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Original Artide

Glycosylated Haemoglobin (HbA1c) as a Diagnostic Criterion for Hyperglycaemia First Detected in Pregnancy

Merry Alali Jaja[1], *Abbey Mkpe[2], Simeon Chijioke Amadi[2], Tehemen Kasso[1], Frederick Allison[3], Olufemi Adebari Oloyede[4], Esther Nonye-Enyidah[2], Kenneth Okagua[2], Ngozi Joseph Kwosah[2], Paul Kua[2], Rose Sitonma Iwo-Amah[2], Alpheaus Gogo Mba[2], Uduak S Ocheche[5], Basil Omieibi Altraide[2], Leesi Sapira-Ordu[2], Dickson Hezekiah John[2], Ada Nkemagu Okocha[2], Nestor Innimgba[5], Christian Ihenachor Akani[1]

[1]Department of Obstetrics and Gynaecology, University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, Nigeria. [2]Department of Obstetrics and Gynaecology, Rivers State University Teaching Hospital, Port Harcourt, Rivers State, Nigeria. [3]Department of Chemical Pathology, University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria [4] Department of Obstetrics and Gynaecology, Olabisi Onabanjo University Teaching Hospital, Sagamu, Ogun State, Nigeria. [5]PAMO University of Medical Sciences, Port Harcourt, Rivers State, Nigeria.

Abstract

Background: The study was prompted by the high prevalence of hyperglycaemia first detected in pregnancy (HIP) which is classified into diabetes mellitus in pregnancy (DIP) and gestational diabetes mellitus (GDM). This study aimed to determine the usefulness of Glycosylated Haemoglobin (HBA1c) in the diagnosis of HIP in the first trimester of pregnancy.

Methodology: The study was of a prospective cross-sectional design carried out between January 2020 and August 2020 at the University of Port Harcourt Teaching (UPTH) and Rivers State University Teaching Hospital (RSUTH). Three hundred and five consecutive pregnant women attending the antenatal clinic at 8 to 13 $^{+6}$ weeks of pregnancy were recruited for the study. Patients' socio-demographic information, anthropometric measurements, and medical, obstetric, and gynaecological history were recorded on a predesigned proforma. Blood was taken for an oral glucose tolerance test (OGTT) and glycosylated haemoglobin (HBA1c) levels. Ethical approval for the study was obtained from the Research Ethics Committee of the UPTH and RSUTH. **Results:** The prevalence of DIP, GDM, and HIP in the study was 2.62%, 28.85%, and 31.48% respectively. The ROC curve for HbA1c in the study showed a significant area under the Curve (AUC) value of 0.653%, 95% CI = 0.59 – 0.72, p = 0.001. The Youden index reached 2.50 and the optimal cut-off for HBA1c for diagnosis of diabetes was 5.25%. The sensitivity, specificity, PPV, and NPV for HbA1c against the Gold standard OGTT in the diagnosis of GDM were 36.5%, 88.5%, 59.3, %, and 75.2% respectively. HbA1c had high specificity and moderately high NPV.

Conclusion: Glycosylated haemoglobin was a fairly good tool for diagnosis of HIP in the first trimester, but it could not replace OGTT which is the gold standard.

Keywords: Glycosylated Haemoglobin; Diagnostic Criterion; Hyperglycaemia; Pregnancy.

Corresponding Author: *Mkpe Abbey, Department of Obstetrics and Gynaecology, Rivers State University Teaching Hospital, Port Harcourt, Rivers State, Nigeria. mkpeabbey@aol.com

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Quick Response Code:

Introduction

Glycosylated Haemoglobin (HbA1c) refers to haemoglobin which is bound to glucose. It reflects the average blood glucose over a period of the past two to three months. [1] HbA1c can be used as a diagnostic test for diabetes if stringent quality assurance tests are in place, assays are standardised to criteria aligned to the international reference values, and there are no conditions present that preclude its accurate measurement. [2] HbA1c of 6.5% was recommended as the cut-off point for diagnosing diabetes outside pregnancy. [1, 3, 4]

HbA1c levels drop significantly in early pregnancy. For 'early GDM', its levels of 40–42 Mmol/mol (5.8–6.0%) were reported to have a high specificity and positive predictive value for detecting women who met OGTT criteria for GDM at some stage in pregnancy. [5, 6] Applying an HbA1c threshold of 48mmol/mol (6.5%) led to missed diagnosis in 47% of the women. The use of HbA1c could help in avoiding the problem of day-to-day variability of glucose values, the need for patients to fast and to have preceding dietary preparations which were associated with OGTT.

