RESEARCH ARTICLE

Glycated Hemoglobin: A Useful Screening Tool for Gestational Diabetes Mellitus

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Abstract

Background: Gestational diabetes mellitus (GDM) and adverse pregnancy outcomes are correlated. The oral glucose tolerance test (OGTT) is the gold standard method for screening GDM. Glycated hemoglobin (HbA1c) levels are a useful screening test for detecting GDM. The use of HbA1c in screening for GDM has been demonstrated by several studies.

Objectives: To find the usefulness of HbA1c levels in diagnosing gestational diabetes mellitus and its association with adverse maternal and neonatal effects.

Materials and methods: This prospective cohort study was conducted at Christian Medical Hospital, Ludhiana. About 500 antenatal women attending the outpatient department were subjected to 75 gm OGTT, and HbA1c and GDM being diagnosed using DIPSI criteria. The perinatal outcomes were compared in women with and without GDM.

Results: Among the 500 antenatal patients evaluated, 23 were lost to follow-up and excluded from the study. The incidence of GDM was 16.8% (n = 80). Women with GDM and without GDM had a mean HbA1c level of 5.55 ± 0.74% and 4.95% ± 0.74%, respectively. The optimal HbA1c cut-off for diagnosing GDM was 5.15% with sensitivity of 74% and specificity of 69.8%.

Conclusions: HbA1c with a cutoff of 5.15% can be used as a screening test and avoid the need of OGTT in approximately 50% of antenatal women.

Keywords: Gestational diabetes mellitus, Glycated hemoglobin, Maternal and neonatal outcome.

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Introduction

The definition of Gestational diabetes mellitus (GDM) is varying degree of carbohydrate intolerance with recognition or first onset during pregnancy.[1] The maternal complications associated with gestational diabetes are hypertensive disorders in pregnancy, hydramnios, preterm labor, operative delivery, shoulder dystocia, and perineal injuries.[2] Screening and treating GDM during the antenatal period reduce the risk of adverse maternal and perinatal outcome.[3] In India, universal screening is preferred over selective screening, which facilitates early detection of cases and improves pregnancy outcomes with appropriate management.[4] Screening for GDM has been controversial from using selective screening to universal screening and measuring plasma glucose levels, glucose challenge test, or performing an oral glucose tolerance test. The gold standard screening modality recommended is oral glucose tolerance test (OGTT). Different criteria use one or more cutoff values for detection of gestational diabetes.[5] The routine use of OGTT is difficult because it is time-consuming, costly, and unpalatable. Therefore, simpler and less cumbersome approaches are being used to diminish the need of OGTT. The measurement of HbA1c levels requires a non-fasting state and a single blood prick, and shows fair correlation for the diagnosis of GDM.[6] The latest studies are now demonstrating that during pregnancy, HbA1c levels show lesser biological variation and may be linked to GDM.[7,8] Measurement of mid-trimester pregnancy HbA1c levels may decrease the number of OGTT.[9] Multiple researches have shown the correlation between obstetrical complications like macrosomia and birth injuries with HbA1c levels in pregnancy.[10–12] Currently, the use of HbA_{1c} as a diagnostic test for GDM is not recommended. Thus, in combination with 75 gm of OGTT (as per DIPSI GUIDELINES), the effectiveness of glycosylated hemoglobin in diagnosing GDM and its association with adverse maternal and neonatal effects were evaluated in this study.

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Materials and Methods

This prospective cohort study was conducted on 500 antenatal patients attending the Outpatient Department of Obstetrics and Gynecology at Christian Medical College and Hospital, Ludhiana, in association with the Department of Endocrinology and Neonatology, and was approved by the Ethics committee. About 500 antenatal patients with a singleton pregnancy were included. Women with Hb <10 gm%, with a history of type 2 diabetes mellitus, known hemoglobinopathy/hemoglobin variant, with a history of chronic kidney disease, hepatic disease, or tuberculosis, and women on corticosteroids were excluded from the study.

After taking informed consent of each participant, data were collected, which included maternal age, parity, BMI, previous history of GDM, past obstetrical events, and family history of diabetes. The participants took a 75 gm 2-hour OGTT after a non-restricted diet of 3 days. Gestational diabetes mellitus was diagnosed according to DIABETES IN PREGNANCY STUDY IN INDIA criteria (DIPSI), i.e., post loading blood glucose levels ≥140 mg/dl. An additional HbA1c test was done at the same time. Quantitative estimation of venous plasma glucose levels was performed using the Hexokinase method on Roche/Hitachi cobas c systems. An automated analyzer (model D10, BioRad) using the principle of ion-exchange high-performance liquid chromatography measured HbA1c levels.

