Effectiveness of Glycated Haemoglobin in the Diagnosis of Gestational Diabetes Mellitus among Pregnant Women in Port Harcourt, Nigeria

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Abstract

Background: Gestational Diabetes Mellitus (GDM) is a common metabolic complication in pregnancy with a broad range of adverse foetal and maternal outcomes if not properly managed. Due to the difficult nature of the Oral glucose tolerance test (OGTT), the utilization of the Glycatedhaemoglobin (HbA1c) test as a simpler and acceptable alternative has been suggested. The aims were to determine the GDM prevalence, the diagnostic accuracy, the optimal cut-off point and the validity of the HbA1c in diagnosing GDM using OGTT as the gold standard in the University of Port Harcourt Teaching Hospital (UPTH).

Methodology: This was a prospective cross-sectional study involving a cohort of 250 antenatal attendees at 24-28 weeks of pregnancy in the UPTH from 1st February 2018 - 30th April 2018. Socio-demographic data and results of the OGTT and HbA1c tests were analysed using SPSS 21.0 for windows® statistical software. The area under the Receiver Operating Characteristics (ROC) curve was used to determine the diagnostic accuracy of HbA1c. The Youden index was used to get the optimal cut–off point for HbA1c. The validity of the HbA1c was determined using sensitivity, specificity, positive predictive value and negative predictive value. The P-value at $p<0.05$ was set as the level of significance.

Results: Out of the 250 women, 36 (14.4%) had GDM hence in this study, the GDM prevalence was 14.4%. Area under the curve (AUC) = 0.649; 95% confidence interval: 0.550 – 0.748; p-value = 0.004. The optimal cut-off point for HbA1c was 5.18% with a sensitivity of 63.9%, a specificity of 59.3%, a positive predictive value of 20.9% and a negative predictive value of 90.7%.

Conclusion: The HbA1c at the Optimal cut-off point of 5.18% in our environment cannot replace the OGTT in the diagnosis of GDM because of its low sensitivity and specificity but will be useful in the screening for GDM because of its high negative predictive value at 24-28 weeks gestation. This will reduce the count of gravidae who undergo the cumbersome OGTT

Keywords: Effectiveness; Glycated Haemoglobin; Gestational Diabetes mellitus; Port Harcourt; Nigeria.

Introduction

Gestational Diabetes Mellitus (GDM) isglucose/carbohydrate intolerance of varying severity that is first recognized during pregnancy and is independent of glycaemic status after delivery.[1] It is estimated that approximately 10% of pregnancies are affected by diabetes and approximately 87.5% of pregnancies complicated by diabetes are estimated to be due to gestational diabetes; 7.5% of pregnancies complicated by diabetes are due to type 1 diabetes and

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the remaining 5% of pregnancies complicated by diabetes are due to type 2 diabetes.[2] The global prevalence of gestational diabetes in women aged 20–49 years was estimated to be 16.2%.[3] About 21.3 million live births were affected by GDM in 2017.[3] More than 88% of these cases were estimated to occur in low and middle-income countries.[3] A study using the new World Health Organization (WHO) criteria found a prevalence of GDM of 14.9% in the University of Port Harcourt Teaching Hospital.[4]

Gestational Diabetes Mellitus (GDM) is a common and potentially serious condition that may result in adverse perinatal and maternal outcomes.[5] Early onset of GDM is associated with an increased risk of foetal anomalies and foetal loss.[6]Pregnancies complicated by gestational diabetes mellitus are at risk of a broad range of antepartum, intrapartum and postpartum complications for both mother and baby.[7, 8]Early diagnosis and prompt treatment of this condition with good glycaemic control minimise the risks of the adverse outcome for both the mother and the baby.[9]It also reduces serious perinatal complications and improves the woman's quality of life as regards her health.[9] Despite the establishment of the risks for the above complications in the presence of GDM, there is considerable controversy regarding its diagnosis.[10]The WHO in 2013 recommendeda 75g 2- hour oral glucose tolerance test (OGTT) at 24–28 weeks of gestation for GDM diagnosis.[11] This is the preferred diagnostic test for GDM in the University of Port Harcourt Teaching Hospital (UPTH). Any one of FBS $\geqslant$ 5.1 mmol/L, 1–hour $\geqslant$ 10.0 mmol/L and/or 2–Hour $\geqslant$ 8.5 mmol/L is diagnostic.[11]

However, OGTT is difficult, labour intensive, often poorly tolerated by antenatal women and time consuming for both pregnant women and the health care facility.[11-14]Furthermore, the recommendation for universal screening has increased the burden of testing significantly.[14, 15]

