



GLYCOSYLATED HEMOGLOBIN AS PREDICTOR OF GESTATIONAL DIABETES MELLITUS

Obstetrics & Gynaecology

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KEYWORDS

INTRODUCTION

- Gestational diabetes mellitus (GDM) is defined when glucose intolerance resulting in different severity level of hyperglycemia is discovered during gestation/pregnancy (3)
- Pregestational diabetes refers to any type of diabetes diagnosed before a pregnancy. Gestational diabetes mellitus (GDM) refers to diabetes diagnosed in the second trimester (T2) or third trimester (T3) of pregnancy that is not clearly overt diabetes (2)
- It is a global health concern, and in India, the condition affects as many as 5 million women annually. (14) There is wide variability in reported prevalence estimates for GD in India, varying from less than 4% to nearly 18% (14)
- According to ACOG, screening is done by 2 step method at 24-28 weeks. In Step 1, glucose challenge test (O'Sullivan test) is done in which 50 g anhydrous glucose irrespective of previous meal status is given and venous sample is taken after one hour. If the value is less than 140 mg/dl it is considered as negative and if the value is more than 140mg/dl then OGTT with 100 gm anhydrous glucose requiring a fasting status of 8-14 hours. is performed and the values are interpreted using Carpenter and Couston criteria (step 2) (8)
- Despite a government mandate to screen all pregnant women for GD, to date there has been incomplete implementation and uptake of screening programs. Existing studies on GD in India are limited to single-center studies, with most conducted in urban, hospital-based populations
- In 1999, for the sake of simplicity, the World Health Organization (WHO) introduced one-step screening and diagnostic test criteria for GDM. Which was based on a single cut-point of 140 mg/dl, 2 hours after a 75 gm glucose load administered in the fasting state. Problem with this test is getting pregnant women for antenatal checkups in fasting status especially in country like India, Where screening is mandatory.(8)
- Recently WHO adopted the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria, which has resulted in an increase in the detected incidence which has resulted in an increase in the detected incidence of GDM. The guidelines recommends that at 24-28 weeks a 75 g oral glucose tolerance test (OGTT) should be done for all pregnant women (7)
- The new guidelines laid down by International Association of Diabetes in Pregnancy Study Group (IADPSG) clearly specifies to screen for diabetes in early pregnancy using Fasting Blood Sugar (FBS) or Glycosylated haemoglobin A1C or Random Blood Sugar (RBS) with their threshold being >126 mg/dl, >6.5%, >200 mg/dl respectively, to recognise early the patients with risk of complications due to GDM (7)
- Based on Anjalakshi et al study, diabetes in pregnancy study group of India (DIPSI) adopted non- fasting 75 gm OGTT as "gold standard" for screening gestational diabetes mellitus. In this test, 75 gm of glucose was dissolved in 200 ml of water and asked to consume over 15 to 20 minutes. The cut off for this test is 140 mg/dl. (8)
- oral glucose tolerance test (OGTT) performed at 24-28 weeks of gestation is the current recommended test to diagnose GDM. However, it necessitates fasting for 10 hours, waiting for at least two hours, require labor and repeated venipunctures. (3) to overcome this cumbersome test HbA1c can be used as predictors of gestational diabetes
- It is the measurement of glycated hemoglobin which is used routinely as an indicator of blood glucose control in the prior 3 months. It may be the way for earlier identification of women at risk of GDM. (3)
- HbA1c is the product of an irreversible non-enzymatic binding of glucose to plasma proteins, specifically haemoglobin (Hb). The mean plasma glucose over the erythrocyte life span is correlated with a degree of glycosylation. (10)
- It is a single, non-fasting blood test and reflects glucose levels over the previous 4–8 weeks. As compared with glucose testing, it has been shown to have greater reliability with <6% interlaboratory variation. Thus, HbA1c test has improved analytical stability with greater standardisation between assays and less preanalytical variation. Further comparisons with fasting blood glucose and 2 h postprandial glucose have shown HbA1c to have less intraindividual variation as it does not appear to be affected by diurnal variation, meals, fasting, acute stress or by the large number of common drugs known to influence glucose metabolism. The test is validated for a red cell survival time of approximately 3 months. Therefore, results need to be interpreted carefully in the clinical situation whereby erythrocyte half-life is significantly shortened by, for example, haemoglobinopathies, haemolysis, transfusion, anaemia and chronic renal failure. (10)
- Dilutional anaemia of pregnancy and increased erythrocyte turnover have, to date, hampered its acceptance as a tool for screening, if not diagnosis, of GDM (10)
- The first-trimester HbA1c level is a reliable predictor of complications during pregnancy, including preeclampsia, fetal macrosomia, and large for gestational age birth weight [8].
- HbA1c has advantages compared to the OGTT as the blood sample can be drawn in a non-fasting state and there is no need for glucose ingestion or timed blood sampling. Further, the sample stability is better for HbA1c than for plasma glucose [1]
- Fasting blood glucose (FBG) is used as an early screening tool for gestational diabetes. However, FBG requires fasting, and as FBG has great variability and poor repeatability, it is not effective in the early screening for GDM. Measuring glycosylated hemoglobin (HbA1c) levels has several advantages over measuring FBG levels, it is more convenient as fasting is not required and more stable and is subject to fewer day-to-day variations due to stress or illness. (9)
- During pregnancy, the HbA1c level exhibits biphasic changes, with decreases between the first trimester and mid-pregnancy, followed by increases in the third trimester. Based on this physiological phenomenon, the HbA1c level at the first trimester, mid-pregnancy and third trimester may represent different biomarkers with different cut-off points, which may be linked to GDM and adverse pregnant outcomes. (4)