HbA1c levels might be affected by a variety of genetic, haematological and illness-related factors. [2] Iron and vitamin B12 deficiency, decreased erythropoiesis, alcoholism, chronic kidney disease, increased red cells lifespan, splenectomy, increased bilirubin, carbamylated HB, large doses of aspirin and alcoholism increase HBA1c levels. Administration of erythropoietin, iron, vitamin B12, reticulocytosis, chronic liver disease, small doses of Aspirin, certain haemoglobinopathies, Vitamin C and E, shortened red cells lifespan, splenomegaly, rheumatoid arthritis, drugs like antiretroviral, ribavirin and dapsone, increased triglycerides and haemoglobinopathies decrease its levels. Haemoglobinopathies, HBf and methemoglobin either increase or decrease HBA1c levels. [7]

In women with diabetes mellitus in pregnancy (DIP), periconception high levels of HbA1c was independently associated with lower birth weight, [8] preeclampsia, [9] and birth defects. [10] It was also interesting that pregnancy-induced hypertension, preterm birth, and caesarean section were t associated with high levels of HbA1c in the second trimester of pregnancy. [11] So using the HBA1C as a diagnostic criterion of diabetes in pregnancy, has an added advantage of predicting the possibility of complications in diabetic patients and to crown it all, it also acts as a screening tool for preeclampsia, preterm births, small for gestational age babies, etc.

Aim

The aim of the study, therefore, was to determine the cut-off levels of HBA1c in the first trimester of pregnancy that could be used to diagnose Hyperglycaemia first detected in pregnancy (HIP), Diabetes in Pregnancy (DIP) and Gestational Diabetes Mellitus (GDM).

Materials and Methods

Study Area -The study was carried out at the University of Port Harcourt Teaching Hospital (UPTH) and the Rivers State University Teaching Hospital (RSUTH). Both are tertiary health facilities and are located in Port Harcourt which is the capital of Rivers State (one of the 36 states in Nigeria.) The subjects for the study were drawn from the antenatal clinic which runs every day of the week, Monday to Friday.

The study was of a cross-sectional design carried out between January 2020 and August 2020.The inclusion criteria were all pregnant women attending antenatal clinics at 8 to 14 weeks of gestation who gave consent for the study irrespective of their age. Patients who had no ultrasonographic estimation of gestational age at between 8 and 14 weeks of pregnancy, known to have pre-existing diabetes mellitus, and patients having babies with fetal genetic and chromosomal abnormalities were excluded.

Consecutive women attending the antenatal clinic that satisfied the inclusion criteria were counselled about the research project and verbal informed consent was obtained. A predesigned proforma was used to record

the socio-demographic information, such as age, tribe, educational status, maternal and husband's occupation, social history, gravidity, parity, and anthropometric measurements (weight, height and body mass index), and also clinical findings for each patient. Obstetric and gynaecological, general medical, and family history were also taken. Pregnant women that did not fully understand English language were provided with interpreters. Consent was obtained from patients for their data to be taken from their medical records and the optional storage of blood for as long as possible with a view of using it for future additional analyses if need be.

Blood for oral glucose tolerant test (OGTT) and HBA1c were taken from all the participants. They also had standard first-trimester ultrasound scans from 8 to 14 weeks of pregnancy in the fetal medicine unit of the participating centres. The ultrasound scan was meant to confirm fetal viability, date the pregnancy, identify any major foetal abnormalities, and confirm the number of fetuses. Pregnancy was followed up and managed, using the Nigerian national guidelines for antenatal care. Specifically, they were seen 4 weekly until 28 weeks then 2-weekly till 36 weeks, and then weekly till delivery. Patients were given malaria prophylaxis and Tetanus immunization as per national protocol.

The WHO 2014 diagnostic criteria for the interpretation of OGTT results were applied. [12] GDM is diagnosed with the following results: Fasting blood glucose (FPG) ≥5.1-6.9, 1-hour plasma glucose levels ≥10.0 mmol/L or 2-hour plasma glucose levels ≥8.5 – 11 mmol/L. Diabetes mellitus in pregnany (DIP) is diagnosed if Fasting blood glucose ≥7.0mmol/L or Random (2-hour postprandial) blood glucose level ≥11.1 Plasma glucose levels of ≤2.5mmol/L were also abnormal and required further clarification. Women who were diagnosed with HIP were treated according to a standard protocol.