The blood glucose is unstable ex vivo and this leads to a variance of results between laboratories by up to 14% in a third of the cases.[16] This makes the reproducibility of the test (OGTT) poor.[17] Even though guidelines are in place, the glucose threshold values for diagnosis and methods of testing differ from one institution to another.[14]OGTT is a specialized test and many centres are not able to provide this service especially in the rural areas hence, disadvantaging an already vulnerable cohort of women.[18] An acceptable screening test for GDM should meet the following requirements: high precision, high reproducibility, convenience and low cost.[19]The need for a simpler, universally acceptable and accessible test for GDM diagnosis is thus apparent.[14]

In the last decades, Glycosylated haemoglobin (HbA1c), a marker showing the average of plasma glucose in the past eight to twelve weeks,has been endorsed as a diagnostic marker for diabetes mellitus outside pregnancy.[20, 21]Glycosylated haemoglobin (HbA1c) is the product of non–enzymatic glycosylation of haemoglobin and the mean plasma glucose over the erythrocyte life span is correlated with the degree of glycosylation.[]The use of (HbA1c) in the diagnosis of GDM has been recommended.[22]

In contrast to OGTT, the HbA1c test does not require any special patient preparation.[21] It is a single non–fasting blood test and there is no ingestion of glucose or timed blood sample collection.[21] Glycosylated haemoglobin (HbA1c) is less expensive, less stressful with minimal side effects and only one venipuncture.[14] Furthermore, the sample stability is better for HbAIc than the plasma glucose.[21]Glycosylated haemoglobin (HbA1c) has greater reliability with a variance of results between laboratories of < 6%.[16]Thus, the HbA1c has improved analytical stability with greater standardization between assays and less pre-analytical variation.[14]When compared to fasting blood glucose and two-hours postprandial blood glucose, HbA1c has less intra-individual variation as it does not appear to be affected by the time of the day it was sampled, meals, acute stress, fasting, diurnal variation or by the many common drugs known to influence glucose metabolism.[23,24] The HbA1c is valid for a red cell survival time of approximately 3 months thus conditions that shorten red blood cells life span like haemolysis, transfusion, haemoglobinopathies, anaemia, chronic renal/liver failure, may affectthe result.[14]Nonetheless, it has been shown that the mean plasma glucose of the last 1 month contributes to 50% of the final result.[25]Therefore, HbA1c may have a role in the screening and management of GDM, especially if lower cut-off values than those recommended for the diagnosis of diabetes mellitus in non-pregnant adults are used, and these values need to be validated by long-term studies.[22]

Genetically determined variations in the degree of Glycosylation of haemoglobin, independent of glycaemia are thought to exist and are reflected in the differences in HbA1c levels.[26, 27]The use of HbA1c as a screening tool for gestational diabetes is yet to be evaluated in our population. This study aims to determine the prevalence of GDM, the diagnostic accuracy, the optimal cut-off point and the validity of HbA1c in the diagnosis of GDM using OGTT as the gold standard in the UPTH.

Materials and Methods

Study design and setting

This prospective cross-sectional study was carried out from 1st February 2018 - 30th April 2018 among antenatal clinic attendees in the UPTH. The University of Port Harcourt Teaching Hospital (UPTH) is an 800-bed tertiary hospital located in Port Harcourt, Rivers State, Nigeria. This health institution provides all levels of health care services for Rivers State and the catchment states of the Niger Delta Area.The Obstetrics and gynaecology department of the UPTH has an annual delivery rate of over 2500 babies. The antenatal clinics holdfrom Monday to Friday, with each day overseen by ateam. The UPTH controls a modern Chemical Pathology laboratory equipped with auto-analyzers. Various biochemical tests are carried out in the laboratory including the blood sugar and glycosylated haemoglobin estimations.

Sample size determination and sampling techniques

The sample size was calculated using the formula: $n = Z^2 P(1-P)/ d^2$ where, n = Minimum Sample size, Z = The standard normal deviation at 95% confidence level. This corresponds to 1.96.P = prevalence of GDM in the antenatal women in Nigeria from previous studies = 14.9% $(0.149)^4$d = level of precision (0.05). The minimum sample size was thus calculated to be 194. Given allowance for a 10% attrition rate (non-response rate),the adjusted sample size for the study was therefore 220 women. A total of 250 consenting pregnant women who were between 24 – 28 weeks pregnant during the study period were however recruited through the simple random sampling method by balloting. Those who did not consent, already diagnosed with diabetes mellitus, had haemoglobinopathies/bleeding disorders, had chronic kidney or liver disease or pancreatic disease, had anaemia (Haemoglobin<10g/dL), had multifoetal pregnancies, and/or had an in vitro fertilization/assisted pregnancies were excluded from the study.

