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Relationship between Glycosylated Haemoglobin Levels and Perinatal Outcome among Women with Gestational Diabetes Mellitus at the University of Port Harcourt Teaching Hospital, Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. Author ECE designed the study, performed the statistical analysis and wrote the protocol. Author JOA wrote the first draft of the manuscript and managed the analyses of the study. Authors ECE and GB managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is a global health challenge and is known to affect pregnancy adversely. Glycosylated haemoglobin (HbA1c) level reflect long term glycaemic control and is a more accurate measure than Fasting Plasma Glucose and post prandial plasma glucose level.
Aims and Objectives: To determine the levels of HbA1c, perinatal outcomes and the relationship between maternal HbA1c level and perinatal outcomes in women with GDM at the University of Port Harcourt Teaching Hospital.
Materials and Methods: This was a longitudinal study of 80 pregnant women from 36 weeks of gestation with GDM attending the antenatal clinic of the University of Port Harcourt Teaching Hospital (UPTH). Blood samples from all consenting pregnant women were collected and sent to

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the Chemical Pathology laboratory to determine the HbA1c level. The blood samples from the babies were also sent to determine the random plasma glucose (RPG) level. A structured proforma was used to obtain socio-demographic characteristics and other information. Data collected was analyzed with SPSS version 22.0.

Results: The mean age of the women was 32.58 ± 4.95 years. A total of 57 (71.3%) women with GDM had elevated HbA1c levels (≥ 6.5%). Fetal macrosomia occurred in 17.5%, while 8.8% had birth asphyxia. The perinatal mortality ratio was 1.3%. There was a statistically significant relationship between HbA1c levels and neonatal hypoglycemia and perinatal mortality ($p < 0.05$).

Conclusion: Despite the higher proportions of adverse perinatal outcomes occurring among those with elevated HbA1c levels, only neonatal hypoglycemia and perinatal mortality were significantly associated with elevated HbA1c.

Keywords: Gestational diabetes mellitus; HbA1c level; feto-maternal outcome; South-south; Nigeria.

1. INTRODUCTION

Gestational diabetes mellitus (GDM) as defined by the American Diabetes Association (ADA) and the World Health Organization (WHO) as diabetes first diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes prior to gestation [1,2]. It recommended that hyperglycemia that is first detected at any time during pregnancy be classified as diabetes mellitus in pregnancy (DIP) if it meets the criteria of overt diabetes prior to pregnancy or GDM. 3 However, most cases of GDM usually resolve within six weeks of delivery [3].

Gestational diabetes mellitus is a global health challenge which is on the increase and complicates more than 200,000 pregnancies annually [1]. The prevalence varies from 1% to 14% [3,4,5,6,7]. A prevalence of 16.3% has been reported in Qatar [8]. The prevalence in Nigeria is about 1.7%, of which 39% are pre-gestational and 61% are GDM [3,4,5,6,7]. At the University of Port Harcourt Teaching Hospital (UPTH), it accounted for 4.7% of pregnancies [9]. Most cases of GDM occur in the second and third trimesters when insulin resistance is at its peak [3]. The glucose levels rise in women who are unable to produce enough insulin to adapt to the increased insulin resistance [3,10,11].

The risk factors for GDM include a family history of type 2 DM, obesity, previous history of GDM, increasing maternal age, Afro Caribbean or Asian ethnicity, unexplained perinatal death, previous macrosomic baby and previous delivery of an infant with congenital anomaly [1,3,7,12, 13].

Although GDM is usually asymptomatic, it has adverse effects. The effect in the mother may include recurrent miscarriages, polyhydramnios, preeclampsia, difficult delivery, increased operative delivery and type 2 DM later in life. Perinatal effects may include congenital anomalies, intra uterine fetal death, fetal macrosomia, premature rupture of fetal membranes, preterm delivery, birth injuries due to macrosomia with subsequent difficult delivery, respiratory distress syndrome and hyperbilirubinaemia [3,10,12,14,15]. Maternal and childhood obesity as well as cardiovascular disease are also potential long term consequences of GDM [13,16-18].