Sample Size Calculation

The sample size of 305 was calculated using the sample size formula for descriptive cross-sectional study with a prevalence of 23.6%, precision of 5%, and standard normal deviation of 1.96 at 95% confidence interval. The prevalence of 23.6% was taken from a study that was conducted at the University of Port Harcourt Teaching Hospital, using fasting blood glucose. [13] Prevalence of diabetes in pregnancy was used because the performance of HBA1c was to be compared with that of the OGTT. Fasting blood glucose which is a component of OGTT was used in the study that gave a prevalence of 23.6% in the Niger Delta. [13]

$n = Z^2 \times PQ / d^2$
Where,
n = sample size
Z = the proportion of normal distribution corresponding to the required significance level (5%) which is 1.96
P = the prevalence of gestational diabetes in the first trimester of pregnancy in the previous study in 2018. [13]
Q = (1.00-P)
d = precision of 0.05
$n = 1.96^2 \times 0.236 \times (1- 0.236) / 0.05^2 = 3.8416 \times 0.236 \times 0.764 / 0.0025 = 277.06 = 277.$
If the attrition rate was considered to be 10%, the study sample size of 305 (277 + 28) was reached.

Data analysis

The sociodemographic, clinical, and anthropometric data and the OGTT and the HBA1c results of the patients were entered into an Excel file, cleaned, and then uploaded onto the Statistical Package for Social Sciences (SPSS) version IBM SPSS Statistics 28.0.1, 2021 for analysis. Data were presented in prose format, frequency distribution tables, and charts as appropriate. Quantitative variables were summarized using means and standard deviation while qualitative variables were expressed as frequencies and proportions. The diagnostic accuracy of HbA1c was determined, using area under the Receiver Operating Characteristics (ROC) curve while the Youden index was used to ascertain the optimal cut–off point for HbA1c in the diagnosis of diabetes. Sensitivity, specificity, positive predictive and negative predictive values were used to assess the validity of HbA1c in the diagnosis of diabetes.

Ethical consideration

Ethical approval for the study was obtained from the Research Ethics Committee of the University of Port Harcourt Teaching Hospital. The ethical clearance certificate number was UPTH/ADM/90/S.II/VOL.XI/902. All participating pregnant women were adequately counselled and written consent was obtained, before enrolment. The study was carried out under strict confidentiality.

Results

Socio-demographic characteristics

Three hundred and fifteen (315) patients were recruited for the study. Ten patients were left out because they could not continue with the oral glucose tolerant test. The age range of the study population was 19 - 43 years with a mean age of 30.99± 4.31 years. Women in the 30 – 34 years age group constituted the highest proportion (40.7%) and almost all the women (96.4%) were married. The majority of them had tertiary education (85.2%) and 83.0% were employed. The socio-demographic and anthropometric characteristics of the participants were shown in Table 1 and Figure 1.

Table 1: Socio-demographic and anthropometric characteristics of the participants in the first trimester

Variables (N = 305)	Frequency	Percentage
Age category		
≤24years,	19	6.2
25 – 29 years	95	31.1
30 – 34 years	124	40.7
35 – 39 years	57	18.7
≥40 years	10	3.3
Marital status		
Single	6	2.0
Married	294	96.4
Separated/divorced	5	1.6
Educational level		
Secondary	45	14.8
Tertiary	260	85.2
Employment status		
Unemployed	52	17.0
Employed	253	83.0
Smoking		
Yes	0	0.0
No	305	100.0
Alcohol intake		
Yes	23	7.5
No	282	92.5
BMI		
Underweight	1	0.3
Normal	51	16.7
Overweight	131	39.7
Class I	94	30.8
Class II	24	79
Class III	14	48

