



ROLE OF FIRST-TRIMESTER HbA1c IN THE PREDICTION OF GESTATIONAL DIABETES MELLITUS.

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is associated with significant maternal and fetal complications, highlighting the need for early risk identification. **Aim:** To evaluate the role of first-trimester HbA1c in predicting subsequent GDM. **Methods:** A total of 435 pregnant women underwent a 75-g OGTT during the second trimester, and HbA1c levels were assessed. **Results:** GDM was diagnosed in 16.0% of women, while 0.6% had impaired glucose tolerance. Women with GDM had significantly higher HbA1c than those without GDM/IGT (5.53% vs. 4.89%, $p < 0.001$). ROC analysis showed an AUROC of 0.758 (95% CI: 0.691–0.824; $p < 0.001$). At an HbA1c cutoff of $\geq 5.4\%$, sensitivity was 58.3% and specificity was 82.4%. The positive and negative predictive values were 40.8% and 90.5%, respectively. **Conclusion:** HbA1c demonstrated moderate discriminatory ability for identifying GDM/IGT in this study population. HbA1c may serve as an adjunctive risk-stratification marker but should not replace the 75-g OGTT.

KEYWORDS : Gestational Diabetes Mellitus; HbA1c; Pregnancy; First Trimester; Prediction; Screening; Oral Glucose Tolerance Test; India.

INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the most common metabolic disorders complicating pregnancy and is associated with adverse maternal, fetal and neonatal outcomes. Women with GDM have an increased risk of hypertensive disorders of pregnancy, excessive fetal growth, operative delivery and subsequent development of type 2 diabetes mellitus, while offspring are at increased risk of obesity and metabolic disorders later in life. [1,2] The burden of GDM is particularly important in India, where the prevalence of diabetes and associated metabolic risk factors is high. Recent national Indian data demonstrate a substantial burden of GDM, with considerable geographical variation across the country. [3] This high prevalence emphasizes the need for effective strategies for early identification of women at increased risk of GDM. Conventionally, GDM screening is performed between 24 and 28 weeks of gestation using an oral glucose tolerance test (OGTT). [4] Although this approach is effective for diagnosis, identification of women at increased risk earlier in pregnancy could facilitate earlier lifestyle modification, nutritional counselling and closer glycaemic surveillance. Glycated haemoglobin (HbA1c) is an attractive potential biomarker for early pregnancy screening because it reflects average glycaemic exposure over a period of several weeks, does not require fasting and is relatively convenient and reproducible. [5] However, physiological changes during pregnancy, including altered erythrocyte turnover, as well as iron deficiency and other haematological conditions, can affect HbA1c concentrations. [6] Therefore, the diagnostic and predictive performance of HbA1c in pregnancy may differ from that observed in the non-pregnant population. Several studies have evaluated the relationship between early pregnancy HbA1c and subsequent development of GDM. Hinkle et al. reported that higher first-trimester HbA1c was associated with an increased risk of subsequent GDM, although HbA1c alone demonstrated limited discriminatory ability. [5]

Indian studies have also demonstrated an association between early pregnancy HbA1c and GDM. In the WINGS study conducted in Tamil Nadu, HbA1c measured during early pregnancy was associated with subsequent GDM; however,

the sensitivity and specificity varied substantially according to the threshold used. At an HbA1c cutoff of approximately 5.0%, sensitivity was around 66%, whereas increasing the threshold to 5.7% substantially increased specificity at the expense of sensitivity. [7] Punnose et al. evaluated 2,275 Asian Indian pregnant women and reported that higher first-trimester HbA1c was independently associated with subsequent GDM. Women with HbA1c values of 5.2–5.5% and $>5.6\%$ had increased odds of developing GDM compared with women with HbA1c $<5.2\%$. However, the discriminatory ability of HbA1c alone was modest, with an area under the receiver operating characteristic curve (AUC) of approximately 0.61. [8] The STRiDE study provided important prospective evidence regarding the role of early pregnancy HbA1c in predicting GDM. Saravanan et al. evaluated HbA1c measured before 16 weeks of gestation in three prospective cohorts, including a large cohort from South India, and assessed subsequent GDM at 24–28 weeks. [9] In the Indian cohort, HbA1c thresholds of approximately 5.4% and $<4.9\%$ were identified as potential rule-in and rule-out thresholds, respectively. [9] Importantly, the study demonstrated that combining HbA1c with maternal age, body mass index (BMI) and family history of diabetes improved predictive performance compared with HbA1c alone. [9] The STRiDE investigators subsequently reported the prevalence and risk factors for early GDM in the Indian cohort. Women with early GDM had higher early-pregnancy HbA1c and higher BMI than women who developed GDM later in pregnancy, further supporting the potential importance of early metabolic risk assessment. [10] A recent Indian prospective cohort study also demonstrated that first-trimester HbA1c could contribute to prediction of GDM, particularly when combined with other clinical and biochemical risk factors. [11] These findings suggest that HbA1c may have greater clinical utility as an early risk-stratification marker rather than as a replacement for conventional OGTT-based diagnosis. Systematic reviews and meta-analyses have similarly concluded that although higher early-pregnancy HbA1c is associated with subsequent GDM, its sensitivity and specificity vary across populations and thresholds, limiting its use as a stand-alone diagnostic test. [12,13]

