following the publication of this Article. The data will be shared with researchers who provide a methodologically sound proposal that has been approved by an independent review committee to achieve the aims described in their proposal. Proposals should be directed to p.saravanan@warwick.ac.uk and y.weldeselassie@warwick.ac.uk to gain access. A data access agreement must be signed before access as per University of Warwick standard operating procedures.

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