ROLE OF GLYCOSYLATED HAEMOGLOBIN IN PREDICTION OF FOETOMATERNAL OUTCOME IN GESTATIONAL DIABETES MELLITUS

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ABSTRACT

OBJECTIVE
To explore the role of Glycosylated Haemoglobin (HbA1c) in predicting foetomaternal outcome in pregnant women with gestational diabetes mellitus (GDM).

METHOD
This was a prospective study of 100 women with singleton pregnancy with <34 weeks of gestation with >140 mg/dL on glucose challenge test enrolled in Kasturba Hospital, Delhi, from 2012 to 2013. A detailed history, examination, routine obstetrical investigations including 75 g Oral Glucose Tolerance Test (OGTT) and HbA1c level were done. Patients were managed accordingly and followed till delivery. Their obstetrical and perinatal outcomes were noted and the data was compared using chi-squared test and Fischer's exact test with a two-tailed p-value <0.05 being considered significant.

RESULTS
Foetomaternal outcomes were compared among patients with >6% HbA1c level and those with abnormal OGTT. Adverse maternal outcomes in patients with >6% HbA1c included excessive weight gain (68% vs. 58.2%), preeclampsia (44% vs. 38.2%), polyhydramnios (44% vs. 35.2%), caesarean section (68% vs. 52.9%), wound sepsis (24% vs. 17.6%) as compared to patients with abnormal GTT. Adverse foetal outcomes and neonatal complications in patients with >6% HbA1c included preterm delivery (36% vs. 32.3%), intrauterine death (12% vs. 8.8%), LGA babies (52% vs. 29.4%), congenital anomalies (13.6% vs. 9.6%), respiratory distress (27.3% vs. 16.1%), hypoglycaemia (36.8% vs. 25.8%), hyperbilirubinaemia (31.8% vs. 29%), and NICU admission >2 days (95.4% vs. 64.5%). A high HbA1c was found to be comparable to OGTT in predicting adverse maternal outcome in GDM patients while a poor foetal outcome was more commonly associated with HbA1c >6%.

CONCLUSIONS
HbA1c is a sensitive tool for prediction of foetomaternal outcomes in patients with abnormal blood glucose value; hence, it should be advised in all pregnant women.

KEYWORDS
Gestational Diabetes Mellitus, Oral glucose Tolerance Test, Glycosylated Haemoglobin.

INTRODUCTION: Gestational Diabetes Mellitus (GDM) is characterised by abnormal high blood glucose level of varying severity with onset or first recognition during pregnancy. Diabetes is a problem that spans the generations. There are genetic factors that pass from generation to generation, but there are environmental components also - the metabolic environment that pregnant woman creates for her foetus in-utero that also contributes to development of diabetes in future.[1]

According to Canadian Diabetes Association 2003, perinatal mortality and morbidity is increased in diabetic pregnancies through increased stillbirths and congenital exposure to maternal hyperglycaemia. Although, glycaemic control is important in reducing microvascular complications due to diabetes in pregnancy. It has not reduced the rate of congenital anomalies, macrosomia, and other adverse outcomes.[2] This maybe as a result of our lack of understanding of the epidemiology and pathogenesis of GDM (Omu et al. 2010) especially the role of inflammation, cytokines, and lipid metabolism.[3]

Detecting the evidence of diabetes mellitus in pregnancy is a major challenge as the condition is associated with diverse range of maternal signs and symptoms and adverse foetal outcome, which can be to some extent prevented if the diagnosis is made in time. Multiplicity of guidelines available is the reflection of lack of available evidence demonstrating a benefit of any national or international standard criteria with regards to any specified foetomaternal outcome. The American Diabetic Association, 2015 recommends Oral Glucose Tolerance Test (OGTT) to be used for diagnosis of GDM as a single step or two step procedures.[4]

