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Uncovering the Silent Epidemic: Insulin Resistance and some Associated Risk Factors Among Pregnant Women with Gestational Diabetes mellitus (GDM) in a Low Resource Setting

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Abstract
The present study sought to identify insulin resistance and related risk factors in pregnant women with gestational diabetes mellitus (GDM). One hundred and eighty-one pregnant women (34 with GDM and 147 without GDM) participated in the study. GDM screening involved a 75g OGTT test, while a structured questionnaire was used to gather socio-demographics data, and HOMA IR was used to

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assess insulin resistance. The study identified a 19.2% prevalence of GDM. Multiple regression analysis revealed that the studied risk factors accounted for 94% of GDM development. Additionally, the ROC curve demonstrated the wealth index as a significant factor for GDM development. The study found a high prevalence of GDM among pregnant women in low-resource settings, highlighting the need for targeted interventions to address the elevated occurrence. Socioeconomic factors such as low income and education were found to increase the risk of GDM

Keywords: Gestational diabetes, HOMA IR, Insulin resistance, Prevalence, Risk factors.

INTRODUCTION

Pregnancy is not a disease; instead, it's a multifaceted bodily transformation that requires a range of adjustments and adaptations within the mother's systems to safeguard the health and welfare of both the mother and the developing fetus, continuing through and after childbirth (Tal and Taylor, 2021). Among the various physiological responses that occur during pregnancy, one noteworthy mechanism involves the role of insulin in regulating glucose levels to maintain normal blood sugar levels (Hill *et al.,* 2021). While the precise nature of insulin resistance is not fully understood (Lee *et al.,* 2021), numerous studies suggest that it arises when the normal endocrine self-regulation and other homeostatic mechanisms fail (Hill *et al.,* 2021; Lee *et al.,* 2021), this phenomenon is commonly recognized as gestational diabetes mellitus (GDM), particularly when it manifests or is first identified during pregnancy (Sweeting *et al.,* 2022). Gestational Diabetes Mellitus (GDM) is a condition characterized by glucose intolerance that first appears during pregnancy. It is associated with adverse outcomes such as macrosomia, preterm birth, and preeclampsia, and increases the risk of future type 2 diabetes for both the mother and the child. Insulin resistance, a state in which normal doses of insulin produce a subnormal biological response, is a key pathophysiological feature of GDM. In low resource settings, the challenges associated with managing GDM are amplified due to limited access to healthcare resources, poor nutrition, and inadequate screening and diagnostic facilities. Furthermore, certain risk factors, such as obesity, sedentary lifestyle, and poor dietary habits, are prevalent among pregnant women in low resource settings, contributing to the burden of GDM (Ye *et al.,* 2022).

In recent years, the prevalence and economic impact of GDM have shown a consistent increase (Juan and Yan 2020). Despite global initiatives to address the challenges posed by GDM, there is a lack of consensus regarding the optimal values for glucose monitoring (Tahapany *et al.,* 2020; Szmuilowicz *et al.,* 2019; McIntyre *et al.,* 2019; Creanga *et al.,* 2022).

IR is a reduced responsiveness to high physiological insulin levels in insulin-targeting tissues and has been linked to pathogenesis of type 2 diabetes mellitus (Lee *et al*., 2022). Gene, age, weight, BMI and previous history of diabetes have been considered as risk factors for gestational diabetes mellitus and diabetes (Bianchi *et al*., 2017; Siddiqui *et al*., 2018). During pregnancy, insulin resistance naturally occurs as a result of hormonal changes and the growth of the fetus. However, in women who develop GDM, this insulin resistance becomes more pronounced, leading to hyperglycemia. The exact mechanisms underlying insulin resistance in GDM are not fully understood, but it is thought to involve a combination of genetic, environmental, and metabolic factors. Elevated levels of adipokines, such as leptin and adiponectin, and inflammatory markers have been implicated in the development of insulin resistance in GDM. In low resource settings, the prevalence of insulin resistance in pregnant women with GDM may be higher due to a higher prevalence of risk factors such as obesity and poor dietary habits.