- Many studies have indicated that in early pregnancy and the first-trimester HbA1c level elevations may represent a useful measurement to screen women with GDM. However, in the second-trimester and later pregnancy, the HbA1c level could not replace the OGTT for GDM diagnosis (4)
- Taking the above physiological changes into consideration it was felt that if there was a biomarker for predicting carbohydrate intolerance in pregnancy, it could help in earlier intervention and mitigate the consequences related to it
- There is an apparent need for a universally acceptable, much simpler and accessible test for GDM screening in first trimester. Glycosylated HbA1c is currently a good measure to know sugar control. (7)
- women without preexisting diabetes, an early pregnancy HbA1c measurement of 5.9% to 6.4% (41 to 46 mmol/mol) identifies a group with a 3-fold increased risk of adverse pregnancy outcomes such as macrosomia and preeclampsia. (6)
- One of the reasons for the lack of consensus on reference range of HbA1c in pregnancy to screen for pre-diabetes or GDM is that HbA1c levels fluctuate with each tri- mester. It is thought that HbA1c levels fall in late pregnancy due to the decreased erythrocyte lifespan along with associated physiological anaemia in pregnancy. Several studies have demonstrated that HbA1c is generally lower in pregnant compared to non-pregnant individuals (12)
- The current study was planned to evaluate the role of HbA1c in the screening of GDM while keeping DIPSI with 75 gram of glucose (diabetes in Pregnancy as study group in India) as results as the primary endpoint.

AIM AND OBJECTIVE OF THE STUDY

Aim is to explore the predictive value of first trimester HbA1c levels in patients with gestational diabetes mellitus

METHODS:

This study was a cross sectional study conducted at antenatal OPD of Department of Obstetrics and Gynecology of Srinivas institute of medical science, mukka, Mangalore from September 2020- September 2022. Five hundred antenatal cases were considered for the study. All antenatal patients before 18 weeks of gestation attending antenatal clinic for the first time were selected for the study.

Patient who were known case of diabetes mellitus, deranged renal functions and HbA1c > 6.5 were excluded from the study.

A written informed consent was taken from all patients participating in the study. The screening procedure, importance of screening, follow-ups and complications of GDM were explained to the patients before being recruited.