Women with gestational diabetes were managed as per the recommended obstetrical guidelines. The mode of delivery, termination, and labor induction were determined by obstetrical indications. All participants in the study were observed till their delivery, and maternal and neonatal outcomes were noted. Maternal effects were assessed in terms of abortion, gestational hypertension, preeclampsia, preterm delivery (<37 weeks), induction of labor, prolonged labor, perineal tears, shoulder dystocia, postpartum hemorrhage, and operative delivery. The important neonatal outcomes assessed were birthweight, APGAR score, the need for NICU care, neonatal hyperbilirubinemia, neonatal hypoglycemia, fetal demise, birth injuries, and congenital anomalies.

Statistical analysis (SPSS software version 22.0) was done, and the results were compared using Chi-square tests. A receiver operating characteristic curve was constructed to determine the association of mid-trimester HbA1c with GDM. To investigate the association of HbA1c levels with adverse perinatal outcomes, multiple logistic regression analysis was done. $p < 0.05$ was considered to be significant.

Results

Among the 477 participants included in the study, 80 antenatal women (16.8%) were diagnosed to have GDM using DIPSI criteria.

Women with gestational diabetes were significantly older and had a positive family history of diabetes. Parity and body mass index showed no significant association in both the groups.

The mean (±SD) HbA1c was 5.55 ± 0.74% in mothers with GDM and it was 4.95 ± 0.74% in non-GDM mothers. The diagnostic performance of HbA1c for GDM was calculated using a ROC curve with an AUC of 0.778 ($p = 0.000$), which represents fair accuracy (Fig. 1). Using 5.15% as the best cutoff for predicting GDM, the positive predictive value (PPV) was 32.96% and a negative predictive value (NPV) was 91.53% with a sensitivity of 74% and specificity of 69.8%, respectively. An HbA1c level at 4.95% showed a sensitivity of 88.75% and a specificity of 49.37%, the PPV was 26.1%, and NPV was 95.61%, whereas an HbA1c level at 5.25% showed a sensitivity of 61.25% with an increment in the specificity and PPV to 76.07% and 34.03%, respectively, but the NPV dropped to 90.69% (Table 1).

In patients diagnosed to have GDM, 73.8% ($n = 59$) had HbA1c levels above 5.15% whereas only 30.2% among non-GDM patients had HbA1c levels more than 5.15%. This association was significant (p-value = 0.000).

The rates of various pregnancy-related complications were greater in women with GDM (Table 2). In mothers with GDM, adverse consequences such as abortion (p-value = 0.026), PPROM (p-value = 0.006), and intrauterine death (p-value = 0.008) showed a significant correlation. The association of preterm delivery rates ($n = 23$) in patients with GDM was statistically

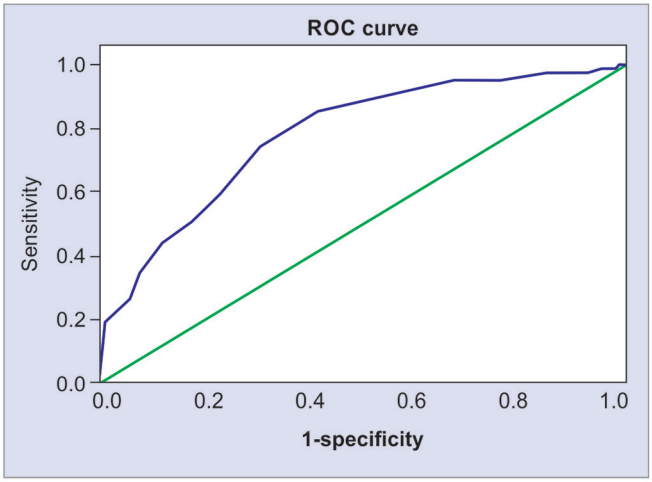

Fig. 1: Diagonal segments are produced by ties

significant. The relationship of mid-trimester HbA1c levels with the rates of threatened preterm (p-value = 0.005) was significant (Table 3). However, it had no relationship with FGR, preeclampsia, and stillbirth rate.