Single Step Method	Two Step Method
75 g OGTT with Plasma Glucose (PG) measurement at fasting, 1 h and 2 h after overnight fasting (>8h)	50 g GLT(non-fasting) with 1h PG measurement if PG >140 mg/dL, then 100 g OGTT
Fasting: 92 mg/dL (5.1 mmol/L)	Fasting: 95 mg/dL (5.3 mmol/L)
1h: 180 mg/dL (10.0 mmol/L)	1h: 180 mg/dL (10.0 mmol/L)
2h: 153 mg/dL (8.5 mmol/L)	2h: 155 mg/dL (8.6 mmol/L)
	3h: 140 mg/dL (7.8 mmol/L)
Table 1: Diagnostic Criteria of GDM by ADA, 2015	

With the OGTT, the patient should be on an appropriate diet for three days beforehand and have had a satisfactory period of overnight fasting. The test is time consuming to perform taking at least two hours and involving three blood glucose samples. It is also labour intensive for pathology laboratories. The test is poorly tolerated by a significant number of people with nausea, vomiting, delayed gastric emptying, and hence has poor patient compliance. Hence, there is a need for more convenient screening alternative.

Glycated Haemoglobin (HbA1c) is formed by the binding of glucose to the C chain or D chain of haemoglobin A and as a result of non-enzymatic catalysis of mature haemoglobin and glucose. HBA1c is an indicator to reflect long-term glycaemic control of the last 2-3 months (the average lifespan of a red blood) and has high reproducibility compared with the Fasting Plasma Glucose (FPG) or OGTT. It offers the advantage of not needing to fast before the test.

The American Diabetic Association, 2015, added HbA1c as a diagnostic tool for individual with type 2 diabetes mellitus with a threshold fixed at 6.5% for diagnosis. It was, however, not recommended for use in GDM for the purpose of diagnosis.

Recent results from the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study showed that HbA1c measurements similar to glycaemia levels were significantly associated with all adverse outcomes and higher levels of maternal HbA1c were related to a greater frequency of adverse outcomes.[5]

According to study by Baxi L et al (1984), patients with GDM who have not been screened in early pregnancy may benefit from determining HbA1c levels as it reflects the blood glucose control of the past 2 to 3 months and high HbA1c level is correlated with increased macrosomia risk.[6]

Saleh A. Aldesouqi et al (2008) studied retrospectively the OGTT and HbA1c values in GDM patients and suggested that with cutoff value of HbA1c level of 6%, 87.1% of GDM patients would have picked up by HbA1c.[7]

This prospective study was undertaken to ascertain the role of HbA1c in predicting foetomaternal outcome in pregnant women with gestational diabetes mellitus.

MATERIAL AND METHODS: A total of 252 antenatal patients registered in Kasturba Hospital were subjected to Glucose Challenge Test (GCT) with 50 g of glucose. Among those, 100 patients with singleton pregnancy with <34 weeks of gestation had plasma glucose value >140 mg/dL on GCT and they were enrolled in the study from 2012 to 2013.

After informed consent, a detailed history and examination were done. They were subjected to oral glucose tolerance test with 75 g glucose after withdrawing fasting blood and venous plasma was drawn at 1 hr and 2 hr and a baseline HbA1c level was done. The plasma glucose was estimated in the central laboratory by the Glucose Oxidase Peroxidase (GOD-POD) method. Pregnant women with two high blood glucose values out of three on OGTT were diagnosed as GDM using the 2-h 75 g OGTT criteria proposed by the ADA and labelled as group-A. In the non-GDM group those with one deranged value were diagnosed to be Impaired Glucose Tolerance (IGT) and women with all three values within normal range were labelled as Normal Glucose Tolerance (NGT).

All those who had baseline HbA1c was more than 6% (the upper limit of normal range) were considered to have gestational diabetes and were labelled as group-B.

