Original Research Article

The study of role of HbA1c as a predictor of gestational diabetes mellitus

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ABSTRACT

Background: India is the diabetic capital of the world and gestational diabetes mellitus contributes to a significant number of cases. Gestational diabetes mellitus is a common medical complication of pregnancy and may lead to serious consequences. Because of these reasons, 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. Hence, for this purpose, the role of HbA1c was studied as a predictor of gestational diabetes mellitus.

Methods: This was a cross sectional study. Five hundred antenatal cases were considered for this study. All antenatal patients before 18 weeks of gestation attending antenatal clinic for the first time were selected and these patients were subjected to HbA1c followed by diabetes in pregnancy study group of India (DIPSI) test between 24-28 weeks and the results were analyzed to find any correlation between the two.

Results: The main objective of the present study was to find whether HbA1c can be used as a predictor of gestational diabetes mellitus. In this study out of 500 women screened, 60 women turned out to have gestational diabetes mellitus. When comparing DIPSI positivity with various levels of HbA1c, it was found that maximum number of DIPSI positive patients (93.33%), had raised HbA1c levels.

Conclusions: Maximum number of DIPSI positive cases had HbA1c level between 5.5 to 6 and this association was found to be statistically significant and a positive correlation was established between the two.

Keywords: Diabetes in pregnancy study group of India, Gestational diabetes mellitus, HbA1c, Predictor, Screening, Significant correlation

INTRODUCTION

India is the diabetic capital of the world with as many as 50 million people suffering from diabetes mellitus. It is a very big challenge that the country has to face! Gestational diabetes is an integral part of the problem.

Gestational diabetes mellitus is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy.[1] It is becoming a common medical complication during pregnancy. The incidence of diabetes complicating pregnancy has increased approximately by 40% between 1989 and 2004.[2] It is a prevalent and potentially serious condition that may affect both mother and neonate. It is associated with preeclampsia, increased caesarean sections, macrosomia and many other high-risk events. This calls for health priority, early detection and treatment of this condition that could reduce the risks for the mothers as well as babies. In pregnant females, in-utero exposure to maternal hyperglycaemia leads to foetal hyperinsulinemia, which in turn causes increase in foetal

fat cells leading to obesity and insulin resistance in childhood. Thus, it is important to screen this condition as early as possible. Normal pregnancy is characterised by mild fasting hypoglycaemia, post prandial hyperglycaemia and hyperinsulinemia. Hence it is considered as a diabetogenic state. Human placental lactogen also increases with gestational age mimicking growth hormone like action, thereby potentiating the diabetogenic state.

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.[3] 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).

In 1999, for the sake of simplicity, the World Health Organization (WHO) introduced one-step screening and diagnostic test criteria for GDM. This was based on a single cut-point of 140 mg/dl, 2 hours after a 75 gm glucose load administered in the fasting state.[4] Due to difficulties in getting women in fasting state in the OPD visiting for antenatal check-up specially in India where screening of GDM should be mandatory as the prevalence rate is high, Anjalakshi et al, conducted a study comparing the GTT done in the fasting and the non-fasting states.[5] They found that the non-fasting OGTT had 100% specificity and sensitivity when compared to the fasting. Based on this 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.[6]

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.

Glycated haemoglobin (HbA1c) is a form of haemoglobin that is measured primarily to identify past 3 month's average plasma glucose concentration. It is a measure of beta-N-1-deoxy fructosyl component of haemoglobin formed in a non-enzymatic glycation pathway by haemoglobin exposure to plasma glucose.[7] Use of HbA1c in monitoring the degree of control of glucose metabolism in diabetic patients was proposed in 1976 by Anthony Cerami, Ronald Koenig and co-workers.[8]

In 2010, the American Diabetes Association (ADA) included HbA1c test as a diagnostic criterion for diabetes (DM) in the general population. A cut-off of HbA1c -48 mmol/mol (6.5%) was established for the diagnosis and was endorsed by the World Health Organization (WHO) in 2011.

Aim of the present study was to explore the scope of HbA1c having a role in predicting GDM.

METHODS

This study was a cross sectional study conducted at antenatal OPD of Department of Obstetrics and Gynecology of Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pimpri, Pune from September 2016 - August 2018. 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. Patients who were known cases of diabetes mellitus, anaemia, deranged renal functions and HbA1c values ≥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 ≥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. Those turning negative for this screening test were made to undergo the test again at 30-32 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 the study with the aim of screening for GDM. The results were tabulated, correlated and statistically analyzed. Patients diagnosed with GDM were further managed as per institutional protocol. The ethical clearance was obtained for this study.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) for Windows 24.0 (SPSS, Inc., Chicago, Illinois) was used for the analysis. Descriptive statistics were used in reporting demographic details. Data from the study was

analysed by using Pearson correlation coefficient. Receiver operating characteristic (ROC) curve was used to evaluate the diagnostic performance of HbA1c. The Youden index formula is defined as J = sensitivity + specificity - 1, which is equivalent to the maximum sum of sensitivity and specificity for all the possible values of the cutoff point. The level of significance was 0.05.