Therefore, the present study was undertaken to evaluate the

role of first-trimester HbA1c in predicting subsequent GDM in patients attending Antenatal OPD at a Primary Health Center in Hyderabad.

Aim

To evaluate the role of first-trimester HbA1c in predicting gestational diabetes mellitus.

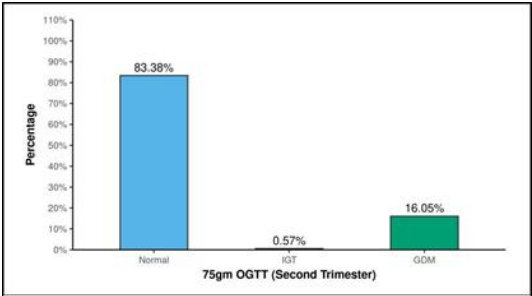
Objectives

- 1. To determine the association between first-trimester HbA1c and subsequent development of GDM.
- 2. To compare first-trimester HbA1c levels between women who develop GDM and those who do not.
- 3. To determine the optimal HbA1c cutoff for predicting GDM using receiver operating characteristic (ROC) curve analysis.
- 4. To determine the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the identified HbA1c cutoff.

RESULTS

A total of 435 pregnant women underwent a 75-g oral glucose tolerance test (OGTT) during the second trimester. Of these, 83.4% had normal glucose tolerance, 0.6% had impaired glucose tolerance (IGT), and 16.0% fulfilled the criteria for gestational diabetes mellitus (GDM). Thus, GDM represented a substantial proportion of the study population during the second trimester, emphasizing the importance of continued glycaemic assessment during pregnancy.

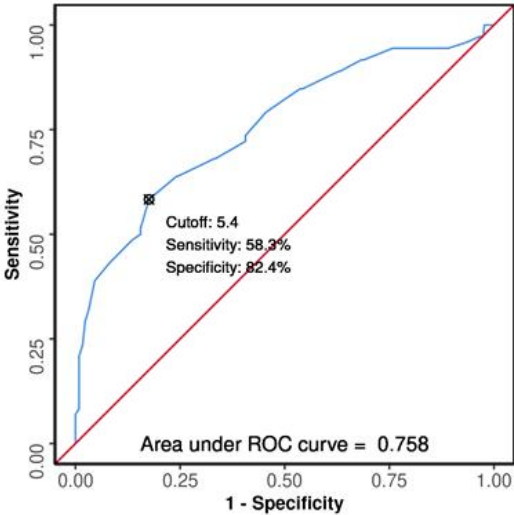
For the analysis of HbA1c, participants were categorized according to the presence or absence of GDM in the second trimester. The mean (SD) HbA1c was 5.53 (0.73)% among women with GDM compared with 4.89 (0.57)% among women without GDM. The corresponding median (IQR) HbA1c values were 5.46% (5.0–6.0) and 4.90% (4.6–5.2), respectively. HbA1c values ranged from 3.9% to 7.5% in the GDM present group and from 2.21% to 6.5% in the GDM absent group. There was a statistically significant difference in HbA1c between the two groups on the Wilcoxon–Mann–Whitney U test $p < 0.001$, with higher HbA1c values observed among women with GDM. Receiver operating characteristic (ROC) curve analysis demonstrated that HbA1c had an area under the ROC curve (AUROC) of 0.758 (95% CI: 0.691–0.824) for discriminating women with GDM/IGT from those without GDM/IGT. The AUROC was statistically significant ($p < 0.001$), indicating that HbA1c demonstrated moderate-to-good discriminatory ability in this study population. At an HbA1c cutoff of $\geq 5.4\%$, the sensitivity for identifying GDM/IGT was 58%, while the specificity was 82%. Thus, the selected cutoff demonstrated relatively higher specificity than sensitivity.



