Original Article

Elevated glycated hemoglobin predicts macrosomia among Asian Indian pregnant women (WINGS-9)

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ABSTRACT

Aim: The aim of this study was to determine the optimal glycated hemoglobin (HbA1c) cut point for diagnosis of gestational diabetes mellitus (GDM) and to evaluate the usefulness of HbA1c as a prognostic indicator for adverse pregnancy outcomes. **Methods:** HbA1c estimations were carried out in 1459 pregnant women attending antenatal care centers in urban and rural Tamil Nadu in South India. An oral glucose tolerance test was carried out using 75 g anhydrous glucose, and GDM was diagnosed using the International Association of the Diabetes and Pregnancy Study Groups criteria. **Results:** GDM was diagnosed in 195 women. Receiver operating curves showed a HbA1c cut point of ≥ 5.0% (≥31 mmol/mol) have a sensitivity of 66.2% and specificity of 56.2% for identifying GDM (area under the curve 0.679, confidence interval [CI]: 0.655–0.703). Women with HbA1c ≥ 5.0% (≥31 mmol/mol) were significantly older and had higher body mass index, greater history of previous GDM, and a higher prevalence of macrosomia compared to women with HbA1c < 5.0% (<31 mmol/mol). The adjusted odds ratio for macrosomia in those with HbA1c ≥ 5.0% (≥31 mmol/mol) was 1.92 (CI: 1.24–2.97, *P* = 0.003). However, other pregnancy outcomes were not significantly different. **Conclusion:** In Asian Indian pregnant women, a HbA1c of 5.0% (31 mmol/mol) or greater is associated with increased risk of macrosomia.

Key words: Adverse pregnancy outcomes, Asian Indians, glycated hemoglobin, macrosomia, South Asians

Introduction

Gestational diabetes mellitus (GDM), a serious metabolic disorder during pregnancy, may lead to several complications including perinatal morbidity and mortality.[1] Women with GDM have higher risk of cesarean section and are also at greater risk of developing type 2 diabetes in the future.[2-4] While the risks and complications due to GDM are well established, there is still considerable debate about the best screening and diagnostic methods for GDM.[5]

Traditionally, an oral glucose tolerance test (OGTT) is employed for diagnosis of GDM, and this is considered

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to be the gold standard. For diagnosis of type 2 diabetes in the nonpregnant state, in 2010, the American Diabetes Association included HbA1c as a diagnostic test with a cut point of 6.5% (48 mmol/mol)[6] which was later supported by the World Health Organization.[7] The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) recommends HbA1c in the first trimester of pregnancy to rule out overt diabetes.[8] An OGTT requires pregnant women to come for the test in the fasting state which can be cumbersome and time-consuming. In contrast, HbA1c has the advantage that it can be measured at any time of the day irrespective of meal timings.

Several studies have reported that HbA1c levels are lower among pregnant women compared to the general population.[9,10] However, thus far HbA1c has not been considered suitable for diagnosis of GDM during pregnancy due to its lower sensitivity and the lack of reliable cut points.[11,12] The utility of HbA1c in screening and diagnosis of GDM as well as using it as a prognostic indicator for pregnancy outcomes has not been studied adequately.

The aim of this study was, therefore, to determine the optimal HbA1c cut point for diagnosis of GDM and to evaluate its usefulness as a prognostic indicator for pregnancy outcomes among Asian Indian pregnant women.

Methods

This study is part of the Women in India with GDM Strategy (WINGS) project of the International Diabetes Federation carried out in Tamil Nadu, South India. The study was conducted between January 2013 and December 2015. Pregnant women (n = 1459) were screened at their first booking at 15 government primary health centers at Kancheepuram and 6 private health centers at Chennai in Tamil Nadu. All baseline data collection was done at the booking visit. Booking visit refers to the first antenatal visit of the pregnant women to the health center at which point they were screened for GDM. Written informed consent was obtained in the local language from all participants, and the study was approved by the Institutional Ethics Committee of the Madras Diabetes Research Foundation (MDRF). Permission was also obtained from the Directorate of Public Health and the Ministry of Health, Government of Tamil Nadu, to conduct the study in the primary health centers.