RESULTS

500 patients at 18 weeks of gestation coming to our outpatient department were randomly selected and recruited for this study after taking into consideration the laid down inclusion and exclusion criteria. On recruitment, HbA1c was carried out 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 18 weeks of gestation 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.

The age group of the patients included in this study varied from 18 to 35 years, from which the maximum, that is, 67.8% were in the age group of 18-25 years, 26% of the patients were aged 26-30 years and 6.2% were above 30 years. The mean age group of the patients in this study was 24.34 years (Table 1). In the present study maximum number of cases (61%) were multigravidas. (Table 2).

60 out of these 500 patients turned out to be DIPSI positive and were labelled as gestational diabetes mellitus. Thus, the prevalence of gestational diabetes mellitus in our study was found to be 12%. The co-relation between HbA1c levels and DIPSI positive cases were analysed in this study.

The analysis showed that the maximum number of cases, that is, 56 out of 60, diagnosed with gestational diabetes mellitus had HbA1c values ranging between 5.5-6% 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 141 to 184 mg/dl with mean being 153.4 mg/dl. Similarly, the DIPSI values at 30 to 32 weeks of

gestation ranged between 141 to 250 mg/dl with the mean value of 151.4 mg/dl. Also, the correlation coefficient between cut off of HbA1c and DIPSI at 24-28 weeks was 0.599 (Table 4) which is highly suggestive of a significant correlation (Table 5). The p value was 0.0001 and therefore it was statistically significant. Similarly, the p value for HbA1c and DIPSI at 30-32 weeks is 0.0001 with correlation coefficient .655 which again suggested highly significant correlation. Overall, the correlation between HbA1c levels at 18 weeks and DIPSI positivity was found to be statistically significant with moderate strength r value of 0.66.

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 0.918 which suggests significant prediction of gestational diabetes mellitus by HbA1c. (Table 6 and Figure 1). The present study shows that at the cut off value of 5.5% the sensitivity and specificity of HbA1c for predicting gestational diabetes 98.6% and 84.9% respectively (Table 7).

Table 1: Distribution of study population as per maternal age.

Age in years	Number of cases	Percentage (%)	Mean±SD
18-25	339	67.8	
26-30	130	26	24.34±3.70
>30	31	6.2	

In this study it is found that maximum number of cases screened positive for GDM have age ranging between 18-25 years. The relation between age and GDM positivity is not found to be statistically significant.

Table 2: Parity status of study population.

Parity	Number of cases	Percentage (%)
Primigravida	195	39
Multigravida	305	61

In the present study maximum number of cases were multigravidas.

The analysis shows that the maximum number of cases diagnosed with GDM had HbA1c values ranging between 5.5-6% and the result was statistically significant with a p value of 0.00001.

Table 3: Correlation of different HbA1c levels and the DIPSI positive cases.

HbA1c (%)	4.1-5	5.1-5.4	5.5-6	6.1-6.5	Total	Chi square value	p-value
DIPSI positive	1	1	56	2	60	385.09	0.00001
DIPSI negative	355	65	10	10	440		

Table 4: Correlation between HBA1c and DIPSI.

Variable		Correlation coefficient	p-value
18 weeks (HbA1c)	24-28 weeks test value in mg/dl	.599**	.0001
	30-32 weeks (test values)	.655**	.0001
	18 weeks (HbA1c)	1	-
= 24-28 weeks (diagnostic test value) in mg/dl	30-32 weeks (test values)	.823**	.0001

Correlation between HbA1c levels at 18 weeks and DIPSI positivity is statistically significant with moderate strength of association between them (r value of 0.66).

Table 5: Strength of HbA1c as a predictor for GDM, as indicated by r-value.

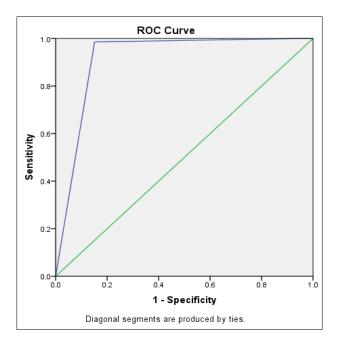| Value of r	Strength of relationship
. -1.0 to -0.5 or 1.0 to 0.5	Strong
-0.5 to -0.3 or 0.3 to 0.5	Moderate
-0.3 to -0.1 or 0.1 to 0.3	Weak
-0.1 to 0.1	None or very weak

Figure 1: ROC curves showing the sensitivity and specificity of HBA1c 18 weeks in predicting GDM.