Several risk factors contribute to the development of GDM in low resource settings. Obesity, sedentary lifestyle, and poor dietary habits are prevalent in these settings and are known to increase the risk of GDM (Creanga *et al.,* (2022). Lack of access to prenatal care and limited healthcare resources may lead to delayed diagnosis and suboptimal management of GDM. Additionally, socio-economic factors, such as lower education levels and limited access to healthy food options, further exacerbate the risk of GDM in low resource settings.

The aim of this study is to shed light on the factors contributing to GDM in our low-resource environment, recognizing the limited available information. Despite international efforts to mitigate the impact of GDM, a universal standard for glucose monitoring remains elusive.

MATERIALS AND METHODS

Study Design and Subjects

This was a prospective cross sectional hospital based study conducted at Rasheed Shekoni Federal University Teaching Hospital Dutse in Jigawa, Northwestern Nigeria. Consecutive consenting pregnant women of reproductive age at 24-28 weeks gestation with no history of Diabetes, Hypertension or any chronic condition prior to the onset of pregnancy were recruited for this study. Simple random sampling was applied for selection of the participant visiting the antenatal care unit (ANC), First 5 participants were chosen daily spanning for 6 months.

Data Collection

Well trained research assistants administered a validated questionnaire to the participants, Sociodemographics such as gestational age, History of Diabetes, Dietary intake, Western education status, ethnicity, parity and wealth index were collected. Weight and height (anthropometric) were collected by a trained nurses following standard protocols. BMI was later calculated by dividing the weight (kg) by the height (meters) squared

Screening and diagnosis of GDM

Pregnant women were screened for GDM using 75g oral glucose tolerance test (OGTT). After fasting for 8-10 hours overnight, peripheral blood glucose levels were collected at 8 am. Subsequently, participants orally received 75g of anhydrous glucose dissolved in water, and blood specimens were collected 1 and 2 hours later to assess glucose levels. In accordance with the guidelines established by the International Association of Diabetes and Pregnancy Study Groups (IADPSG), pregnant women were categorized as having GDM if their fasting blood glucose was ≥92 mg/dl, 1-hour blood glucose was ≥180 mg/dl, and/or 2-hour blood glucose was ≥153 mg/dL.

Specimen Collection and Processing

Five milliliters (5mls) of blood were collected from each participant using a standard venipuncture, 3mls were delivered into fluoride oxalate container for determination of sugar levels, and the remaining 2mls were dispensed in a plain container to obtain sera after centrifuging at 15,000 r/min for 5 min. The separated sera were used for fasting insulin analysis.

Insulin resistance (IR): IR was determined using the homeostatic model assessment of insulin resistance (HOMA-IR), adopted by Matthews, *et al.,* (1985). It was calculated using the formula below;

Fasting insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5.

Analytical methods: Serum insulin was analyzed using enzyme-linked immunosorbent assay (ELISA) kit for quantitative determination of insulin levels in Human serum. The serum glucose was determined using glucose oxidase peroxidase method Burrin and Price (1985). All chemicals and reagents were of analytical grade and purchased from Sigma Chemical Company, USA.

Statistical analysis

The research data were extracted from the forms into Microsoft Excel worksheet and subsequently imported into SPSS version 25.0 for data analysis. Outliers were identified and addressed through a systematic cleaning process using box plot to ensure the accuracy of statistical analyses and prevent distortions in the interpretation of research findings. Categorical variables were presented with frequencies and percentages while continuous variables with means ± standard deviation (SD) which were compared between two or more groups using one way analysis of variance (ANOVA). Differences were considered as significant when $P<0.05$. Multiple linear regression was conducted with HOMA IR values as dependent against studied risk factors. Receiver operating characteristics (ROC) curves were used to predict the specificity and sensitivity of these variables for insulin resistance among pregnant women with GDM.