Data collection

Five research assistants who were resident doctors in the department and a dedicated medical laboratory scientist in the Chemical pathology department were recruited and trained for the study. The research assistants recruited the patients who met the inclusion criteria daily from the antenatal clinic. The recruited participants were counselled and informed consent was obtained. The data in their antenatal cards (age, tribe, marital status, educational status, parity, religion, Last Menstrual Period, Expected Date of Delivery, gestational age), were transferred into the proforma.

The participants were scheduled for the sample collection at 7:00 hours in a fasted state on the convenient day chosen by each of them within the week. They were reminded with text messages, WhatsApp messages and phone calls. They presented at 7:00 hours in the antenatal clinic on the appointment days in a fasted state. Blood specimens for fasting blood sugar and HbA1c assay were collected aseptically at 8:00 hours and put in fluoride oxalate vacutainer tube (for fasting blood sugar)and EDTA Vacutainer tube (for HbA1c estimation) respectively. Following the ingestion of the 75 g of glucose in 250 ml of water, blood specimens were aseptically collected from a peripheral vein at the 1 hour and the 2 hours and put in fluoride oxalate bottles for glucose estimation using the glucose oxidase method and read spectrophotometrically by the dedicated laboratory scientist. GDM was defined as present if fasting blood glucose was $\geqslant$ 5.1 mmol/L and/or glucose tolerance test (GTT) 1 hour$\geqslant$ 10.0 mmol/L and/or GTT 2 hour$\geqslant$8.5 mmol/L. The diagnostic criteria are defined by the ADA/WHO 2013 guidelines for the testing and diagnosis of GDM.[11]

Data Management

All results of the investigations were entered into the proforma. The data were collated, entered in a private computer (PC) with SPSS for windows version 21.0 software and analysed. Qualitative variables were expressed as frequencies and proportions. The optimal cut-off point for HbA1c was determined using Youden Index. The diagnostic accuracy of HbA1c was assessed using the Receiver Operator Characteristics (ROC) curve and the area under the curve (AUC) was determined. The validity of HbA1c against a gold standard of OGTT was calculated using Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV).

Ethical approval

Ethical clearance was given by the Hospital Research Ethics committee of the UPTH, Port Harcourt, Rivers State (Approval Number - UPTH/ADM/90/S0.II/VOL.XI/538). Ethical principles according to the Helsinki Declaration were adhered to during the research. Informed consent was obtained from individual participants.

Results

The mean age of the women was 31 years with a range of 20 -43 years. The prevalence of GDM was 14.4% (36 out of the 250 women who were sampled).

The mean age of women who participated in the study was 30.8 ± 4.6years with a range from 20-43 years. Two hundred and twenty-six (90.6%) of the women had a tertiary level of education, 247 (98.8%) of the participants were married and 246 (98.4%) of the participants were Christians (Table 1). Mean parity was Para 5 with a range of 0-5. One hundred and seven (42.8%) of the participants were Para 0. (Fig 1).

Fig 2 shows the Receiver Operator Characteristics (ROC) Curve for HbA1c. Area under the curve (AUC) = 0.649; 95% confidence interval: 0.550 – 0.748; p value = 0.004

Fig 3 shows the determination of the optimal cut off point for HbA1c from Youden Index. The optimal cut off point was 5.18%. The Youden Index was 0.234.

The sensitivity, specificity, positive predictive value and negative predictive value of HbA1c against the gold standard of OGTT in the diagnosis of GDM were 63.9%, 59.3%, 20.9%, and 90.7% respectively. (Table 2).

Table 1: Socio-demographic characteristics of the women

Variables N = 232	Frequency	Percentage
Age category		
20 – 24 years	23	9.2
25 – 29 years	80	32.0
30 – 34 years	94	37.6
35 – 39 years	47	18.8
⩾40 years	6	2.4
Marital status		
Married	247	98.8
Unmarried	3	1.2
Educational level		
Secondary	24	9.4
Tertiary	226	90.6
Occupational status		
Unemployed	55	22.0
Employee	109	43.6
Self-employed	86	34.4
Religion		
Christian	246	98.4
Muslim	4	1.6