GDM women were advised Medical Nutrition Therapy (MNT) for two weeks and those who did not respond to MNT sufficiently by having FPG >95 mg/dL or post meal >140 mg/dL were advised insulin. Maternal and foetal outcomes were compared among group A and group B and statistically analysed using SPSS version 15 and the data was compared using chi-squared test and Fischer exact test with a two tailed p-value <0.05 being considered significant.
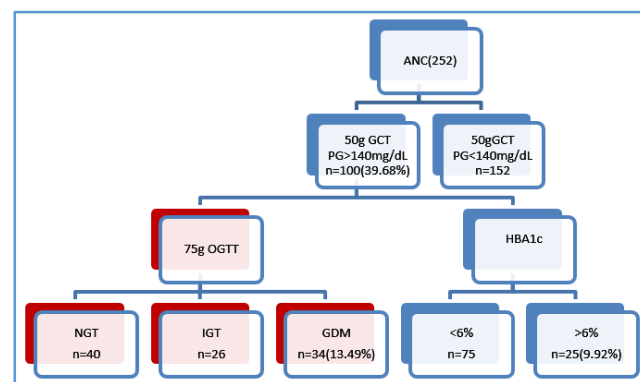

Figure 1: Study Plan and Distribution of Cases

RESULTS: In our study, the prevalence of GDM by OGTT in all antenatal women was 13.49% and by HbA1c 9.92%. While considering the 100 enrolled patients (39.68%) with 1 hr PG >140 mg/dL after 50 g glucose load, 34% were diagnosed to have GDM by OGTT, 26% had Impaired Glucose Tolerance (IGT) and 40% had Normal glucose tolerance (NGT).

25% of study group had HbA1c more than 6%. The mean HbA1c of GDM group by OGTT was 6.26% and of non-GDM group by OGTT was 4.48%. There were 3 women with high HbA1c who had Impaired Glucose Tolerance (IGT) by

OGTT. 65% of GDM group by OGTT had HbA1c more than 6%.

22% had both abnormal OGTT and elevated HbA1c.

OGTT	HbA1c <5.3	HbA1c - 5.3-6	HbA1c >6 (Group B)	Mean HbA1c
NGT (n=40)	40	0	0	4.122
IGT (n=26)	18	5	3	5.03
GDM (n=34) (Group A)	1	12	22	6.26
Total (n=100)	59	17	25	
Table 2: Correlation of HbA1c with OGTT				

Antenatal complications in group-B included excessive weight gain >10 kg (68% vs. 58.2%), preeclampsia (44% vs. 38.2%), polyhydramnios (44% vs. 35.2%) as compared to group-A. Major intrapartum complications in group-B were caesarean section (68% vs. 52.9%), assisted vaginal delivery (8% vs. 5.9%) as compared to group-A. There was no incidence of shoulder dystocia in our study. Postpartum complications in group-B were fever (12% vs. 17.6%), wound sepsis (24% vs. 17.6%), deep vein thrombosis (4% vs. 2.9%) as compared to group-A [Figure-2]. Although, the rate of maternal complications were more in women diagnosed as GDM by HbA1c method than by OGTT, the difference was not statistically significant. (P-value >0.05).

Adverse foetal complications in group-B as compared to group-A included preterm delivery (36% vs. 32.3%), intrauterine death (12% vs. 8.8%) [Figure-3]. Large for Gestational Age (LGA) is defined as birth weight >90th percentile of birth weight adjusted to gestational age. LGA babies in group-B were 52% as compared to 29.4% in group-A. The difference was statistically significant (p-value <0.05) [Figure-3].