RESULTS AND DISCUSSION

A total of 182 pregnant women were recruited for the study. GDM developed in 35 (19.2%) of the pregnant women whereas 147 (80.8%) had no GDM. Both the GDM and NGDM groups have almost a similar height. Also, based on parity, GDM was found in 25.7% of the nulliparous pregnant women, 31.4% of the primiparous pregnant women and 42.9% of the multiparous pregnant women. Body weight of the pregnant women in the GDM category was also found to be higher than that of the NGDM. 71.4% of pregnant women with family history of diabetes developed GDM while 28.6% of pregnant women without family history developed GDM. The current study categorized the BMI of the study subjects into underweight, normal weight, Overweight and obese. The incidence of GDM was found higher in pregnant women with normal body weight (54.3%) followed by over weight (34.3%) and obese (11.4%). Based on ethnicity, Hausa ethnic group have the highest incidence (82.8%) of GDM compared to the Yoruba (14.3%) and Igbo (2.9%) ethnic groups. The study also categorized the participant according to western education level into illiterate, primary, secondary and tertiary categories respectively. Highest prevalence (51.4%) of GDM was seen amongst individuals in the illiterate category. Based on dietary intake pattern, 74.3% of the GDM cases consumes mainly carbohydrate and this accounts for the highest incidence based on the dietary intake **(Table 1)**.

Table 1: Sociodemographics characteristic of the study population

Parameters		GDM (n=35)	Non GDM (n=147)
Mean GA(IQR)		30.5±0.84 (8.25)	28.7±1.11 (10.75)
Weight		74.3±7.16	67.1.0±10.1
Height		1.72±0.08	1.72±0.06
BMI			
	Under weight (<18.5)	0(0)	6(4.1)
	Normal weight (18.5-24.9)	12(34.3)	113(76.8)
	Over weight (25.0-29.9)	19(54.3)	26(17.7)
	Obese (>30)	4(11.4)	2(1.4)
History	Yes	25(71.4)	23
	No	10(28.6)	124
Ethnicity			
	Hausa	29(82.8)	124(84.4)

	Yoruba	05(14.3)	23(15.6)
	Igbo	01(2.9)	00 (0)
Parity			
	Nulliparous	09(25.7)	84(57.1)
	Primaparous	11(31.4)	30(20.4)
	Multiparous	15(42.9)	33(22.4)
Western education			
	Illiterate	18(51.4)	28(19.0)
	Primary	11(31.4)	63(43.0)
	Secondary	02(5.7)	28(19.0)
	Tertiary	04(11.5)	28(19.0)
Dietary intake Pattern			
	Mainly carbohydrate	26(74.3)	62(42.2)
	Carbohydate&protein	05(14.3)	51(34.7)
	Relatively balanced	2(5.7)	18(12.2)
	Others	2(5.7)	16(10.9)
Wealth index			
	Bottom	21(60)	24(16.3)
	Middle	08(22.9)	20(13.6)
	Top	06(17.1)	103(70.1)

Diabetic profile parameters and HOMA-IR values were compared between the GDM and NGDM groups. FBS, 1hr glucose, 2hr glucose, HbA1c, insulin and HOMA-IR were found to be significantly higher in the GDM group compared to the NGDM **(Table 2)**.

Table 2: Comparison of Diabetic profile parameters and HOMA IR values among the study groups

Parameters	GDM (n=35)	Non GDM (n=147)	Total (n=182)
FBS	102.0±7.5	80.2±7.6	84.5±11.5
1hr glucose	186.0±6.0	114.2±23.2	128.0±35.3
2hr glucose	158.4±6.3	120.5±12.9	127.8±19.1
HbA1c	6.4±0.7	4.1±0.5	4.6±1.0
Insulin	9.1±1.7	5.4±0.6	6.2±1.7
HOMA IR values	2.28±0.5	1.0±0.1	1.3±0.5