A detailed history was elicited from the participants including obstetric history and other past medical history, family history and personal history followed by physical examination in the antenatal OPD. BMI of the patient was calculated in kg/m^2 before 18 weeks of gestation. Venous blood sample of participants were taken between 18-20 weeks of gestation for HbA1c, complete hemogram and renal function test. An ultrasonography was also carried out. Cases with anemia, deranged renal functions, HbA1c $\geq 6.5\%$ were excluded.

Cases with HbA1c levels less than 6.5% were finally selected for further evaluation in the study. These cases also underwent routine screening for GDM between 24-28 weeks of gestation DIPSI guidelines were chosen as the screening test. A venous blood sample was taken 2 h after giving the mother 75 gm of oral glucose irrespective of fasting state. The cut-off value for diagnosis of GDM was 140 mg/dl or more 2 hours after 75 gm glucose.

We carried out study with aim of screening for GDM. The results were tabulated, corrected and statistically analyzed.

Patient diagnosed with GDM were further managed as per institutional protocol. The ethical clearance was obtained for this study.

RESULTS

All 500 patients at 1st trimester coming to our outpatient department after taking into consideration the laid down inclusion and exclusion criteria, underwent HbA1c along with other routine investigations. This was followed up by doing a glucose tolerance test as per the DIPSI (diabetes in pregnancy study group of India) criteria. The date obtained was analyzed.

DIPSI was chosen in this study as the diagnostic test for gestational diabetes mellitus after evaluating HbA1c values at 1st trimester as it was convenient to perform it in the antenatal clinic. This screening test does not require fasting state and single venous sample was needed.

Among them, 191 participants were diagnosed as having GDM, and 309 participants had normal blood glucose levels.

The age group of the patients were distributed between 19 to 39 years out of which maximum, i.e. 50.2 % between the age group of 26-30 years and 24 % in the range of 31 to 35 years and 6 % above 35 years. The mean age group of the patient was 28.6 ± 3.43 % (Table 1)

Table 1 Distribution Of Study Population As Per Maternal Age

AGE	NUMBER OF CASES	PERCENTAGE	MEAN +/- SD
19-25	99	19.8%	28.6 +/- 3.43
26-30	251	50.2%	
31-35	120	24%	
36-39	30	6%	

In the present study the maximum were multigravida 311 (62.20 %) than primigravida which is 189 (37.80 %) (Table 2) the incidence of gestational diabetes were slightly higher than that in the primiparous participants

Table 2 Parity Status Of Study Population

PARITY	NO OF CASES	PERCENTAGE
PRIMI	189	37.80%
MULTI	311	62.20%

In the present study 191 were DIPSI positive and were labelled as gestational diabetes mellitus. And remaining 309 were found to be DIPSI negative. the relation between HbA1c levels and DIPSI positive cases were analyzed in this present study

Table 3 Correlation Of Different Hba1c Levels And The Dipsi Positive Cases

HBA1C	NO.OF CASES	DIPSI POSITIVE	PERCENTAGE OF DIPSI POSITIVE CASES
3.6-4.5	50	0	0
4.6-5	90	12	13.3
5.1-5.5	122	13	10.6
5.6-6	116	58	50
6.1-6.4	122	108	88.5

The analysis showed that the maximum number of cases, that is, 166 out of 191, diagnosed with gestational diabetes mellitus had HbA1c values ranging between 5.6-6.4 % and this correlation was statistically significant with the p value of 0.00001 (Table 3).

The range of DIPSI values at 24 to 28 weeks of gestation was between 98 to 270 mg/dl with median being 128 mg/dl. Also, the correlation coefficient between cut off of HbA1c and DIPSI at 24-28 weeks was 0.51 which is highly suggestive of a significant correlation and with 30-32 weeks FBS/PPBS was 0.34 which is highly suggestive of significant correlation. The p value was 0.00001 and therefore it was statistically significant. (Table 4) Overall, the correlation between HbA1c levels at 1st trimester and DIPSI positivity was found to be statistically significant with moderate strength r value of 0.686.