Major neonatal complications in group-B were congenital anomalies (13.6% vs. 9.6%), respiratory distress (27.3% vs. 16.1%), hypoglycaemia (36.8% vs. 25.8%), and hyperbilirubinaemia (31.8% vs. 29%) as compared to group-A. NICU admission >2 days in group-B was 95.4% as compared to 64.5% in group-A, which was statistically very significant (p-value <0.001). [Figure-4].
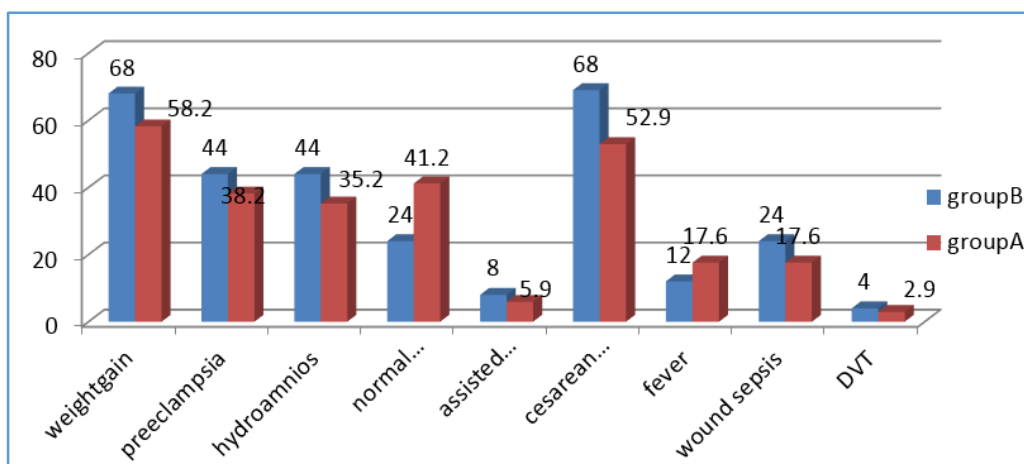

Figure 2: Comparison of Maternal Complications in Group-B (n=25) and Group-A (n=34)
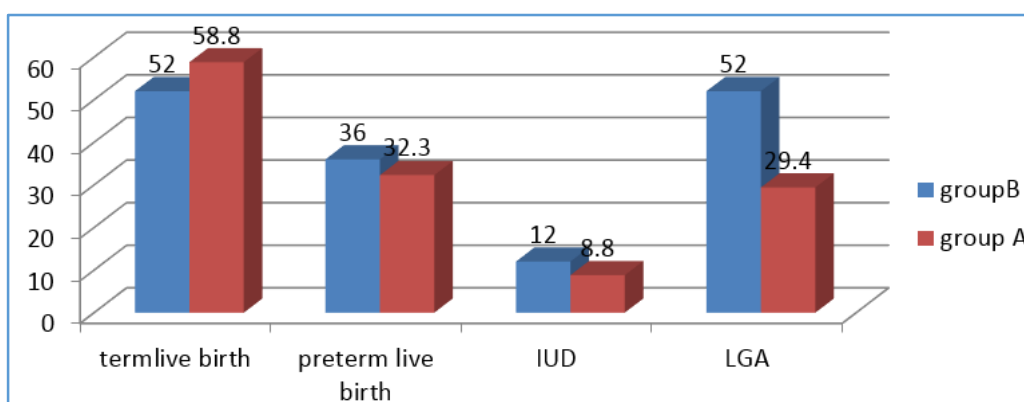