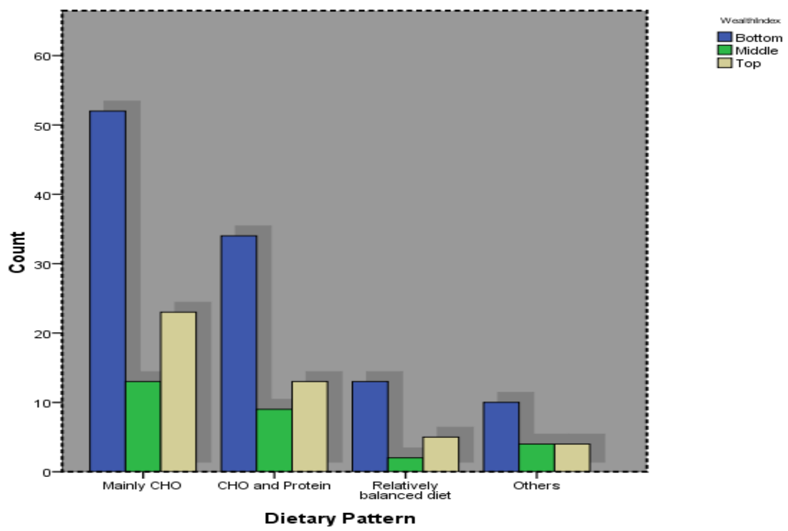

Figure 1: Association of Dietary intake with Wealth index among pregnant women with GDM

According to the results obtained from this research, economic status dictates dietary pattern. Subjects with low economic status consumes mainly carbohydrates alone as compared with middle and top economic that have access to proteins and relatively balance diet.

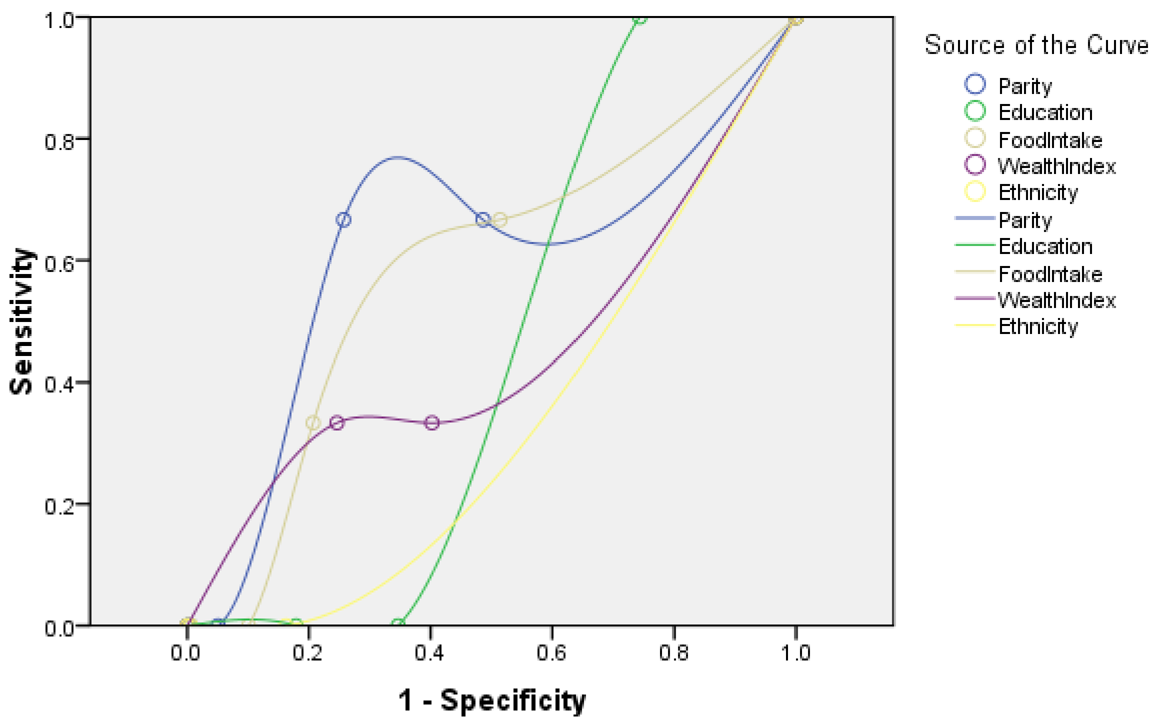

Figure 2: Receiver operating characteristic curve of some variables on insulin resistance
Receiver operating characteristics (ROC) curves for variables such as Parity, western education status, Dietary intake pattern, wealth index and ethnicity were determined to predict the specificity and sensitivity of these variables for occurrence of GDM among the study population. Accordingly, the area under the ROC curve (AUC) calculated for Parity, western education status, Dietary intake pattern, wealth index and ethnicity are .650, .455, .576, .492, .419 respectively.