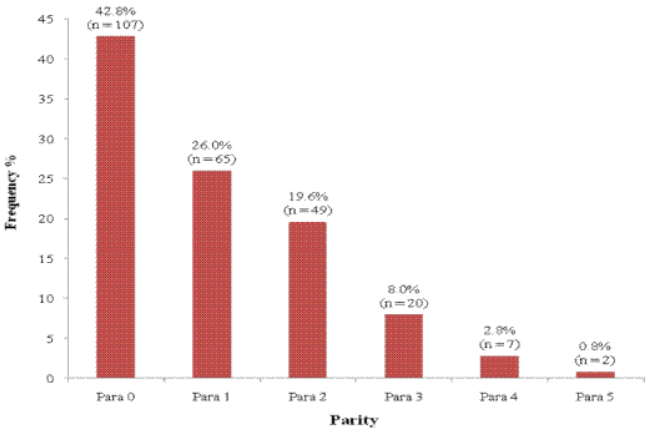

Figure 1: Parity of the Women

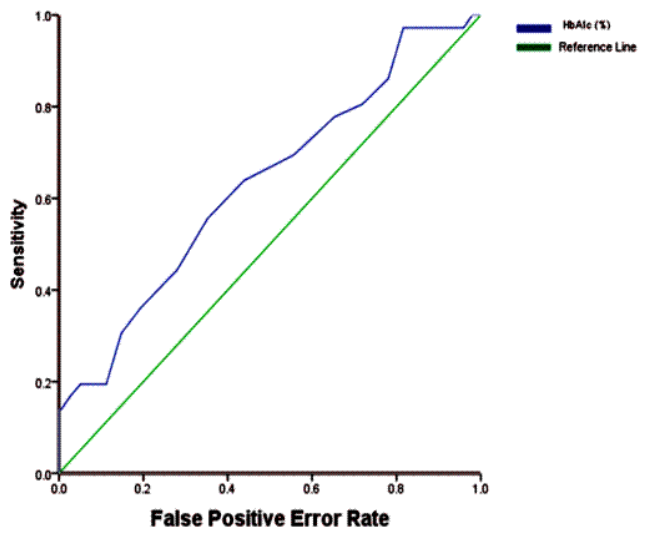

Figure 2: Receiver Operator Characteristics (ROC) Curve for HbA1c

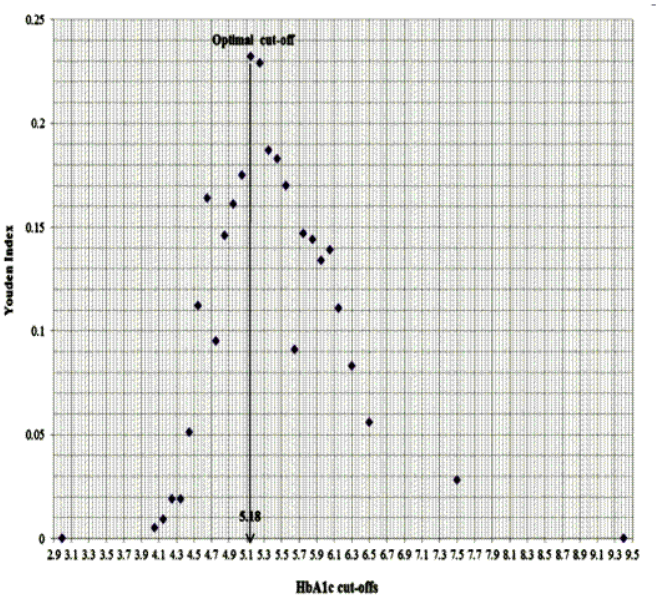

Figure 3: Determination of optimal cut off point for HbA1c from Youden Index.

Table 2: Validity tests for HbA1c as a screening tool for GDM against a gold standard of OGTT among ANC attendees in UPTH

		OGTT (Gold Standard)		
		GDM	**No GDM**	**Total**
HbA1c (screening test)	**GDM (≥5.18)**	23 True positive	87 False-positive	110
	No GDM (<5.18)	13 False-negative	127 True negative	140
	Total	36	214	250

$$Sensitivity = \frac{TruePositive}{TruePositive+FalseNegative} \times 100 = \frac{23}{23+13} = 63.9\%$$

$$Specificity = \frac{TrueNegative}{TrueNegative+FalsePositive} \times 100 = \frac{127}{127+87} = 59.3\%$$

$$Positive\ Predictive\ Value\ (PPV) = \frac{True\ Positive}{TruePositive+False\ Positive} \times 100 = \frac{23}{23+87} = 20.9\%$$

$$Negative\ Predictive\ Value\ (NPV) = \frac{True\ Negative}{TrueNegative+False\ Negative} \times 100 = \frac{127}{127+13} = 90.7\%$$

Discussion

Gestational Diabetes Mellitus (GDM) is a common metabolic complication in pregnancy.[11]

In this study, the prevalence of gestational diabetes mellitus was 14.4%. This is similar to the prevalence of 14.9% noted in a previous study using the OGTT screening method in this centre by Oriji et al.[] But it is higher than findings from other studies in the same centre.[28, 29] The prevalence found in this study is similar to the prevalence of 13.9% found in Ibadan by Kuti et al but higher than the prevalence recorded in the study in Lagos by Adegbola et al (5.4%).[30, 31]The differences may be due to the different diagnostic methods, diagnostic criteria and screening approaches (risk factor-based or universal) used in the studies and the year of the study. This study used the universal screening approach and 2013 WHO criteria for GDM diagnosis.