Mothers with GDM and without GDM had a mean gestational age at delivery of 36 weeks 3 days and 38 weeks 2 days, respectively. Labor occurred spontaneously in 57% GDM patients and in 61.7% non-GDM patients. The rates for induction of labor were higher in GDM patients (43%) when compared with non-GDM patients (38.3%). The incidence of labor induction (43% vs 38.3%) and cesarean section (49.4% vs 42.3%) was also higher in GDM mothers. Among the babies born to GDM mothers, 41.1% weighed more than 3 kg and 24.2% weighed between 2.75 and 3 kg. This difference in birthweight was statistically significant (p-value = 0.036). There was no correlation of mid-trimester HbA1c levels with birthweight, rates of instrumental or cesarean delivery, or labor complications.

Neonates born to GDM mothers had higher rates of neonatal hypoglycemia, neonatal jaundice, and NICU admission (Table 2). The correlation was statistically significant for RDS (p-value = 0.022), birth injuries (p-value = 0.025), and jaundice (p-value = 0.017). The association between neonatal hypoglycemia and HbA1c levels was significant (p-value = 0.002). However, no association was found with respect to the APGAR score, neonatal jaundice, or NICU admission (Table 3).

Discussion

The need for a single-best screening tool for diagnosing GDM has always been controversial. Various protocols for screening and detecting gestational diabetes have been recommended in the past and continues to cause uncertainty in clinical practice.[13,14] Despite the distinguished complications associated with GDM, the controversy regarding its diagnosis continues.[15] Good control of blood sugars has shown a reduction in the occurrence of adverse effects in babies born to these mothers.[16]

As per our study, the incidence of GDM is 16.8% ($n = 80$), and GDM women showed greater adverse effects such as preeclampsia, PPROM, FGR, stillbirth rate, and abortion. The rates of preterm delivery (29.1% vs 13.9%), induction of labor (43% vs 38.3%), and cesarean section (49.4% vs 42.3%) were greater in GDM women. The average gestational age at delivery in GDM patients was

Table 1: Glycated hemoglobin in the diagnosis of GDM

HbA1c cutoff value	*Sensitivity*	*Specificity*	*Positive predictive value*	*Negative predictive value*	*Accuracy*	*Number of women with GDM misclassified as normoglycemic*	*Number of normoglycemic women misclassified as GDM*
4.95	88.75%	49.37%	26.10%	95.61%	55.97%	11.30%	50.60%
5.05	85.00%	59.19%	29.57%	95.14%	63.52%	15%	40.80%
5.15	**73.75%**	**69.8%**	**32.96%**	**91.53%**	**66.98%**	**26.30%**	**30.20%**
5.25	61.25%	76.07%	34.03%	90.69%	73.58%	38.80%	23.90%

Bold values denotes the Hba1c of 5.15% was used as the best cut off for predicting GDM in our study with optimal sensitivity and specificity

Table 2: Complications associated with pregnancy, as well as maternal and fetal outcomes, in women with gestational diabetes mellitus (using OGTT cutoff) and normoglycemia

Parameter	*Women with GDM (by OGTT cutoff)*	*Normoglycemic women*	*p-value*
Abortion	1 (1.3%)	0	**0.026**
Gestational hypertension	3 (3.8%)	23 (5.8%)	0.476
Preeclampsia	4 (5.1%)	16 (4.0%)	0.676
PPROM	7 (8.9%)	10 (2.5%)	**0.006**
Preterm	5 (6.3%)	16 (4.0%)	0.364
FGR	8 (10.1%)	31 (7.8%)	0.493
Polyhydramnios	1 (1.3%)	4 (1.0%)	0.837
Stillbirth	4 (5.1%)	2 (0.50%)	**0.008**
Birth injuries	2 (2.7%)	0	**0.025**
NICU admission	38 (50.7%)	89 (22.5%)	**0.000**
Neonatal jaundice	11 (14.7%)	26 (6.6%)	**0.017**
Respiratory distress syndrome	9 (12%)	20 (5.1%)	**0.022**
Neonatal hypoglycemia	5 (6.7%)	11 (2.8%)	0.089

Table 3: Complications associated with pregnancy, as well as maternal and fetal outcomes, in women with gestational diabetes mellitus (using HbA1c cutoff) and normoglycemia