Height was measured using a stadiometer (SECA Model 213, Seca Gmbh Co, Hamburg, Germany) to the nearest 0.1 cm, and weight was measured with an electronic weighing machine (SECA Model 803, Seca Gmbh Co.,) to the nearest 0.1 kg. The body mass index (BMI) was calculated as weight (kg) divided by height (in meters) squared. Participants were requested to report in the fasting state (at least 8 h of overnight fasting). A fasting venous sample was drawn for plasma glucose (PG) estimations. 82.5 g oral glucose (equivalent to 75 g of anhydrous glucose) was then dissolved in 300 ml of water and was given to the pregnant women who consumed it within 5 min. Further venous samples were drawn at 1 h and 2 h after the ingestion of oral glucose. 5 ml of venous blood was drawn for measuring glycated hemoglobin (HbA1c).

PG was estimated by the glucose oxidase–peroxidase method using autoanalyzer AU2700 (Beckman, Fullerton, CA, USA). HbA1c was measured using high-performance liquid chromatography using Variant II Turbo machine (BIORAD, Hercules, CA, USA). The intra- and inter-assay coefficients of variation for the glucose and HbA1c ranged from 0.78%–1.68% to 0.59%–1.97%, respectively. All samples were processed in our laboratory which is certified by the College of American Pathologists and by the National Accreditation Board for Testing and Calibration Laboratories, Government of India.

Definitions

GDM was diagnosed by the IADPSG criteria. Accordingly, in the first trimester, GDM was diagnosed if fasting PG value was between 5.1 and 7.0 mmol/l (92–126 mg/dl) and in the 2/3rd trimester, if fasting or 1 h or 2 h PG values met or exceeded 5.1 mmol/L (≥92 mg/dl), 10.0 mmol/L (≥180 mg/dl), and 8.5 mmol/L (≥153 mg/dl),[8] respectively. Commonly, infants exceeding the 90th percentile for any specific gestation age are considered macrosomic or large for gestation age. In Indians, 3.45 kg corresponds to the 90th percentile of birth weight and hence the cutoff for macrosomia used is 3.5 kg.[13]

Statistical analysis

All analyses were done using Windows-based SPSS statistical package (version 15.0, Chicago, IL, USA). Estimates were expressed as mean ± standard deviation or proportions. $P < 0.05$ was considered significant. Receiver operating characteristic (ROC) curves were plotted using sensitivity and 1-specificity for different HbA1c values against GDM diagnosed by IADPSG criteria, and the C-statistic was calculated. Binary logistic regression analysis was used to evaluate the association of HbA1c with pregnancy outcomes.

Results

A total of 1459 pregnant women who were screened for GDM under the WINGS project had booking visit HbA1c estimations and pregnancy outcomes data available. Mean age of these women was 26.1 ± 3.9 years, BMI was

24.5 ± 4.8 kg/m^2, mean HbA1c was 4.9% ± 0.5%, and mean week of gestation was 19.5 ± 7.6 weeks.

GDM was identified in 195 women (n = 33 in the first trimester and n = 162 in the 2nd/3rd trimester). Table 1 shows the clinical characteristics of women with and without GDM. Women with GDM were significantly older and had higher BMI at booking, higher HbA1c at booking, greater history of previous GDM, and greater family history of type 2 diabetes than women without GDM. There was no significant difference in the mean week of gestation between women with and without GDM.

To analyze the utility of HbA1c in diagnosing GDM, we constructed a ROC curve keeping the OGTT as reference diagnostic criteria (IADPSG). The resulting ROC curve showed that a HbA1c cutoff of ≥5.0% (≥31 mmol/mol) had a sensitivity of 66.2% and specificity of 56.2% with a C-statistic of 0.679 (confidence interval [CI]: 0.655–0.703) [Figure 1]. When the HbA1c cut points were increased to 5.5% (37 mmol/mol) and 5.7% (39 mmol/mol), the specificity improved to 92% and 96.8%, respectively, but the sensitivity drastically came down to 24.6% and 14.9%, respectively. Conversely, when the HbA1c cutoff was lowered to 4.7% (28 mmol/mol), the sensitivity increased to 88.2%, but specificity decreased to 27.8% [Table 2].