The prevalence of gestational diabetes mellitus as recorded in this study is higher than the findings by Seyeoum et al in Ethiopia (3.7%) and Nwanri et al in Tanzania (5.9%).[32,33]

The differences in the prevalence recorded in these studies may be due to the differences in the diagnostic methods, diagnostic criteria, screening approach (risk factor-based or universal) and ethnicity and/or body composition. The prevalence of GDM found in this study is less than the 33% recorded in Brazil by Renz et al.[34] It is higher than the 6.7% recorded in Norway and3-7% in North America.[, 35]It is similar to the 11.9% by Khalafallah et al in Australia.[14]

The Receiver Operator Characteristics (ROC) Curve for HbA1c in this study, had an Area under the curve (AUC) = 0.649; 95% confidence interval: 0.550 – 0.748; p-value = 0.004. This is similar to the AUC obtained for the ROC curve in another study.[34] The AUC recorded in this study is slightly higher than the 0.54 (95% confidence interval [CI] 0.46-0.61) found by Aggarwal et al.[36] This AUC as found in this study is slightly less than 0.852 and 0.826 recorded by Ryu et al and Soumya et al respectively.[36,37] These AUCs for the ROC curve in this study and previous studies all point to the fact that HbA1c has a role in the diagnosis and management of GDM since they all tend toward the integer 1 (one).

The Youden index in this study was 0.234. This is slightly less than the Youden Index of 0.581 obtained by Ryu et al.[36]Both values indicate that HbA1c has a diagnostic value in the evaluation of patients with GDM because the values are above zero and tend toward 1(one).

This study found an optimal cut off point for HbA1c determined from Youden Index to be 5.18%. The sensitivity, specificity, positive predictive value and negative predictive value of HbA1c against the gold standard of OGTT in the diagnosis of GDM as seen in this study were 61.1%, 64.8%, 24.1%, and 90.1% respectively. In this study, HbA1c does not have adequate sensitivity and specificity for the diagnosis of GDM and hence cannot effectively replace an OGTT for diagnosis of GDM but because of the high negative predictive value, HbA1c may play a role in the screening of GDM. At the determined optimal cut off point of 5.18% as found in this study, HbA1c has a high negative predictive value of 90.1% meaning that it can be used for screening antenatal women for GDM and reduce the number of women who will proceed to OGTT. In that, any woman with an HbA1c level less than 5.18% at 24-28 weeks gestation is most likely negative for GDM in that pregnancy. Women with HbA1c values of 5.18% and above at 24-28 weeks gestation will proceed to do the confirmatory OGTT for GDM diagnosis. The optimal cut-off value and the NPV recorded in this study are similar to the findings in previous studies.[, 36-38]The optimal cut-off value and the sensitivity and specificity noted in this study are similar to the findings recorded by other studies.[8, 14, 34] The sensitivity of 63.9% in this study is less than 95.6% recorded by Soumya et al.[38] The specificity

and the NPV in this study are similar to the values in another study.[38] The difference in sensitivity and specificity may be due to the different prevalence in the studies caused by the difference in the diagnostic criteria, screening approach and study design.

Limitations

This study is limited by the fact that it is hospital-based research and may not be transposed to the general population. Nonetheless, given a permissible error margin, the results of this study should give the true reflection of the effectiveness of HbA1c in the diagnosis of GDM in our population since this research was done in the University of Port Harcourt Teaching Hospital which is the largest referral health facility in Rivers State and a leading tertiary hospital in the Niger Delta region of Nigeria.

Conclusion

The result of this study showed that GDM is a major metabolic condition in our centre with a prevalence of 14.4%. The optimal cut-off point of HbA1c of 5.18% at 24-28 weeks gestation as obtained in this study cannot replace OGTT in the diagnosis of GDM but has a role in the evaluation/screening of women with GDM. At 24-28 weeks of gestation, HbA1c assay will reduce the number of women who undergo an unnecessary and cumbersome OGTT.

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