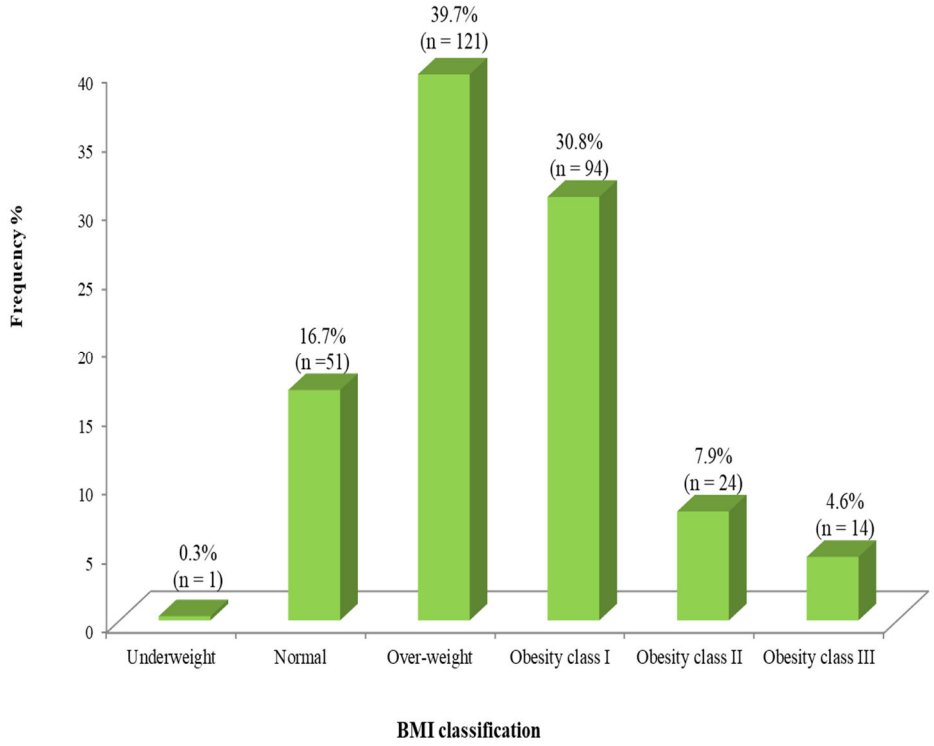

Figure 1: BMI classification of the pregnant women

Summary of the results of the Oral glucose tolerance test among the study population.
The result was as shown in Table 2 and Figures 2 and 3. Using only the fasting blood glucose (FBG) as a diagnostic criterion, 83 (27.2%) and 7 (2.3) out of the 305 participating patients were diagnosed with GDM and DIP respectively. With 1-hr and 2-hr plasma glucose, only 6 new cases of abnormal glycemia were added to the already diagnosed abnormal cases that were picked up, using FPG. In general, out of the total 305 study population, the prevalence of hyperglycemia first detected in pregnancy (HIP) was 83+5 = 88 (28.85%), 8 (2.62%), and 96 (31.48%) patients for GDM, DI, and for both (HIP) respectively.

Table 2: Summary of the results of the Oral glucose tolerance test among pregnant women in their first trimester

	Blood glucose (mmol/L)	
Time interval	**Mean ± SD**	**Median (range)**
Zero hour (Fasting blood glucose)	4.83±0.98	4.70 (3.20 – 13.80)
One-hour	7.80±1.88	7.70 (3.80 – 19.80)
Two-hour	6.46±1.58	6.20 (2.40 – 19.80)