We next compared the baseline clinical characteristics and pregnancy outcomes in women who had a HbA1c of ≥5% (n = 683) and <5% (n = 776), irrespective of their GDM status [Table 3]. Age, BMI, previous history of GDM, and macrosomia were significantly higher among pregnant women whose HbA1c were ≥5.0% (≥31 mmol/mol) than those <5.0% (<31 mmol/mol). Normal vaginal delivery was significantly higher in women with HbA1c <5.0% (<31 mmol/mol). There were no significant differences in any of the maternal and neonatal complications other than macrosomia between the two groups.

The unadjusted odds ratio (OR) for pregnant women (irrespective of their glycemic status) with HbA1c ≥ 5.0% (≥31 mmol/mol) to have a macrosomic baby was 2.03 (CI: 1.32–3.12, P = 0.001) and after adjusting for age, BMI, family history of type 2 diabetes, and previous history of GDM, the OR was 1.92 (CI: 1.24–2.97, P = 0.003) [Table 4].

Discussion

This study shows the following findings:

1. HbA1c does not have adequate sensitivity and specificity for diagnosis of GDM and hence cannot effectively replace an OGTT for diagnosis of GDM
2. A HbA1c cut point of ≥5.0% (≥31 mmol/mol) is associated with an increased risk of macrosomia.

Table 1: Comparison of clinical characteristics between women with and without gestational diabetes mellitus

Parameter	GDM (n=195)	Non-GDM (n=1264)	P
Age (years)	27.3±4.4	25.9±3.9	<0.001
BMI (kg/m^2)	25.7±5.9	23.7±6.0	<0.001
Gestational age at booking (weeks)	19.7±7.6	19.4±7.6	0.712
Fasting plasma glucose (mg/dl)	94±12	78±11	<0.001
1 h plasma glucose (mg/dl)	168±35	123±26	<0.001
2 h plasma glucose (mg/dl)	142±32	108±24	<0.001
HbA1c (%)	5.2±0.5	4.9±0.5	<0.001
Previous history of GDM (%)	11 (5.6)	16 (1.3)	0.0105
Family history of Type 2 diabetes (%)	77 (39.5)	315 (24.9)	0.0001

BMI: Body mass index, HbA1c: Glycated hemoglobin, GDM: Gestational diabetes mellitus

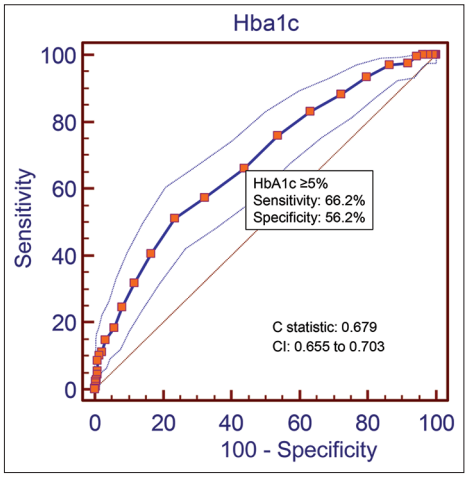

Figure 1: Receiver operating characteristic curve of glycated hemoglobin versus diagnosis of gestational diabetes mellitus

HbA1c has been a well-established tool for screening and management of type 2 diabetes. However, HbA1c measurements during pregnancy have been unreliable.[14,15] Nielson *et al*.[15] found that in normal pregnancy, HbA1c was reduced in the first trimester and it further decreased in the third trimester. Versantvoort *et al*.[16] showed that HbA1c was lower at all three trimesters in normal pregnant women compared to their nonpregnant counterparts. Although there is no consensus on the reference range of HbA1c in pregnant women, the optimum glycemic goal of <6.0% (<42 mmol/mol) recommended in pregnant women with preexisting type 1 or type 2 diabetes may be too high for women with GDM.