In Nigeria, the prevalence of GDM has been reported to be between 0.6% and 15.7%, depending on the study population and diagnostic criteria used (Olumodeji *et al.,* 2020; John *et al.,* 2019; Onyenekwe *et al.,* 2019). The current research revealed 19.2% prevalence of GDM among pregnant women in the study area and is consistent with Yanbei *et al.,* (2023) among Chinese population of 22.34% as well as the global estimate of GDM prevalence, which is around 16.9%, according to a systematic review and meta-analysis of 13 studies involving 15,000 women from various regions of the world (Seshiah *et al.,* 2019). However, the prevalence of GDM varies widely across different regions and populations, ranging from 1.4% in Africa to 25.5% in the Middle East (Seshiah *et al.,* 2019). Recently, Umar and colleagues (Umar *et al.,* 2021) reported a lower prevalence rate of 7.7% in Sokoto state capital of Northwestern Nigeria. Similarly several other studies (Olumodeji *et al.,* 2020; Chinuma *et al.,* 2022) documented lower values in comparison to our own study. Ultimately, a research initiative conducted in Sierra Leone by Putato *et al.,* (2020) examined the practicality of a streamlined diagnostic approach for GDM and discovered that the prevalence of GDM was greater than anticipated, pointing to the difficulties in detecting affected individuals. Mitigating the high occurrence of GDM in low resource settings presents unique challenges due to limitations in healthcare infrastructure, including diagnostic facilities, access to medications, and healthcare professionals with expertise in GDM management, however, implementing community-based screening programs, promoting healthy lifestyle interventions, and providing education and support for women with GDM may serve as vital interventions towards reducing high prevalence rate in our low resource environment.

HOMA-IR has been used to assess insulin sensitivity in this study due to its good correlation to glycemic clamp, moreover it has been widely utilized as insulin resistance index in clinical and epidemiological studies (Chen *et al*., 2005), although, the threshold of HOMA-IR for evaluating insulin resistance has not been unified because of various associated factors of HOMA-IR such as age, sex, race and weight (Shashai *et al*., 2016;Yang *et al*., 2009).

According to the results obtained from this study, HOMA IR values were significantly higher in GDM group compared to NGDM, this finding is in line with several other studies (Sonogra *et al*., 2014; Young *et al*., 2016; Reyes-Munoz *et al*.2017; Mahjabeen *et al*., 2020; Mohammed *et al*., 2020) who documented higher HOMA IR values in pregnant women with GDM than those without GDM. Paracha *et al.,* 2021 suggests that HOMA IR > 2 could replace 75g OGTT as a screening tool for GDM at 24-28weeks of pregnancy. HOMA-IR has been a strong predictor in some studies (Alptekin *et al*., 2016; Kumru *et al*., 2016). Furthermore, R squared value strongly suggests that more than 80% of the studied risk factors can contribute to the higher HOMA IR values as well as GDM development.

Our results showed that wealth index as a strong variable to GDM development, this may be due the influence it may have on feeding and access to health care delivery, this is in line with previous research in Assam, India by Chanda *et al*., (2020) which found a high prevalence of GDM in low-resource settings owing to low socioeconomic status.