SD = Standard deviation

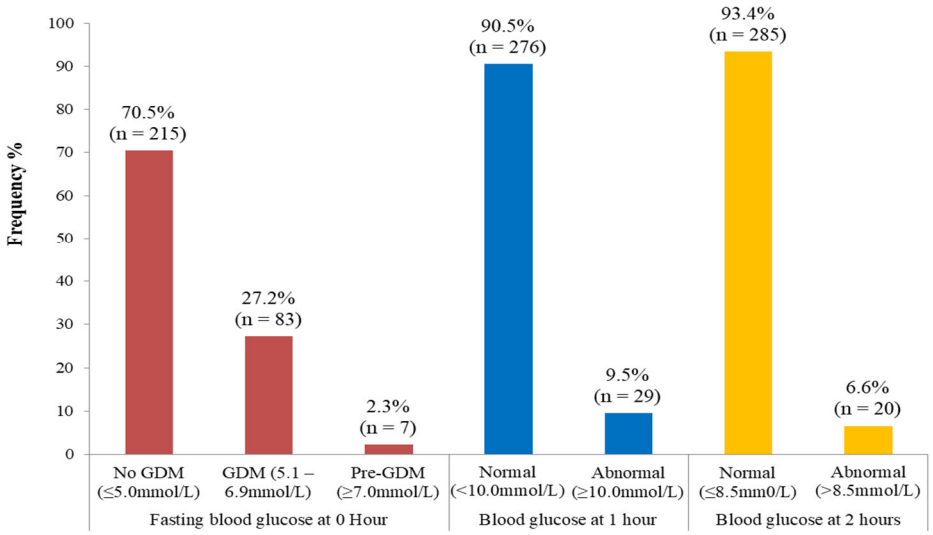

Figure 2: Distribution of blood glucose levels at different time intervals among the participants

In Figure 2, Pre-GDM stands for DIP.

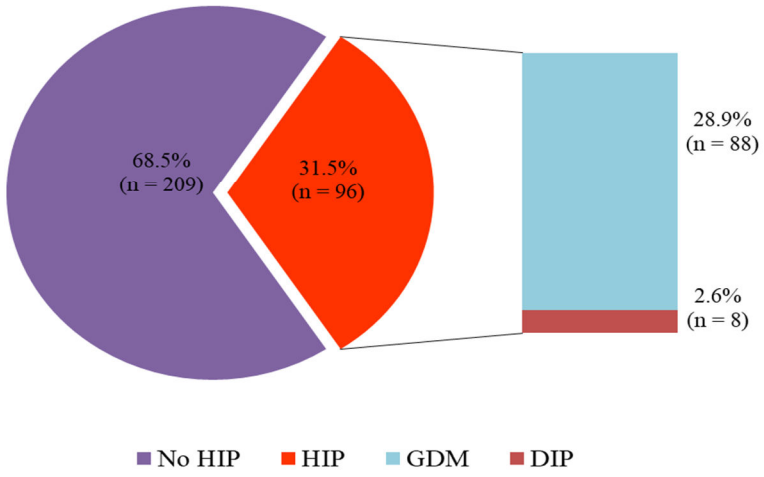

Figure 3: Showing the prevalence of HIP among pregnant women in their first trimester

Receiver operating characteristic curve (ROC) for the determination of the accuracy of HBA1c in the diagnosis of HIP, using OGTT as the gold standard.

The test results of HBA1c and of OGTT were obtained as continuous values and required a process of conversion and interpretation into a dichotomous form to determine the presence of diabetes. The ROC curve was used to assess the diagnostic accuracy of HBA1c by comparing its results with those of the gold standard OGTT in the diagnosis of diabetes (Figure 4). The ROC curve was created by plotting the sensitivity on the Y-axis and 1 minus specificity on the X-axis for various cut points of HBA1c as a diagnostic criterion for diabetes with the OGTT as the goal standard. The cut point was used to determine the diagnostic results, e.g., positive or negative, diseased or healthy. From the graph, the AUC of 0.655 (95% CI: 0.59 – 0.72, p = 0.001) was considered to be meaningful since it was greater than 0.5 but it was interpreted as 'poor.'[18] Therefore, HBA1c was not as good as the OGTT for diagnosing diabetes in pregnancy.