Figure 3: Comparison of Foetal Complications in Group-B (n=25) and Group-A (n=34)
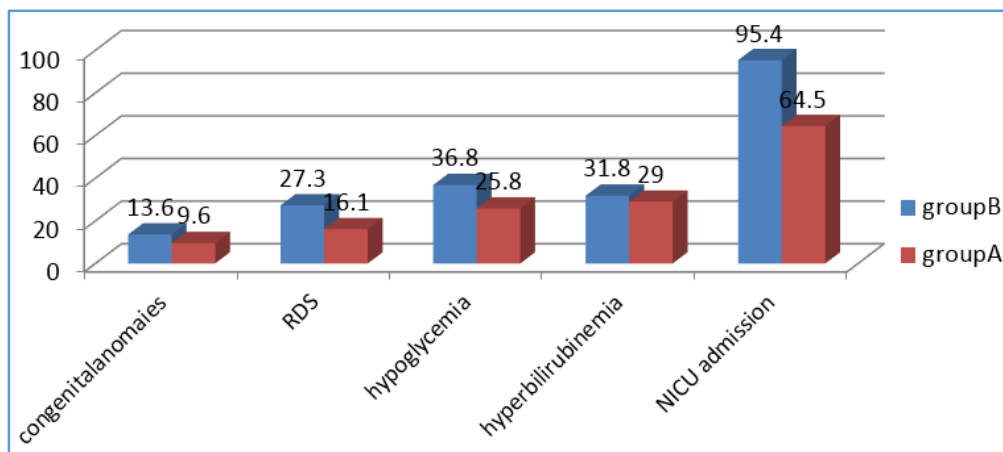
Figure 4: Comparison of Neonatal Complications in Group-B (n=25) and Group-A (n=34)

DISCUSSION: Indian women have high prevalence of diabetes and their relative risk of developing GDM is 11.3 times compared to white women.[8] Seshiah V (2004) reported an overall prevalence proportion of GDM at 17.7% in young population of pregnant women from Chennai.[9] Beside ethnicity, the prevalence is affected by multiple factors such as higher maternal age, higher pre-pregnancy weight and BMI, more sedentary lifestyle, and women of higher socioeconomic status.

In our study, out of 252 antenatal women, 100 (39.68%) had plasma glucose more than 140 mg/dL one hour after 50 g glucose load. These 100 women were subjected to both oral glucose tolerance test and baseline HbA1c levels. Out of 100 patients, more women (34) were diagnosed to have GDM by OGTT (13.49% out of all ANC) as compared to GDM by an elevated HbA1c >6% (25% of study group or 9.92% of all ANC). Majority of GDM by OGTT (65%) had elevated HbA1c. Mean HbA1c of GDM by OGTT was higher (6.26%) than non-GDM (4.48%). This suggests a reasonable sensitivity of HbA1c as a predictor of OGTT.

In study by Balaji et al in 2007, normal mean HbA1c values in Asian Indian pregnant women as 5.36+/-0.36% was reported. Deriving a reference range of +/-2 standard deviations of 4.64-6.08 from these data. The resulting cutoff value of 6.08% is reasonably comparable to our study. [10]

In our study, 3% of women had elevated HbA1c >6% who were diagnosed as non-GDM by OGTT. They all had Impaired Glucose Tolerance (IGT). This might be a reflection of mild insulin resistance and poor glycaemic control in them. Cianni et al reported in 2007 that pregnant women with one abnormal value on OGTT (IGT in our study) have impairment of insulin secretion and insulin sensitivity, although these defects are more pronounced in women with GDM.[11] Sermer et al stated that increased carbohydrate intolerance in women without overt GDM was associated with a graded increase in the incidence of macrosomia.[12]

In both the group-B and group-A antenatal complications like antenatal weight gain (68% vs. 58.2%), preeclampsia (44% vs. 38.2%), polyhydramnios (44% vs. 35.2%) were higher as compared to their reference group with their respective normal GTT or HbA1c level <6%. The

difference in predicting antenatal complications was not statistically significant between group B and group A.

According to study by Baxi L et al (1984), the sensitivity and specificity of glycosylated haemoglobin for the diagnosis of gestational diabetes were 63.6 and 81.6%, respectively. Fifty percent of patients with an initially elevated glycosylated haemoglobin value delivered macrosomic infants whereas no patient with a normal glycosylated haemoglobin value had a macrosomic infant. An elevated glycosylated haemoglobin value may alert the obstetrician of a potentially elevated mean blood sugar level and may warrant aggressive management of gestational diabetes.[6]

V. Hiilesma et al (2000) reported the adjusted ratio for preeclampsia as 1.6 for each increment in the HbA1c value at 4-14 (median 7) weeks of gestation. They reported that changes in glycaemic control during 2nd half of pregnancy didn't significantly alter the risk of preeclampsia.[13]

Major intrapartum complications in group-B like caesarean section (68% vs. 52.9%), assisted vaginal delivery (8% vs. 5.9%) were comparable to group-A. Postpartum complications in group-B like fever (12% vs. 17.6%), wound sepsis (24% vs. 17.6%), and deep vein thrombosis (4% vs. 2.9%) were comparable to group-A. Although, the rates are more in group-B, the difference was not statistically significant.