Graph 1: Distribution of 75gm OGTT (Second Trimester)

Table 1. Association Between 'GDM (Second Trimester)' and 'HbA1c'

Hba1C	GDM/IGT (Second Trimester)		Wilcoxon-Mann-Whitney U Test	
	Present	Absent	W	p value
Mean (SD)	5.53 (0.73)	4.89 (0.57)	18931.500	<0.001
Median (IQR)	5.46 (5-6)	4.9 (4.6-5.2)		
Min - Max	3.9 - 7.5	2.21 - 6.5		



Graph 2. Receiver operating characteristic curve demonstrating the discriminatory performance of HbA1c for identifying second-trimester GDM/IGT.

Table 2: ROC Curve Analysis Showing Diagnostic Performance of Hba1C in Predicting GDM Present vs Absent

Parameter	Value (95% CI)
Cutoff (p value)	≥ 5.4 (<0.001)
AUROC	0.758 (0.691 - 0.824)
Sensitivity	58.3% (46-70)
Specificity	82.4% (78-86)
Positive Predictive Value	40.8% (31-51)
Negative Predictive Value	90.5% (87-94)
Diagnostic Accuracy	78.3% (74-82)
Positive Likelihood Ratio	3.32 (2.46-4.48)
Negative Likelihood Ratio	0.51 (0.38-0.67)
Diagnostic Odds Ratio	6.56 (3.81-11.31)

DISCUSSION

The present study evaluated the association and discriminatory performance of HbA1c for identifying GDM during the second trimester. We observed significantly higher HbA1c concentrations among women with GDM compared with those without GDM/IGT. The median HbA1c was 5.46% in the GDM-present group compared with 4.90% in the GDM-absent group, and this difference was statistically significant ($p < 0.001$). Furthermore, ROC analysis demonstrated an AUROC of 0.758 (95% CI 0.691–0.824), indicating that HbA1c had useful discriminatory ability in our study population.

The observed association between HbA1c and GDM is consistent with previous research demonstrating that higher HbA1c during pregnancy is associated with abnormal glucose metabolism and increased risk of GDM. Hinkle et al. reported that women who subsequently developed GDM had higher first-trimester HbA1c values than women who remained normoglycaemic, and each 0.1% increase in HbA1c was associated with an increased risk of subsequent GDM. [1] These findings support the concept that abnormalities in glucose homeostasis may be detectable before conventional GDM diagnosis.

Evidence from Indian populations is particularly relevant to the present study. In the WINGS-9 study involving 1,459 pregnant women from urban and rural Tamil Nadu, HbA1c $\geq 5.0\%$ demonstrated a sensitivity of 66.2% and specificity of 56.2% for identifying GDM, with an AUC of 0.679. [2] The AUROC of 0.758 observed in our study is numerically higher than that reported in WINGS-9, although direct comparison should be made cautiously because the timing of HbA1c measurement, study population, diagnostic criteria and outcome definition may differ. Importantly, the WINGS study

also demonstrated that higher HbA1c was associated with adverse pregnancy characteristics, including higher BMI and previous GDM. [2]

Punnose et al. evaluated 2,275 Asian Indian women and found that women with higher first-trimester HbA1c had greater odds of subsequently developing GDM. Compared with women with HbA1c <5.2%, the adjusted odds ratio was 1.63 for HbA1c 5.2–5.5% and 2.60 for HbA1c >5.6%. [3] However, the discriminatory performance of HbA1c alone was modest. [3] The stronger discrimination observed in our study may partly reflect the fact that our HbA1c measurement and GDM/IGT outcome were assessed within the second-trimester period rather than evaluating HbA1c exclusively as a first-trimester predictor.

An important comparison is provided by the STRiDE study, which specifically investigated early pregnancy HbA1c as a screening strategy in prospective cohorts, including a large South Indian cohort. [4] In the Indian cohort, the HbA1c-alone model identified approximately 5.4% as a potential rule-in threshold and 4.9% as a rule-out threshold. [4] Our finding of an HbA1c cutoff of $\geq 5.4\%$ is therefore particularly noteworthy because it corresponds to the rule-in threshold reported in the Indian STRiDE cohort. However, the purpose and timing of the HbA1c measurement differ between the two studies, and therefore the thresholds should not be assumed to be interchangeable.

At the cutoff of $\geq 5.4\%$ in our study, HbA1c demonstrated 58% sensitivity and 82% specificity. The relatively higher specificity indicates that this threshold may be more useful for identifying women at increased likelihood of GDM than for excluding the condition. In practical terms, approximately four out of five women without GDM/IGT would be correctly classified using this threshold, whereas approximately two out of five women with GDM would not be identified by HbA1c alone. Consequently, HbA1c at this cutoff should not be interpreted as a replacement for OGTT.