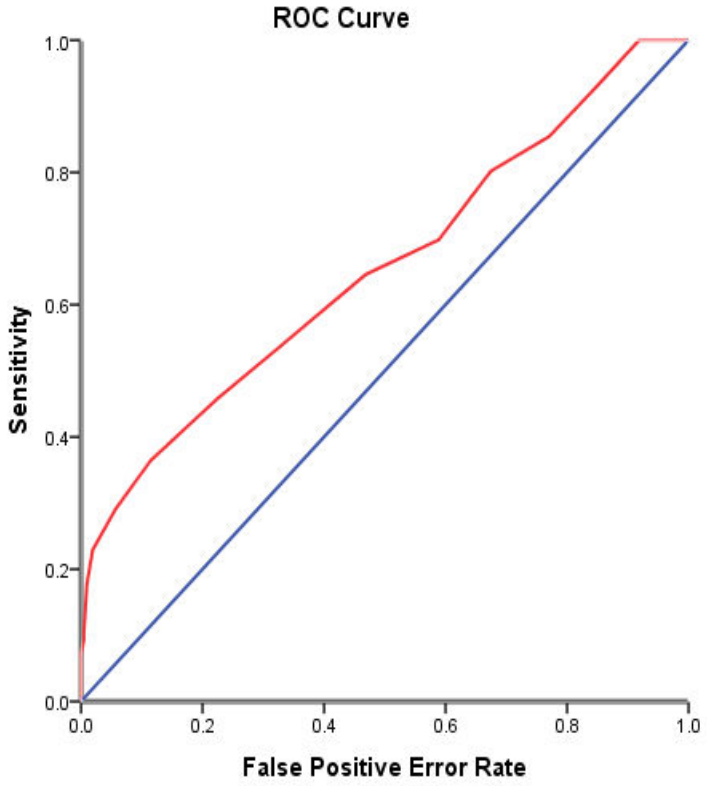

Figure 4: Receiver Operating Characteristics (ROC) Curve for HbA1c in predicting HIP among women in their first trimester of pregnancy.

Determination of the optimal cut-off point of HBA1c in the diagnosis of diabetes in the first trimester using the Youden index.

The Youden Index is a summary measurement of the receiver operating characteristic (ROC) curve for the accuracy of a diagnostic test with ordinal or continuous endpoints (Figure 5). The range of the cut point on the ROC is generally from −1 to +1. It is of interest to find the optimal cut point to increase the accuracy of a diagnostic test. [14]

The Youden Index (J) is a well-known tool for the ROC curve to measure the clinical diagnostic ability of a test. [15] J = Max [Sen(c) + Spe(c) + 1] where c is the cut point. Diagnostic tests with higher J values would be preferable. The Youden Index is an optimal trade-off between sensitivity and specificity with an equal weight being assigned to sensitivity and specificity. For given total sample sizes in the diseased group and the non-diseased group, the optimal cut point would lead to the maximum number of subjects being correctly diagnosed. Although the theoretical range of the Youden Index is from -1 to 1, the practical range in use is often from 0 to 1 since negative values of the Youden Index do not have meaningful interpretations in practice. J = 1 represents a perfect diagnostic test and J = 0 indicates that the diagnostic test is not effective to determine the disease status. The Youden index = 0.250; the optimal cut-off for HBA1c was therefore determined at 5.25 (Figure 5.)

Validation of HBA1c in the diagnosis of HIP against the gold standard OGTT

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPP) of HBA1c when validated against the gold standard OGTT in the diagnosis of HIP were 36.5%, 88.5%, 59.3%, and 75.2% respectively, using the new cut-off point of 5.25% that was gotten from the Youlden index (Table 3). Using the new cut-off means that HbA1c could be used to screen out the true negative cases thereby reducing the number of people that will progress to do OGTT.