The present study suggests that HbA1c better predicted the perinatal outcome as depicted by a higher rate of congenital anomaly (13.6% vs. 9.6%), macrosomia (52% vs. 29.4%) in group-B, and also the neonatal respiratory (27.3% vs. 16.1%) and metabolic complications. Major neonatal complications were more frequent in group-B than in group-A. NICU admission >2 days was higher in group-B (95.4%) than in group-A (64.5%), which was statistically very significant (p-value <0.001).

This is supported by the study by Choi Y. J. et al (2009) who reported there is more incidence of LGA babies in GDM population with >7% HbA1c level.[14]

Rajput et al. reported that HbA1c levels cannot replace OGTT for the diagnosis of GDM. However, it can be used in combination with OGTT to obviate the need for further OGTT.[15]

Katon et al studied the relationship of HbA1c in pregnancy with the outcomes of women and their offspring. They reported that in GDM women, an increment of HbA1c by 1% may increase the risk for abnormal glucose metabolism by 2.63 folds within 6 weeks after delivery. However, the results are conflicting on the association between HbA1c and neonatal birth weight and the correlation coefficient ranges from 0.11 to 0.51. Thus, they speculated that, when compared with OGTT, which has complex detection procedures and is costly, HbA1c seems an attractive indicator used to predict the poor outcome of GDM women.[16]

Paula Breitenbach Renz (2015) used 5.8% HbA1c as cutoff point to detect participants with and without GDM and found that those classified as having the condition were more likely to be older and to have had previous GDM and a family history of DM as well as higher BMI, blood pressure (systolic and diastolic), higher glycaemia (fasting, 1h and 2hG) and cholesterol levels. These characteristics have been found to be related to an increased probability of adverse outcomes for both the mother and the babies.[17]

Our study has limitations as the number of subjects included is too small to calculate sensitivity and specificity. Secondly, the cut off for HbA1c is taken arbitrarily as 6%. More studies should be carried out to ascertain the range of HbA1c in normal pregnancy and its cut off for abnormal glucose tolerance.

In India, more than 70% of population live in rural settings and facilities for diagnosing diabetes itself is limited. In this scenario, performing OGTT as recommended by other associations [e.g., American Diabetes Association, National Diabetes Data Group, International Association of Diabetes, and Pregnancy Study Groups] to diagnose GDM is not possible as the cost and the cumbersome process involved is prohibitive to perform three blood tests after a glucose load and thus not favoured by both healthcare providers and specifically the seekers. This maybe one of the reasons why the program for universal screening for all pregnant women is not implemented. Most importantly detection and care of GDM has become a public health priority as the stillbirth rate is high in India and one of the causes is gestational diabetes mellitus.[18] Hence, the need is for a simple and economical test to diagnose GDM. In this context, determining baseline HbA1c level from one blood sample without any glucose load is cost effective and evidence based as revealed by the pregnancy outcome in this study and study done by Gunnar L. Nielsen et al (2006).[19]

CONCLUSION: Patients with >6% HbA1c level are at high risk for developing pregnancy complications and at higher risk of having LGA babies and NICU admission. HbA1c is a sensitive tool for prediction of foetomaternal outcomes in patients with abnormal blood glucose value; hence, it should be universally recommended. Further studies are warranted to substantiate this suggestion and to establish the role of HbA1c in predicting foetomaternal outcome in GDM patients.

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