HbA1c measures average glucose concentration over time rather than an acute response to a glucose challenge [19]. Consequently, the level of HbA1c at a certain point reflects the glycaemic history of the past 120 days [19,20]. Glycosylated haemoglobin levels are now extensively used as a measure of glycaemic control in diabetics [20-22].

Glycosylated haemoglobin is used as an index of long-term glycemic control because its measurement values is not affected by fasting or post prandial states, fasting is not required, a single blood sample is needed, reflects the glycemic level over a 2-3 months period prior to the test, it is standardized as compared to glucose, unaffected by acute stress or illness and has less biological variability [23].

Despite all the numerous advantages, it has some limitations. The values are affected by conditions that shorten erythrocyte survival, iron deficiency anaemia, iron replacement therapy and some drugs like ribavirin, antiretrovirals, trimethoprim-sulfamethoxazole, hydroxyurea, vitamin C, vitamin E and aspirin [24-26].

This is a pioneer study in UPTH which aimed to determine the relevance of maternal HbA1c to the perinatal outcome in all patients with GDM.

2. MATERIALS AND METHODS

2.1 Study Site

This study was carried out at the antenatal clinic and labour ward of the University of Port Harcourt Teaching Hospital (UPTH). The University of Port Harcourt Teaching Hospital is a 649-bed tertiary hospital located at Alakahia in Obio Akpor Local Government Area of Rivers State, South-South Nigeria. An average of 3000 deliveries are conducted annually. The unit has a total of 153 beds, with 30 beds in the antenatal ward, 40 beds in the postnatal ward, 40 beds in the unbooked ward, 13 beds in the first stage room, 4 beds in the second stage room and 8 beds in the private/semi-private rooms. There are five units, each unit has five consultant obstetricians, five specialist senior registrars and five registrars with many experienced nurses and midwives. There are also paediatricians and anaesthetists on call. The hospital laboratory has a Chemical Pathology department staffed with consultant chemical pathologists, resident doctors and laboratory scientists.

2.2 Methods

This was a longitudinal study involving all pregnant women diagnosed with GDM using glycosylated HbA1c assay attending the antenatal clinic of the University of Port Harcourt Teaching Hospital during the study period. All consenting pregnant women diagnosed with GDM from 36 weeks of gestation were recruited into the study. Pregnant women with pre-gestational DM, anaemia, multiple gestation, sickle cell anaemia, hypertensive disorders, antepartum haemorrhage, fever, premature rupture of fetal membranes, preterm labour, meconium stained liquor, breech presentation, cord prolapse and oligohydramnios were all excluded from the study. Also excluded were women with assisted conception and those on diuretics or adrenergic drugs. The purpose and benefits of the study were duly explained to the participants at the antenatal clinic and an informed written consent was obtained. This was indicated on their antenatal cards. Their socio-demographic characteristics were obtained during the antenatal period while the perinatal outcomes (birth weight, APGAR scores at 1 and 5 minutes respectively, RPG and perinatal mortality) were obtained at delivery. This information was entered into a structured proforma specifically designed for this purpose. Five milliliters of blood were collected into ethylenediamine tetra-acetic acid (EDTA) bottles under aseptic conditions from the pregnant woman at 36 weeks gestation and stored at a temperature of 2°C- 8°C. The level of HbA1c was estimated using the turbidimetric immunoassay method. One milliliter of haemolysis reagent was dispensed into a test tube with twenty microliters of well mixed whole blood. It was mixed well then allowed to stand for 5 minutes or until complete lysis was evident. Twenty microliters of lysed sample were pipetted into a cuvette with seven hundred and fifty microliters of reagent 1 (latex 0.13% buffer, stabilizer sodium azide 0.95 g/L) which was mixed properly and incubated for 5 minutes. Two hundred and fifty microliters of Reagent 2 (buffer, mouse anti-human HbA1c monoclonal antibody 0.05 mg/mL, goat anti-mouse IgG polyclonal antibody 0.08 mg/dL) was then added, mixed well and incubated for 5 minutes at 37°C. Absorbance A was read and a calibration curve was plotted and interpreted. Women diagnosed with GDM were co-managed with the endocrinologist and dietician. A meal plan was designed for each woman by the dietician. The meal plan consisted of reduced carbohydrates and sugar, and more of greens and vegetables. Counseling and review of the meal plan was done at each antenatal visit. They were also asked to do 30 minutes of brisk walking daily. Pregnant women with GDM who did not respond to diet and exercise were commenced on insulin therapy in addition to diet and monitored accordingly. At delivery, APGAR scores at the first and fifth minutes of the neonates were recorded and their weights taken using a weighing scale (Salter, model 180 made in England). The babies were managed by the neonatologists at the special care baby unit. One milliliter of blood was collected from a peripheral vein into a fluoride oxalate bottle under aseptic conditions from the neonates at birth and centrifuged to collect the plasma. The plasma glucose level was estimated spectrophotometrically using the glucose oxidase method and a level less than 2.6 mmol/l was regarded as hypoglycaemia.