Table 2: Comparison of sensitivity and specificity of different glycated hemoglobin cut points in comparison with the International Association of the Diabetes and Pregnancy Study Groups criteria to diagnose gestational diabetes mellitus

HbA1c cutoff % (mmol/mol)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)	Percentage of population who have HbA1c above this value
≥4.0 (20)	100.0	0.6	13.4	100	99.5	99.5
≥4.2 (22)	100.0	3.6	13.8	100	97.0	96.8
≥4.4 (25)	97.4	8.2	14.1	95.4	90.8	92.5
≥4.6 (27)	93.3	20.3	15.3	95.2	79.9	81.6
≥4.8 (29)	83.1	36.7	16.8	93.4	67.3	65.9
≥5.0 (31)	66.2	56.2	18.9	91.5	60.8	46.8
≥5.2 (33)	51.3	76.4	25.1	91	69.6	27.3
≥5.4 (36)	31.8	88.4	29.7	89.4	80.3	14.3
≥5.6 (38)	18.5	94.3	33.3	88.2	88.7	7.4
≥5.8 (40)	11.3	97.9	44.9	87.7	95.0	3.4
≥6.0 (42)	8.7	99.1	60.7	87.6	97.4	1.9
≥6.2 (44)	4.6	99.2	47.4	87.1	98.0	1.3
≥6.4 (46)	2.6	99.5	45.5	86.9	98.8	0.8
≥6.6 (49)	2.1	99.6	44.4	86.8	99.0	0.6
≥6.8 (51)	1.0	99.7	33.3	86.7	99.3	0.4

HbA1c: Glycated hemoglobin

Table 3: Comparison of baseline clinical characteristics and pregnancy outcomes of women with glycated hemoglobin <5.0% (<31 mmol/mol) and ≥5.0% (≥31mmol/mol)

Parameter	HbA1c <5.0% (<31 mmol/mol) (*n*=776)	HbA1c ≥5.0% (≥31 mmol/mol) (*n*=683)	*P*
Baseline clinical characteristics			
Age (in years)	25.8±3.9	26.4±4.0	0.004
BMI (kg/m^2)	23.2±5.9	24.7±5.9	<0.001
Previous history of GDM (%)	8 (1)	19 (2.8)	<0.001
Family history of Type 2 diabetes (%)	203 (26.2)	189 (27.7)	0.51
GDM (%)	66 (8.5)	129 (18.9)	<0.001
Pregnancy outcomes			
Mean birth weight (kg)	2.9±0.4	2.9±0.5	0.43
Macrosomia (%)	36 (4.7)	61 (9.2)	0.001
Low birth weight (excluding preterm) (%)	50 (6.6)	58 (8.8)	0.12
Preterm delivery (%)	45 (5.9)	39 (5.9)	1.0
Mode of delivery (%)			
Normal vaginal delivery	393 (50.6)	310 (45.4)	0.04
Instrumental delivery	41 (5.3)	35 (5.1)	0.36
Cesarean section	326 (42)	314 (46)	0.12
Abortion	10 (1.4)	19 (2.8)	0.06
Still birth	5 (0.6)	2 (0.3)	0.38
Intrauterine death	1 (0.1)	3 (0.4)	0.26
Maternal and neonatal complications (%)			
Oligo/polyhydramnios	38 (4.9)	22 (3.2)	0.09
Preeclampsia	6 (0.8)	5 (0.7)	0.82
Neonatal death	1 (0.1)	2 (0.3)	0.40
Hyperbilirubinemia	10 (1.3)	5 (0.7)	0.24
Fetal distress	11 (1.4)	8 (1.2)	0.73
Respiratory distress syndrome	3 (0.4)	1 (0.1)	0.24
Neonatal hypoglycemia	5 (0.6)	3 (0.4)	0.58

GDM: Gestational diabetes mellitus, HbA1c: Glycated hemoglobin

Several studies have tried to evaluate the use of HbA1c to diagnose GDM. Our study supports earlier studies[9,12] that due to its low sensitivity, HbA1c cannot be used as an alternative to OGTT to diagnose GDM. In a study conducted by O'Shea *et al*.,[17] it was shown that 46% of women with GDM could be diagnosed with HbA1c cut point of 5.4% (36 mmol/mol). Similar to these results, our study also showed that HbA1c of ≥5.0% (≥31 mmol/mol) could identify 46.8% of women with GDM diagnosed by the IADPSG criteria. The HAPO study showed that adverse outcomes were significantly stronger with glucose measures than with HbA1c, and they concluded that HbA1c

Table 4: Binary logistic regression showing risk of adverse outcomes in women with glycated hemoglobin ≥5.0% (≥31 mmol/mol) using glycated hemoglobin <5.0% (<31 mmol/mol) as reference