Table 4 Correlation Between Hba1c And DIPSI And With FBS/PPBS

VARIABLE		CORRELATION COEFFICIENT	PVALUE
First trimester HbA1c	24-28 weeks DIPSI	0.51	0.00001
	30-32 weeks FBS/PPBS	0.34	0.00001
24-28 weeks DIPSI	30-32 weeks FBS/PPBS	0.41	0.00001

HbA1c	3.4	6.6	Mean	5.44	SD	0.686
DIPSI	98	270	Median	128		

The receiver operating characteristic (ROC) curve is a graphical plot that illustrates the diagnostic ability of a binary classifier system. This ROC curve analysis has showed an AUC (area under the curve) of 0.882 which suggests significant prediction of gestational diabetes mellitus by HbA1c. (Figure 1).

The present study shows that at the cut off value of 5.7 % the sensitivity and specificity of HbA1c for predicting gestational diabetes 81.25 % and 81.49 % respectively (Table 5).

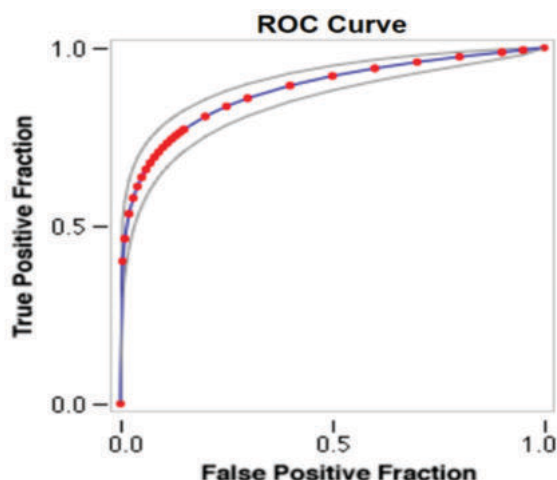


Figure 1 ROC Curves Showing The Sensitivity And Specificity Of HbA1c 1st Trimester In Predicting GDM]

Fitted ROC Area: 0.882 (p-value-0.001)

ROC curve analysis reveals AUC of 0.882 which suggest significant prediction of GDM by HbA1c

Table 5 The values of HbA1c to predict GDM

HbA1c	sensitivity	specificity	Ppv	npv	p-value
5	93.75%	41.50%	50%	91.40%	<0.05
5.5	86.45%	70.12%	64.34%	89.25%	
5.6	83.45%	76.21%	68.42%	88.21%	
5.7	81.25%	81.49%	73.23%	87.45%	
5.8	70.30%	86.03%	75.84%	82.29%	

5.7 is the best cut off with high sensitivity and high specificity.

Correlation between HbA1c levels at 1st trimester and DIPSI positivity is statistically significant with moderate strength of association between them (r value of 0.882).

DISCUSSION

An early screening of GDM before 20 weeks is desirable. By early interventions which can be targeted at the screened positive population, we can reduce the growing burden on health care

Gestational diabetes poses a risk for both mother and fetus which is associated with maternal and fetal morbidity such a polyhydramnios, preeclampsia, operative delivery, macrosomia, shoulder dystocia, intrauterine growth retardation, neonatal hypoglycaemia and perinatal mortality (7) (14) it also associated with elevated risk of GD in future pregnancy and the development of type 2 diabetes and cardiovascular diseases in later life (14)

A study has found that elevated level of glyco Hb was associated with congenital anomaly. The risk of congenital malformation is related to maternal glycemic status as poor glycemic control has teratogenic effect during embryogenesis

HbA1c has been widely used in the diagnosis and management of diabetes patients, but its use in the diagnosis of gestational diabetes remains controversial as HbA1c levels fall during the first trimester [10]. This study was aimed at exploring the value of first- trimester HbA1c levels in predicting GDM. (9)

In this prospective study among women without pre-existing medical conditions, we systematically examined HbA1c measured across pregnancy starting in the first trimester and its relation with GDM risk. The risk of GDM increased in a profound linear fashion in women with an HbA1c of 5.7%, which is the best cut off with high sensitivity and specificity. Furthermore, we observed a significant improvement in GDM prediction with the inclusion of first trimester HbA1c over conventional risk factors alone. Thus, in low-risk women without pre-existing medical conditions, HbA1c measured in the first trimester improved GDM prediction.