2.3 Statistical Analysis

Data analysis was done using Statistical Package for Social Sciences (SPSS) for windows® version 22.0. Results are presented as frequency tables and charts. Chi square test was used to compare categorical variables while student's t-test was used to compare mean HbA1c levels across the outcomes. Pearson's correlation was used to determine the correlation between HbA1c level and perinatal outcomes (APGAR scores, random blood sugar levels and

birth weight). Statistical significance was set at P<0.05. Statistically significant variables were then entered into multiple linear regression models to control for confounders.

3. RESULTS

The mean age of the women was 32.58 ± 4.95 years. Most (35%) of the women were in the 30 – 34 years age group and almost all the parturients (97.5%) were married. Majority (75%) of the women had tertiary education and were employed (53.8%). Table 1 shows the socio-demographic characteristics of the participants. Majority (48.7%) of the women registered for antenatal care in the second trimester and they were mostly nulliparous as shown in Table 2. Table 3 showed that only 11.3% of the women had a previous history of GDM while 31.3% had previous macrosomic babies. Also, 8.8% of the participants had a previous unexplained intra uterine fetal death. However, none of them had a history of congenital anomaly. Only 27.5% of the women had a family history of Diabetes Mellitus (DM). Of the 80 women, only 13 (16.25%) were managed with both dietary modification and subcutaneous insulin as is shown in Fig. 1. The mean HbA1c value was 8.76 ± 3.46% with a range of 4.4%-22.9%. Most (71.3%) of the women had high levels of glycated haemoglobin. Fig. 2 shows the distribution of HbA1c levels among women with GDM.

Women in the 20-24 years age-category had the highest proportion of elevated HbA1c level (85.7%) while the least level was reported among women aged ≥40 years (40.0%). All nine of the 80 patients (100%) who had GDM in their previous pregnancies had elevated HbA1c levels while 67.6% of patients with no previous history of GDM had high HbA1c levels. This difference was not statistically significant (p=0.053). Elevated HbA1c level was reported among patients with previous macrosomic babies (76.0%). Concerning congenital anomaly, none of the women had a previous history of a baby with congenital anomaly. Previous IUFD (p=0.404) and family history of DM (p=0.198) showed no significant relationship with elevated HbA1c level (Table 4). Fig. 3 shows the incidence of the adverse perinatal outcomes associated with GDM. A large number of the neonates had macrosomia, with an incidence of 17.5%.

Table 5 shows the comparison between the maternal HbA1c levels and perinatal outcomes. The mean maternal HbA1c values for neonatal hypoglycemia and perinatal mortality were 13.10±5.12% and 16.70±0.00% respectively.

The multiple linear regression analysis of maternal HbA1c levels and perinatal outcomes showed that only neonatal hypoglycemia and perinatal mortality were statistically significant (Table 6).