Adverse outcomes in women with HbA1c ≥5.0% (≥31 mmol/mol)	*B*	SE	OR*	95% CI	*P*
Macrosomia	0.65	0.22	1.92	1.24-2.97	0.003
Low birth weight	0.37	0.21	1.45	0.96-2.19	0.07
Cesarean section	0.10	0.11	1.11	0.89-1.37	0.34
Preeclampsia	0.10	0.64	1.10	0.31-3.87	0.87
Hyperbilirubinemia	−0.85	0.59	0.42	0.13-1.37	0.15
Oligo/polyhydramnios	−0.38	0.27	0.68	0.39-1.17	0.16
Fetal distress	−0.33	0.49	0.71	0.27-1.86	0.49
Preterm	−0.11	0.23	0.89	0.56−1.40	0.62
Neonatal hypoglycemia	−0.13	0.74	0.87	0.20-3.74	0.85

*OR adjusted for age, BMI, family history of Type 2 diabetes, and previous history of GDM. OR: Odds ratio, GDM: Gestational diabetes mellitus, BMI: Body mass index, SE: Standard error, CI: Confidence interval, HbA1c: Glycated hemoglobin

could not be used as an alternative to OGTT.[18] A recent study from China suggested that a HbA1c cut point of 5.3% (34 mmol/mol) could be used along with fasting PG 79 mg/dl (4.4 mmol/l) as a first step screening test for GDM.[19] Another study from Brazil which evaluated the performance of HbA1c as diagnostic tool for GDM showed that a cutoff of 5.4% (36 mmol/mol) has the optimal sensitivity and specificity, but the sensitivity of 70% is still not satisfactory.[20]

There is growing data to suggest that HbA1c can be used for predicting adverse pregnancy outcomes in women with GDM. Lowe *et al*.[18] and Capula *et al*.[21] have shown that higher HbA1c levels are significantly associated with primary and secondary outcomes studied under HAPO study.[18,21] We found that pregnant women with HbA1c of ≥5.0% (≥31 mmol/mol) were significantly older and had higher BMI and higher previous history of GDM. These characteristics have been related to adverse pregnancy outcomes for both mother and baby.[2,3] This is confirmed in our study as women with HbA1c ≥5.0% (≥31 mmol/mol) were at a higher risk of delivering macrosomic babies. However, other pregnancy outcomes did not statistically differ in women who had HbA1c cut points below this level.

Several authors have found a correlation between HbA1c and macrosomia. Baxi *et al*.[22] found that all GDM women who had HbA1c ≥6.7% (≥50 mmol/mol) delivered macrosomic babies. Djelmis *et al*.[23] showed that macrosomic babies were born to women with HbA1c >6.3% (>45 mmol/mol) in the last month of pregnancy. A study from Denmark showed that macrosomia was three times higher in women who had Hba1c of ≥5.6% (≥38 mmol/mol).[24] We found that pregnant women who had a HbA1c of ≥5.0% (≥31 mmol/mol) had higher risk of macrosomia, majority of whom did not have GDM. This finding is of particular interest because it shows that HbA1c may be used as a marker for macrosomia, independent of the diagnosis of GDM. Macrosomia in normal pregnant women has been previously reported in other populations.[25,26] Recently, Koyanagi *et al*.[25] reported a rising prevalence of non-GDM macrosomia worldwide, implying that GDM is not the only reason for macrosomic babies. Walsh *et al*.[26] reported that majority of macrosomic infants are born to nondiabetic mothers, and women with multiple prior macrosomic infants were at a higher risk of delivering macrosomic babies.

This study has several strengths: first, it is a prospective study with fairly large sample size. Second, our data report on association between HbA1c and adverse pregnancy outcomes, especially macrosomia. One of the limitations of the study was that repeated measures of HbA1c were not done during pregnancy, so we could not look at the effect of serial changes in HbA1c during pregnancy on outcomes. Earlier studies have reported that changes in HbA1c during pregnancy from first to second to third trimester were associated with birth weight.[16,27]

Conclusion

This study shows that HbA1c due to its low sensitivity is not useful for screening or diagnosis of GDM subjects and hence is not an effective replacement for OGTT in diagnosing GDM. Nevertheless, baseline HbA1c levels could be used to predict pregnancy outcomes, especially fetal macrosomia.

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Conflicts of interest

There are no conflicts of interest.

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