A recent study by Hughes et al. conducted in New Zealand among 16,122 pregnant women found an early pregnancy HbA1c 5.9% (41 mmol/mol) to be a clinically relevant marker for major congenital anomaly, preeclampsia, shoulder dystocia, and perinatal death, although the results could not be adjusted for potential confounding factors (11)

In our present study maximum number of DIPSI positive cases i.e., 108 (88.5 %) who has 1st trimester HbA1c in the range of 6.1-6.4 and 58 (50 %) cases were DIPSI positive with HbA1c value of 5.6-6. thus the correlation coefficient between the first trimester HbA1c and DIPSI at 24 -28 weeks were 0.51 with the p value of 0.00001 and correlation coefficient of first trimester HbA1c and with 30-32 weeks FBS and PPBS is 0.34 and P value of 0.00001. the study also evaluated the correlation of 24-28 weeks DIPSI with 30-32 weeks FBS/PPBS which has correlation coefficient of 0.41 with p value of 0.00001

Thus present study shows HbA1c of 5.7 is the best cut off with high sensitivity (81.25 %) and high specificity of (81.49 %) which is of statistically significant with p value of <0.05. many studies have been conducted to find a correlation between the two parameters .few of them have been mentioned below

Rayis DA, Ahmed ABA et al conducted a study on reliability of glycosalted hemoglobin in the diagnosis of gestational diabetes mellitus he conducted a study among 348 women he had HbA1c level of 5.850 % the sensitivity and specificity for the diagnosis of GDM was 13.24 % and 91.43 % respectively. In our study sensitivity (81.25 %) and specificity (81.49 %) has been increased for the HbA1c value of 5.7 %

Ho YR, Wang P et al, studied regarding the Associations of mid-pregnancy HbA1c with gestational diabetes and risk of adverse pregnancy outcomes in high-risk Taiwanese women he determined the optimal cut off point of HbA1c level to predict GDM was 5.7 % and with the sensitivity of 45 % and the specificity of 84 %. Our study showed a higher sensitivity and specificity (4)

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Khan SH, Manor R, Baig AH et al conducted a study about role of HbA1c in diagnosis of gestational diabetes mellitus he included 280 subjects among which 50 (17.85) was found to be gestational diabetes and differences in Glycated hemoglobin between the groups was significant (p<0.002). Glycated hemoglobin test provided sensitivity of 70 % and specificity of 84.78 % (5)

Shrivastava N, Durugkar K et al conducted a study about role of HbA1c as a predictor of gestational diabetes mellitus he include 500 pregnant women among them 60 turned out to be gestational diabetes and found maximum number of DIPSI positive cases (93.33 %) have raised HbA1c levels and cut of value of 5.5 % of HbA1c has 98.6 % sensitivity and 84.9 % specificity in predicting Gestational diabetes mellitus. Comparatively our study HbA1c of 5.7 % has higher sensitivity (81.25 %) and specificity (81.49 %) in predicting GDM.

CONCLUSION

Diabetes mellitus is one of the most important medical disorders in pregnancy which can lead to various adverse pregnancy outcomes. India being diabetic capital of the world it is of prime importance to screen and diagnose diabetes mellitus at earliest stage during pregnancy. Among the various screening test used for

identifying early GDM recently DIPSI has been widely accepted due to its feasible and less cumbersome nature

The present study was done on 500 antenatal cases and it was found that maximum number of antenatal cases diagnosed with gestational diabetes had HbA1c value ranging between 5.5 to 6.4 %. Hence, we conducted this study to find out any association between HbA1c and DIPSI positive cases and a positive correlation between them.

On the basis of above observations, it was concluded that HbA1c can employed as a predictive biomarker for detecting gestational diabetes mellitus at early stage in antenatal period.

It is felt that future study with a larger sample size can help in further confirmation and validation of the correlation between HbA1c and positive screening test for GDM. A reliable predictor will help in earlier detection and treatment of GDM and thereby reduce the number of complications associated with gestational diabetes mellitus in pregnancy.