4. DISCUSSION

The mean age of this study population was similar to previous studies done in Abeokuta and Port Harcourt [27,28]. However, most of the women were nulliparous which was at variance with the study in Abeokuta where majority of the

Table 1. Socio-demographic characteristics of women with GDM

Variables (N = 80)	N	%
Age in years		
20-24	7	8.8
25-29	14	17.5
30-34	28	35.0
35-39	26	32.5
≥40	5	6.3
Marital status		
Single	2	2.5
Married	78	97.5
Educational level		
Primary	2	2.5
Secondary	18	22.5
Tertiary	60	75.0
Occupational status		
Unemployed	13	16.3
Self employed	24	30.0
Employed	43	53.8

Table 2. Obstetric characteristics of women with GDM

Variables	N	%
Gestational age at booking		
First Trimester	16	20.5
Second Trimester	38	48.7
Third Trimester	24	30.8
Parity		
Nulliparous	29	36.3
Primiparous	23	28.7
Multiparous	28	35.0

Table 3. Past medical history of women with GDM

Variables	N	%
Previous history of GDM		
Yes	9	11.3
No	71	88.7
Previous macrosomic baby		
Yes	25	31.2
No	55	68.8
Previous Congenital Anomaly		
Yes	0	0.0
No	80	100.0
Previous IUFD		
Yes	7	8.7
No	73	91.3
Family History of DM		
Yes	22	27.5
No	58	72.5

parturients were multiparous [27]. This difference may be due to delays in onset of childbearing as more women are advancing their education and careers [29]. This may also be as a result of the urban population used for the study.