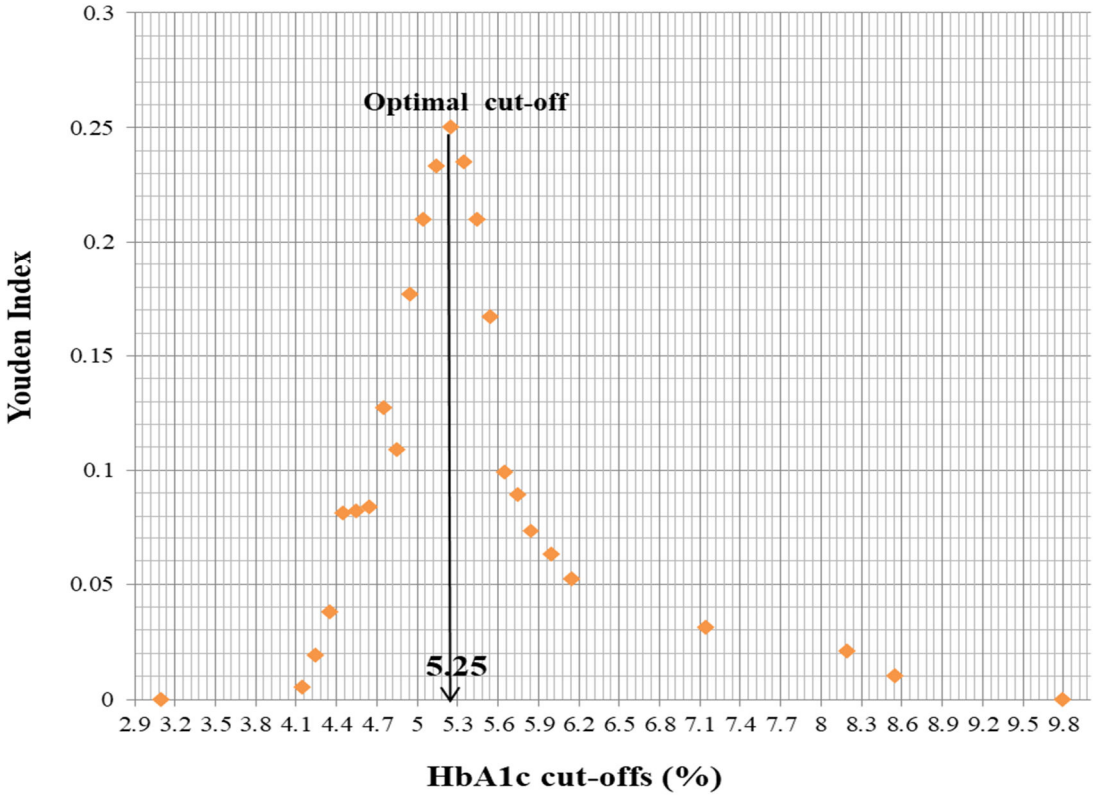

Figure 5: Determination of optimal cut-off point for HbA1c from Youden Index

Table 3: Validity tests for HbA1c category as a predictor for GDM (OGTT) among women in their first trimester of pregnancy

HbA1c category From Test results	**OGTT (Gold Standard)**		
	GDM	**No GDM**	**Total**
GDM (>5.25%)	35 True positive	24 False positive	59
No GDM (≤5.25%)	61 False negative	185 True negative	246
Total	96	209	305

$$Sensitivity = \frac{True\ Positive}{True\ Positive + False\ Negative} \text{x } 100$$

$$= \frac{35}{35+61} = 36.5\%$$

$$Specificity = \frac{True\ Negative}{True\ Negative + False\ Positive} \text{x } 100$$

$$\frac{185}{185 + 25} = 88.5\%$$

$$Positive\ Predictive\ Value\ (PPV) = \frac{True\ Positive}{True\ Positive + False\ Positive} \text{x } 100$$

$$\frac{35}{35 + 24} = 59.3\%$$

$$Negative\ Predictive\ Value\ (NPV) = \frac{True\ Negative}{True\ Negative + False\ Negative} \mathbf{X\ 100}$$

$$\frac{185}{185 + 6} = 75.2\%$$

Discussion

The study was prompted by the high prevalence of diabetes in the Niger Delta as demonstrated in the previous studies that were carried out in the same tertiary health facility where the present study was executed.[13, 16, 17] The prevalence of 31.5% for diabetes mellitus in HIP found in the present study using the gold standard OGTT was closer to the prevalence of 23.6% noted in the previous one where fasting blood glucose only was used but higher than the findings from other studies in the same centre. [16, 17] It was also higher than the prevalence of 4.8% recorded in Jos, Nigeria, [18]10.7% (95% CI: 9.5–12.0) and 8.9% (95% CI: 7.9–10.0) in Western Europe and Northern Europe respectively, [19] but similar to 27.5% recorded in India, [20]and 31.5% (95% CI: 19.8–44.6) in Eastern Europe. [19]

The findings were in contrast to those of the IADPSG 2010 review of HAPO study. [21, 22] The review showed that measuring fasting plasma glucose (FPG) alone identified 8.3% of the cohort as having GDM. Adding measurement of the 1-h plasma glucose identified an additional 5.7%; adding the 2-h plasma glucose measurement identified another 2.1% of the cohort. Therefore, early screening, diagnosis of the disorder using potent diagnostic criteria, and offering suitable and adequate care to women who had HIP early in pregnancy could largely impact the health of the population. It would also help in arresting the increase in the prevalence of the disorder in children delivered by mothers with gestational diabetes mellitus and in their future generations. [23]

The index study was therefore performed to ascertain the performance of HBA1c as a diagnostic criterion, using the OGTT as a gold standard. Although HbA1c levels drop significantly in early pregnancy, its use could help in avoiding the problem of day-to-day variability of glucose values, the need for the patient to fast and to have preceding dietary preparations which were associated with OGTT.