The p-value of this ROC curve between GDM and HbA1c is 0.001 and area under curve (AUC) is above 0.5 i.e., 0.918. This means that HbA1c can significantly diagnose GDM with specific sensitivity and specificity. If we consider a cut off value of 5.5 for HbA1c, then the sensitivity to GDM is 98.6% and specificity is 84.9%.

Table 6: AUC of (18 weeks) HbA1c in predicting GDM.

AUC	Std. error	p-value	Confidence interval	
			Lower bound	Upper bound
.918	.014	.000	.891	.944

ROC curve analysis reveals AUC of 0.918 which suggests significant prediction of GDM by HbA1c.

Table 7: The values of HbA1c to predict GDM.

Cut off values	Sensitivity	1-Specificity	Specificity
3.00	1.000	1.000	0
4.50	1.000	.953	0.047
5.50	.986	.151	0.849

DISCUSSION

The main objective of the present study was to find out the correlation of different HbA1c levels with OGTT positivity and whether HbA1c can be used as a predictor of gestational diabetes mellitus. When comparing DIPSI positivity with various levels of HbA1c, it was found that maximum number of DIPSI positive patients (93.33%), had HbA1c ranging between 5.5 to 6%. The correlation coefficient between cut off of HbA1c and DIPSI at 24-28 weeks was 0.599 which is highly suggestive of a significant correlation. The p-value was 0.0001 and therefore it was statistically significant. A lot of studies have been conducted to find a correlation between the two parameters. Some of them have been mentioned blow.

Renz PB et al, analysed that the at the cut off value of 5.8% the sensitivity and specificity of HbA1c as a predicting marker for GDM is 26.4% and 94.9% respectively. In the same study the sensitivity and specificity with the cut off value of 5.5% was 50.6% and 82.9% respectively. The association between the two parameters was significant with the p value <0.001. Thus, it was concluded that different HbA1c cut off points in combination with the screening test may be used as a diagnostic tool for GDM.[9]

Khalafallah A et al, reported that in a study of 480 antenatal patients at the cut off value of HbA1c of 5.4%, the sensitivity and specificity was 27% and 95% respectively. Spearman correlation between HbA1c and screening test of GDM showed significant association with p value less than 0.0001. Their study concluded that with the HbA1c cut off of >/=5.4% can be used as a predictor of GDM.[10]

Ye M et al, conducted a similar study amongst 1989 women and concluded that for a cut off value of HbA1c ≥5.5% the sensitivity was 14.8% and specificity was 95.7%. Thus, HbA1c might be used as a tool to predict the increased risk of GDM.[11]

Wu K et al, carried out a study on 690 women. They concluded that with the HbA1c cut off value of 5.55 the specificity of diagnosing GDM was 99.8% and the sensitivity was 4.7%. The study concluded that HbA1c is a reliable test for predicting GDM.[12]

Y Ran Ho et al, conducted a similar study amongst 1989 women and the results revealed that at a cut off value 5.7%, the sensitivity and specificity of HbA1c for predicting GDM was 45.2% and 84.1% respectively.[13]

Similar studies have been carried out and results showed conclusions as depicted in Table 8.

Table 8: Comparison of sensitivity and specificity of HbA1c as a predictor for gestational diabetes mellitis across various studies.

Study	HbA1c cut off (%)	Specificity (%)	Sensitivity (%)
Ho YR et al	5.7	84.1	45.2
Breitenbach P et al	5.8	94.9	26.4
Wu K et al	5.55	99.8	4.7
Ye M et al	≥5.5	95.7	14.8
Khalafallah A et al	5.4	95	27
Rajput et al	≥5.4	85.7	61.1
Present study	5.5	84.9	98.6

Thus, this study shows that at a cut off value of 5.5%, the specificity for predicting GDM is 84.9% which is comparable to the results from other studies. However, the sensitivity of prediction of GDM was found to be 98.6% which was higher as compared from the values derived in other studies.

CONCLUSION

Diabetes mellitus is one of the most important medical disorders in pregnancy which can lead to various adverse pregnancy outcomes. Various screening tests for detecting glucose intolerance have been recommended. In India DIPSI test, is being widely used for GDM screening as it found to be patient friendly. 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%. 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 be employed as a predictive biomarker for gestational diabetes mellitus. 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.

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