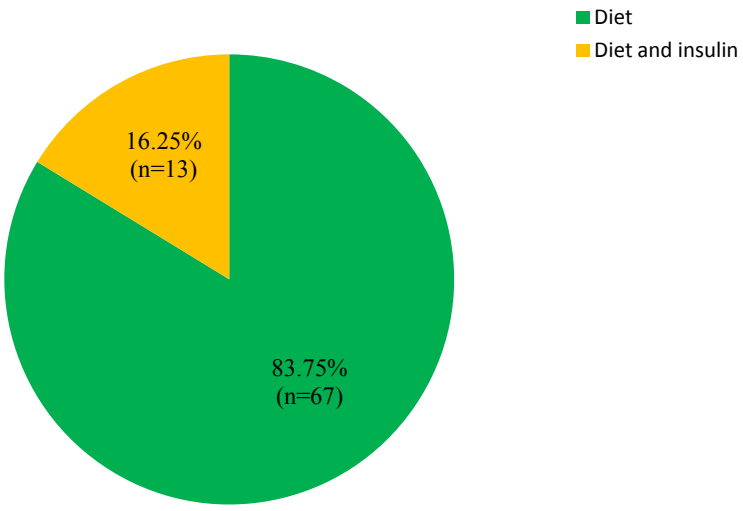

Fig 1. Modality of treatment of women with GDM

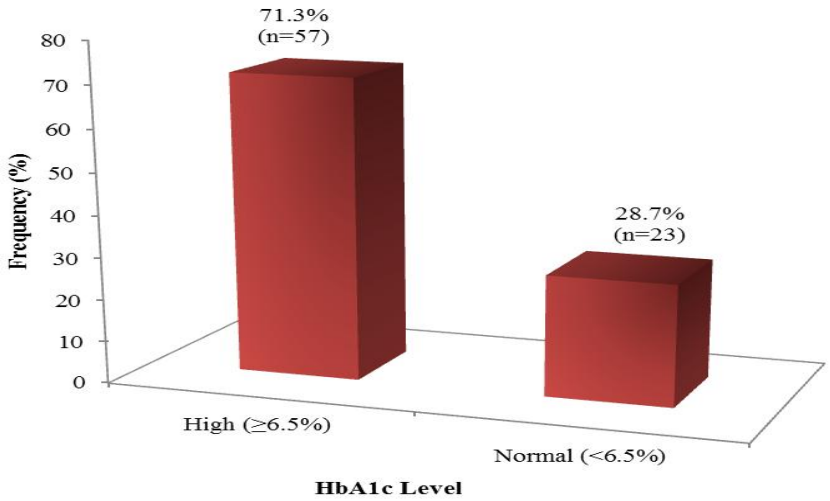

Fig 2. The HbA1c Levels among women with GDM

Table 4. Risk factors of high HbA1c among women with GDM

Variables	High HbA1c n (%)	Normal HbA1c n(%)	Total HbA1c n (%)
Age category			
20-24	6 (85.7)	1 (14.3)	7 (100.0)
25-29	10 (71.4)	4 (28.6)	14 (100.0)
30-34	21 (75.0)	7 (25.0)	28 (100.0)
35-39	18 (69.2)	8 (30.8)	26 (100.0)
≥40	2 (40.0)	3 (60.0)	5 (100.0)
	Fisher's exact =3.122	p value =0.562	
Previous history of GDM			
Yes	9 (100.0)	0 (0.0)	9 (100.0)
No	48 (67.6)	23 (32.4)	71 (100.0)
	Fisher's exact p value =0.053		
Previous macrosomic baby			
Yes	19 (24.0)	6 (24.0)	25 (100.0)
No	38 (69.1)	17 (30.9)	55 (100.0)
	Chi-square =0.401	p value =0.527	
Previous congenital anomaly			
Yes	0 (0.0)	0 (0.0)	0 (0.0)
No	57 (71.2)	23 (28.8)	80 (100.0)
	Chi-square =0.00	p value =1.000	
Previous IUFD			
Yes	4 (57.1)	3 (42.9)	7 (100.0)
No	53 (72.6)	20 (27.4)	
	Fisher's exact p value =0.404		
Family History of DM			
Yes	18 (81.8)	4 (18.2)	22 (100.0)
No	39 (67.2)	19 (32.8)	58 (100.0)
	Chi-square =1.654	p value =0.198	

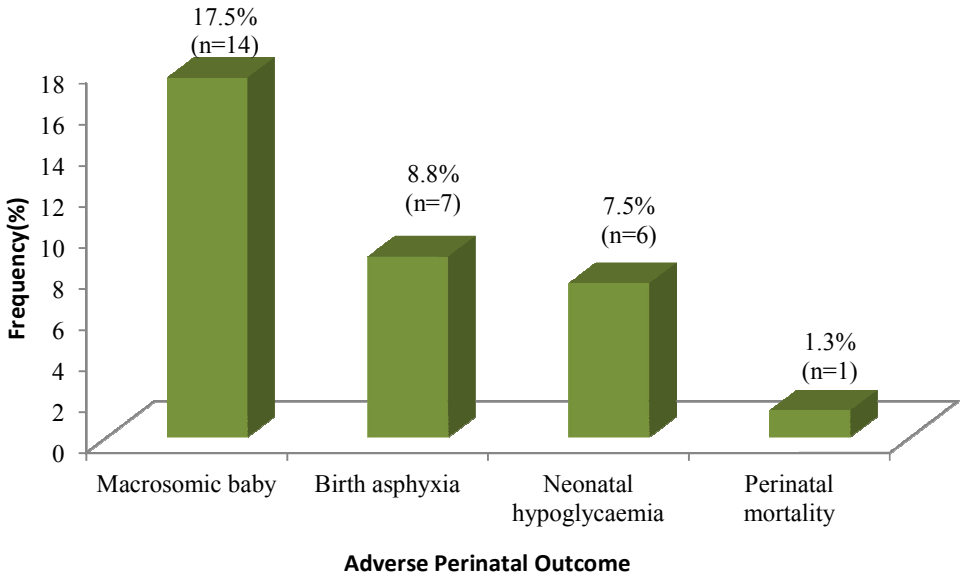

Fig 3. Distribution of adverse perinatal outcome among neonates born to women with GDM

Table 5. Comparison of maternal HbA1c levels across the perinatal outcome categories