A non-pregnancy threshold for HBA1c of 6.5% (48mmol/mol) could not be recommended in pregnancy. The receiver operating characteristics (ROC) curve was used to assess the overall diagnostic performance of HBA1c by comparing its results with those of the gold standard OGTT in the diagnosis of diabetes. The curve was created by plotting the sensitivity on the Y-axis and 1 minus specificity on the X-axis for various cut points of HBA1c as a diagnostic criterion for diabetes.

The ROC curve for HbA1c showed a significant area under the Curve (AUC) value of 0.655 (95% CI: 0.59 – 0.72, p = 0.001) which was considered to be meaningful since it was greater than 0.5 but it was generally interpreted as 'poor.' [24] Therefore, HBA1c was not as good as the OGTT for diagnosing diabetes in pregnancy. The result was similar to the AUC obtained for the ROC curve in other studies where they were 0.649 and 0.679 respectively. [25, 26] It was however lower than the 0.852 and 0.98 that were obtained from other studies. [22, 27]

The Youden Index is an optimal trade-off between sensitivity and specificity with equal weight being assigned to sensitivity and specificity. For a given total sample size in the diseased group and the non-diseased group, the optimal cut-off point would determine the maximum number of subjects being correctly diagnosed. In the present study, the Youden index was 0.250; the optimal cut-off point for HBA1c in the diagnosis of diabetes in pregnancy was therefore determined to be 5.25%.

In a large observational study in early pregnancy, the optimal HbA1c for diagnosis of diabetes in pregnancy, using the IADPSG OGTT criteria before 20 weeks was 41mmol/mol (5.9%). [5] The threshold detected all cases of diabetes and was highly specific 98.4% (95% CI 97–99%) for early GDM. Applying an HbA1c threshold of 48mmol/mol (6.5%) led to a missed diagnosis in 47% of the women.

Using the optimal cut-off point of 5.25% that was determined by Youden index in the present study, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of HbA1c levels against the gold standard OGTT in the diagnosis of diabetes were 36.5%, 88.5%, 59.3%, 75.2% respectively. HbA1c did not have adequate sensitivity and PPV for diagnosis of GDM but it had high specificity and moderately high NPV. Therefore, it could play a role in the diagnosis of HIP but could not effectively replace OGTT which was the gold standard in the diagnosis.

The relatively high specificity and the NPV for HBA1c that was achieved in the present study theoretically made it useful in screening the antenatal population for GDM and reducing the number of women that would proceed to do OGTT. That means any pregnant woman with an HbA1c level less than 5.25% in early pregnancy was unlikely to have GDM in the index pregnancy. On the other hand, any pregnant woman with HbA1c of 5.25% and above in the first trimester would have to do the confirmatory test OGTT for HIP diagnosis.

The optimal cut-off value and the NPV recorded in this study were like the values that were obtained in previous studies. [28] The sensitivity of 36.5% was in contrast with 63.9% that was recorded by Soumya et al. [28] The differences in sensitivity and specificity might be due to the difference in the prevalence of the disease, differences in diagnostic criteria, screening approach, and study design. In addition, the HbA1c assay had not been well standardized in many countries; a variety of factors namely genetic, haematological and illness-related factors affect its assay. [2] More studies need to be conducted with correction for those factors that affect the levels of HBA1c as enumerated above.

Limitations

This study was carried out between January and June 2020 at the peak of covid-19 pandemic and therefore some patients could not attend the antenatal clinic during the lockdown as movement was restricted. This delayed the work so much that it was stretched beyond June. The study was carried out in tertiary institutions of the State and therefore those in the rural areas were not captured. Many of the pregnant women registered for antenatal care late, mostly in the second and third trimesters; this also affected the recruitment of patients into the study.

Conclusion

The high prevalence of HIP in the first trimester of 31.5% underscored the urgent need for universal screening of pregnant women early in pregnancy so that timely diagnosis could be made, and treatment initiated. HBA1c was a fairly good tool for the diagnosis of diabetes but it could not replace OGTT which was the gold standard. The area under the ROC curve (AUC) for HBA1c was 0.653%, 95% CI = 0.59 – 0.72, p = 0.001. The Youden index was 2.50 and the optimal cut-off for HBA1c for diagnosis of diabetes was 5.25%. The sensitivity, specificity, PPV, and NPV for HbA1c against the Gold standard OGTT in the diagnosis of GDM were 36.5%, 88.5%, 59.3%, and 75.2% respectively.

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