The findings also support the concept that HbA1c may have greater value as a risk-stratification marker than as a definitive diagnostic test. The STRiDE study demonstrated that combining HbA1c with maternal characteristics, including age, BMI and family history of diabetes, improved the prediction of GDM compared with HbA1c alone. [4] Similarly, previous Indian evidence indicates that clinical risk factors and metabolic parameters contribute substantially to the identification of women at increased risk. [2,3]

The difference between the mean HbA1c values in our study was also clinically relevant. Women with GDM had a mean HbA1c of 5.53%, compared with 4.89% among women without GDM. This difference suggests that HbA1c may reflect an underlying degree of dysglycaemia that is associated with abnormal glucose tolerance during pregnancy. Nevertheless, the overlap in HbA1c distributions between the two groups indicates that HbA1c alone cannot perfectly distinguish women with and without GDM.

The prevalence of GDM observed in our study was 16.0%, with an additional 0.6% having IGT. This demonstrates that abnormal glucose regulation remains an important finding during the second trimester. The presence of GDM during this period is consistent with the physiological increase in insulin resistance that occurs as pregnancy progresses. Therefore, continued assessment during the second trimester remains important even when early pregnancy glycaemic measurements are not abnormal.

Our findings have particular relevance for Indian clinical practice because Indian women have a high background risk of dysglycaemia and GDM. The WINGS and STRiDE studies

demonstrate that HbA1c-based thresholds may differ across populations and that Indian-specific data are therefore important when considering the clinical application of HbA1c. [2,4]

An important limitation of interpreting HbA1c during pregnancy is that pregnancy-related changes in red blood cell turnover and iron status can influence HbA1c independently of glucose concentration. Therefore, HbA1c should be interpreted alongside conventional glucose measurements and clinical characteristics rather than in isolation.

The present study has several strengths. First, the study directly assessed HbA1c in relation to second-trimester glucose tolerance. Second, because HbA1c was non-normally distributed, an appropriate non-parametric comparison was used. Third, ROC analysis allowed assessment of the discriminatory performance and identification of a clinically interpretable cutoff. Finally, the results can be compared with important Indian datasets, particularly WINGS and STRiDE. [2,4]

Several limitations should also be considered. First, the study outcome combined GDM and IGT for the HbA1c analysis. Therefore, the reported AUROC and cutoff describe discrimination of GDM, rather than GDM alone. Second, sensitivity of 58% indicates that a substantial proportion of women with GDM/IGT would not be detected using HbA1c $\geq 5.4\%$ alone. Third, the study does not establish whether HbA1c-based screening improves maternal or neonatal outcomes. Finally, factors such as maternal BMI, age, family history of diabetes, iron deficiency and haemoglobinopathies may influence HbA1c and should be considered in future analyses.

CONCLUSION

The present study demonstrated a significant association between HbA1c and second-trimester GDM. Women with GDM had significantly higher HbA1c concentrations than women without GDM, with median values of 5.46% and 4.90%, respectively ($p < 0.001$). HbA1c demonstrated moderate discriminatory performance for identifying GDM/IGT, with an AUROC of 0.758 (95% CI: 0.691–0.824). An HbA1c cutoff of $\geq 5.4\%$ yielded a sensitivity of 58% and specificity of 82%. The HbA1c threshold of 5.4% is of particular interest because it is similar to the Indian rule-in threshold identified in the STRiDE study. [4] However, the sensitivity observed in our study indicates that HbA1c alone would fail to identify a proportion of women with GDM. Therefore, HbA1c should be considered a potential risk-stratification tool rather than a replacement for the 75-g OGTT. Overall, our findings support the potential role of HbA1c as part of an early or adjunctive screening strategy, particularly when combined with established maternal risk factors.

Future Implications

Multicentre Indian studies involving diverse geographical and ethnic populations are required to validate the 5.4% threshold and determine whether the same cutoff can be applied across different Indian populations. The variability in HbA1c performance observed across Indian studies suggests that population-specific validation is important. [2–4]. Future studies should also assess the effect of iron deficiency, haemoglobinopathies and other haematological factors on HbA1c interpretation during pregnancy. Such information may help determine whether HbA1c thresholds need adjustment in populations with a high prevalence of anaemia. Another important area for investigation is the development of a combined prediction model incorporating HbA1c and routinely available clinical variables. Such a model could potentially identify women who require closer surveillance or earlier intervention while retaining OGTT as

the definitive diagnostic assessment. Finally, prospective interventional studies are required to determine whether identifying women at increased risk using HbA_{1c} and initiating lifestyle or nutritional interventions before conventional GDM diagnosis can improve maternal and neonatal outcomes. Until such evidence is available, HbA_{1c} should be regarded as an adjunctive risk marker rather than a substitute for established diagnostic testing.

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