Perinatal outcome	Mean HbA1c ± SD
Birth weight category	9.91±3.55
Macrosomia	8.52±3.42
Normal	t= 1.377; p= 0.172
Neonatal hypoglycaemia	13.10±5.12
Yes	8.41±3.08
No	t= 3.395; p= 0.001*
Birth asphyxia	9.20±3.87
Yes	8.72±3.45
No	t= 0.348; p= 0.729
Perinatal mortality	16.70±0.00
Yes	8.66±3.37
No	t= 2.372; p= 0.020*

Table 6. Multiple linear regression analysis of maternal HbA1c levels (dependent variable) and perinatal outcomes (independent variables)

Independent variables	Coefficient β	Standard error	P-value
Neonatal random plasma glucose	-0.820	0.370	0.030*
Perinatal mortality	7.070	3.335	0.037*

**Statistically significant*

Most of the women had no risk factors for GDM. Similar results were noted in the studies done in Ibadan and Abeokuta where most of the participants had no history of diabetes mellitus in a first degree relative or history of previous macrosomic babies [14,27]. This is however at variance with the study in Jos, which noted that a higher proportion of participants had history of previous macrosomia [7]. The study by Anzaku et al, unlike the present study reported a significant relationship between history of previous macrosomia and HbA1c [7]. This dissimilarity was probably because most of the parturients were nulliparous in the present study.

This study found that 71.3% of the women had elevated levels of HbA1c and 28.7% had normal

values. The mean HbA1c value of 8.76 ± 3.46% reported in the index study is much higher than a similar study in Australia which noted a mean HbA1c of 4.8 ± 0.36% [30]. This disparity in the HbA1c values could be explained by the fact that most of our staple foods are carbohydrates. Also, the gestational ages of the women in the present study were from 36 weeks and beyond while the study by Khalafallah et al comprised of women in gestational ages between 24 to 28 weeks [30].

Majority of the participants had no prior history of GDM mainly because this was their first pregnancy. However, all the parturients with a previous history of GDM had elevated HbA1c levels though this was not statistically significant. This further emphasizes the need for close monitoring and adequate follow-up of women with previous history of GDM.

The incidence of macrosomia in this study was 17.5% which is at variance with an earlier study in Port Harcourt in which a much higher incidence of 49% was reported [28]. This difference may be due to the interventions of dietary modification and insulin administration carried out by the participants of this study. However, the incidence of macrosomia among women reported in the index study reveals that it is not uncommon and therefore optimal interventions for women with GDM are advocated.

The occurrence of birth asphyxia and hypoglycemia was far less than what was noticed in studies done in India and Egypt [15,31]. This difference may probably be due to a poorer glycemic control in those study populations in comparison to the index study. The incidence of perinatal mortality in this present study was much lower than previous studies done in Port Harcourt [10,32]. This finding may be due to earlier detection, better management and improved neonatal care in recent times.

There was a statistically significant association between HbA1c levels and neonatal random plasma glucose levels which was in agreement with a study done in Egypt and Malaysia [15,21]. These studies showed that HbA1c levels in late pregnancy are good predictors of hypoglycemia in the neonates.

5. CONCLUSION

There was a significant correlation between HbA1c and perinatal outcome. Therefore, universal screening for all pregnant women at first contact and subsequent antenatal visits is recommended for early detection and treatment of GDM. Also, future research should determine the optimal levels of HbA1c in GDM pregnancies so as to prevent adverse perinatal outcomes.

6. LIMITATIONS

This study was conducted at a tertiary health facility and within a short time frame of three months, so may not be fully representative of the general population. However, the results may indicate that utilization of HbA1c assay does have a clinical value worthy of further research. HbA1c assay was done from 36 weeks of gestation which was close to time of delivery, hence there was limited time for the interventions to make a significant impact on the perinatal outcome.

CONSENT

The purpose and benefits of the study were duly explained to the participants at the antenatal clinic and an informed written consent was obtained.

ETHICAL APPROVAL

All authors hereby declare that the study has been examined and approved by the Ethics review board of the University of Port Harcourt Teaching Hospital and have therefore been carried out in accordance with the ethical standard laid down in the 1964 Declaration of Helsinki. The protocol number of the Ethical approval is UPTH/ADM/90/SII/VOL.XI/489.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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