Parameter	*Women with GDM (using HbA1c cutoff)*	*Normogylcemic women*	*p-value*
Abortion	0	1 (0.3%)	0.438
Gestational hypertension	11 (6.1%)	15 (5.1%)	0.611
Preeclampsia	6 (3.4%)	14 (4.7%)	0.473
PPROM	9 (5%)	8 (2.7%)	0.184
Preterm	14 (7.8%)	7 (2.4%)	**0.005**
FGR	14 (7.8%)	25 (8.4%)	0.818
Polyhydramnios	3 (1.7%)	2 (0.7%)	0.299
Stillbirth	3 (1.7%)	3 (1.0%)	0.528
Birth injuries	2 (1.1%)	0	0.067
NICU admission	54 (30.7%)	73 (24.8%)	0.167
Neonatal jaundice	14 (8.0%)	23 (7.8%)	0.959
Respiratory distress syndrome	11 (6.3%)	18 (6.1%)	0.956
Neonatal hypoglycemia	12 (6.8%)	4 (1.4%)	**0.002**

36.84 weeks ± 3.08 days. The mean birthweight in GDM patients was 2.7 ± 0.66 kg. The study conducted by Soumya et al.[1] reported that GDM mothers had significantly greater incidence of oligohydramnios, FGR, macrosomia, polyhydramnios, and neonatal complications like neonatal hypoglycemia, RDS, and jaundice, and needed NICU admission. The mean birthweight reported in their study of GDM patients was 2.7 ± 0.7 kg.

Our study reported a mean HbA1c of 5.55% and 4.95% in GDM and non-GDM mothers, respectively. In the study conducted by Soumya et al.,[1] 500 patients were tested for HbA1c levels during GDM screening, i.e., 24–28 weeks, and in the study conducted by Rajput et al.,[16] 607 patients were tested during 24–28 weeks of gestation, and the mean HbA1c value in patients with GDM was 6.2 ± 0.6% and 5.73 ± 0.34%, respectively.

In the present study, the best cutoff value of HbA1c for detecting GDM, with optimal sensitivity (74%) and specificity (69.8%), was 5.15%, and the AUC value was equal to 0.778. Rajput et al.[17] conducted a similar study and the HbA1c cutoff point to diagnose GDM was 5.95% showing a sensitivity of 28% and specificity of 97% and the AUC of ROC curve of glycated hemoglobin was 0.805. Soumya et al.[1] reported a cutoff of 5.7%, showing a sensitivity of 73.3% and specificity of 75.6% for the diagnosis of GDM, and the AUC of ROC curve of glycated hemoglobin was 0.826. A case–control study conducted by Mousavi et al.,[18] for diagnosing GDM in Iranian women reported the best HbA1c cutoff point as 5.05% with sensitivity and specificity of 80% and 76%, respectively, and the AUC of ROC curve of HbA1c was 0.82.

Mid-trimester HbA1c levels more than 5.15% were associated with antenatal complications like gestational hypertension, polyhydramnios, and PPROM, but showed significant correlation with threatened preterm and no correlation with the rates of induced labor, perineal injury, shoulder dystocia, or occurrence of cesarean or instrumental delivery. The results were similar to a study conducted by Soumya et al.,[1] where HbA1c levels at 24–28 weeks of gestation showed good correlation with polyhydramnios, oligohydramnios, and macrosomia, but showed significant correlation with the occurrence of shoulder dystocia and blood loss at delivery and no correlation with FGR, congenital malformation, rates of perineal injury, and occurrence of cesarean section. HbA1c level showed a significant correlation with adverse neonatal outcomes in terms of hypoglycemia but showed no correlation with birthweight, gestational age at birth, and APGAR score at birth.

The glycation of hemoglobin is an irreversible non-enzymatic process between glucose beta chain of hemoglobin (Hb). HbA1c, expressed as the percentage of total hemoglobin, indicates the average levels of blood glucose over the last 4–6 weeks and its effectiveness as a diagnostic test for GDM requires validation with further studies.

Limitations

The limitations of our study were the small sample size and it was conducted at one center only.

Conclusion

Oral glucose tolerance test is the benchmark test for GDM screening although poorly tolerated by antenatal women and labor-intensive. HbA1c is an easy and convenient test with lesser day-to-day variation.[19] The precision of using HbA1c for screening and diagnosing GDM is still uncertain. In conclusion, HbA1c cannot replace the role of OGTT in diagnosing GDM but it can result in a significant reduction in the burden of testing with OGTT, if a cutoff of 5.15% is used.

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