BMI is considered as an independent risk factor to GDM development, based on the current finding, higher incidence of GDM was seen in the overweight compared to the normal weight category, this is in agreement with previous researches of Chen *et al.,* 2014; De Souza *et al*., 2015; Sun *et al.,* 2020, Similarly, Casagrande *et al.,* 2018 noted the incidence of GDM for normal, overweight and obese pregnant women as 4.7%, 6.5% and 10.5% respectively. Considering these evidences, overweight women needs to be given appropriate guidance to prevent GDM occurrence because overweight category are next to the normal category in terms of incidence of GDM. Our study also noted that high occurrence of GDM among normal weight, this may suggest other mechanisms are involved in the pathogenesis of GDM.

Several studies (Lin *et al*., 2016; Lee *et al*., 2018; Abu-Heija *et al*., 2017) believed that number of times a woman has given birth may be represented as an additional risk factor for GDM, the elevated risk of developing GDM has been linked to parity as low as two (Lee *et al*., 2018; Lin *et al*., 2016). Our report noted more incidence of GDM in the multiparous than primiparous and nulliparous women, therefore suggesting a link between parity and GDM development, Yanbei *et al*. (2022) reported similar finding but with nulliparous having the highest incidence of GDM than multiparous and primiparous women as opposed to our recent work. GDM is been considered as a multifactorial disease, with family history of diabetes in the first degrees as strong independent risk factor (Cypryk *et al.,* 2008; Duo *et al*. 2022**).** Different studies have shown a direct link between a family history of diabetes and the occurrence of GDM (gestational diabetes mellitus) (Cypryk *et al.,* 2008; Duo *et al.* 2022). Our findings corroborate these results, indicating a higher prevalence of GDM in women with a family history of diabetes. Additionally, Yang *et al*. (2009) noted that pregnant women with a first-degree family history of diabetes were about twice as likely to develop GDM compared to those without such a history.

Early prediction of GDM is important for life style modifications in order to prevent development of GDM. Low resource environment like the study area, lacks the basic tools for overall identifying and mitigating the sudden surge of GDM which may lead to different complications for pregnant women and the baby through pregnancy, delivery and thereafter (Saravanan *et al.,* 2020).

Our study has identified western educational status as a risk factor for GDM. Bouthoom *et al.,* 2015 and Bo *et al.,*(2002) agreed with our findings that pregnant women with low or no western education are at risk of GDM development, however, Shen *et al.,* (2016) and Janghorbani *et al.,* 2006 reported contrary evidence of no association between education and GDM development. Similarly, a prevalence study among Egyptian population (Ghada *et al.,* 2018) revealed that majority of pregnant GDM women possess secondary education and higher. In the same vein, Chionuma *et al.,* (2022), studied insulin resistance in the southern Nigeria with majority of study population having tertiary education.

The study exhibits strengths in its relevance, diversity of participants, study design, contextualization of findings, and identification of potential strategies for addressing the challenges identified. However, the study has limitations such as using of single hospital which may limit the generalizability of the findings to other geographical locations with different healthcare infrastructures, Furthermore, the study is limited to a cross-sectional analysis, and there was no provision for long-term follow-up to assess the outcomes for both mothers and children, which is crucial for understanding the impact of insulin resistance and GDM.

CONCLUSION

In conclusion, the study focused on identifying insulin resistance and associated risk factors among pregnant women with gestational diabetes mellitus (GDM) in a low-resource setting. The research revealed a high prevalence of GDM (19.2%) in the study area, highlighting the need for targeted interventions. Factors such as low income, education levels, and dietary habits were linked to an increased risk of GDM. The wealth index was found to influence GDM development, reflecting the impact of economic status on healthcare access and diet. Elevated HOMA-IR values in pregnant women with GDM emphasized the role of insulin resistance in GDM. Factors like BMI, parity, family history of diabetes, and education status were identified as risk factors for GDM development, showcasing the complex nature of the disease. Early prediction and interventions are crucial to address GDM's impact on maternal and fetal health outcomes in low-resource settings. The study's insights into key risk factors and insulin resistance contribute to the understanding of GDM and support future research and interventions in low-resource environments. While the study had strengths in participant diversity, contextualized findings, and identified limitations like the single hospital setting and cross-sectional design, further long-term studies are needed to assess outcomes for mothers and children affected by GDM.

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