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Predictors of postpartum glucose intolerance in women with gestational diabetes mellitus: A prospective cohort study in Ethiopia based on the updated diagnostic criteria

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Abstract

Objective: This study aimed to identify the prevalence of post-partum glucose intolerance and to develop a prediction model based on antenatal characteristics to predict postpartum glucose intolerance.

Methods: A prospective cohort study was conducted on women with gestational diabetes mellitus (GDM) diagnosed using the updated international diagnostic criteria. All women who had GDM were advised to undergo postpartum oral glucose tolerance test (ppOGTT) at 6-12 weeks of delivery. Predictors of post-partum glucose intolerance were identified using the multivariate analysis. The discriminative power of the predictable variables for postpartum glucose intolerance and the model accuracy were computed by the area under the receiver operating characteristic (ROC) curve and estimated by the area under the curve (AUC) with 95% confidence interval.

Results: Of all women with GDM, 112 (85.5%) attended and completed the ppOGTT. The prevalence of postpartum glucose intolerance was 21.4% (95% CI: 14.3–28.4) inclusive of 18.7% prediabetes and 2.7 % diabetes. Multivariate logistic regression analysis revealed that advanced maternal age, high fasting plasma glucose (FPG) level at diagnosis, overweight and/or obesity, and antenatal depression were significant predicting factors for post-partum glucose intolerance. The AUC of the final reduced model to predict post-partum glucose intolerance was 0.884 (95% CI: 0.821 to 0.939). The FPG at GDM diagnosis [AUC= 0.736 (95% CI: 0.616-0.845)] and overweight and/or obesity [AUC = 0.718 (95% CI:0.614- 0.814)] were better predictors of postpartum glucose intolerance**.** Moreover, the AUC for the combined predictors of FPG at diagnosis and mid-upper arm circumference(MUAC) was 0.822 (95% CI:0.722- 0.907), which was the best predictor.

Conclusions: Our finding confirmed prevalence of post-partum glucose intolerance is high among women with GDM. Antenatal factors were modestly predicted post-partum glucose intolerance. The findings suggested the ongoing glucose screening is indicated for all women with GDM.

Keywords: gestational diabetes mellitus, post-partum glucose intolerance, prediction

Strengths and limitation of the study

- This prospective cohort study involved GDM patients identified using the updated diagnostic criteria with uniform protocols for all women and followed them till 6-12 weeks of delivery.
- This prognostic risk prediction models introduced post-partum glucose intolerance in women with GDM can be easily predicted by antenatal factors.
- The study used relatively a small sample size and that ongoing sampling in the future months may change the chances of some variables as significant risk factors and improve a wide range of confidence intervals (CI) in the multivariate analysis.

Introduction

Gestational diabetes mellitus (GDM) is defined as "hyperglycemia first detected during pregnancy that is clearly not preexisting or overt diabetes" (1). Although GDM normally disappears after a birth, women previously diagnosed with the disease are at high risk of developing long-term metabolic disorders such as type 2 diabetes (2-5).

Postprandial hyperglycemia is common among women with GDM, more than half develop type 2 diabetes 5 years after delivery (6, 7). Literature showed that the occurrence of diabetes ranged from 2.6% to over 70% corresponds to 6 weeks to 28 years of postpartum. The prospect of incident was also high at subsequent pregnancies with GDM (8).

Even though international guidelines recommend early screening to explore post-partum pre-diabetes or diabetes in women with gestational diabetes at 6–12 weeks of delivery (9, 10), evidence based on the updated GDM diagnostic criteria are limited. In resource-limited settings, pregnancy often marks the first formal exposure to healthcare. The identification of potential future progression predictors of pre-diabetes and/or diabetes in women with GDM could improve accurate risk stratification of patients during pregnancy. This provides an opportunity for appropriate, cost-effective, and priority intervention programs of high-risk group. If the persistence risk can be estimated accurately, treatment may be tailored to individual patient needs. Low persistence risk warrants adoption of a watchful waiting policy, while a high persistence risk may call for immediate and possibly more aggressive treatment (e.g., life style modification and behavioral change in combination with drug treatment).

The few available studies on risk factors for persistent diabetes mellitus, present don't allow predictions of the absolute risk in individual patients in daily practices (11-13). Setting a prognosis

in individual cases with GDM, however, is notoriously difficult and a lack of empirical evidence has already occurred earlier. We sought to (1) identify the prevalence of post-partum glucose intolerance; and (2) develop a prediction model to enable objective estimations of outcome probabilities (risks) according to different combinations of predictor values for women with GDM in the Ethiopian context by using the updated international diagnostic criteria. We hypothesized that using antenatal clinical characteristics would improve identification of women with GDM at high risk for post-partum glucose intolerance.

Materials and methods

Study design and population

A prospective cohort study was conducted among pregnant women recruited at the antenatal care (ANC) clinics of selected health facilities of Gondar town and followed till 6-12 weeks after delivery. Women were enrolled if they were aged 18 years or more with 20 - 23^{+6} weeks of gestational age and singleton pregnancy. Pregnant women who had pre-existing diabetes mellitus or overt DM, chronic diseases, medications that may affect glucose metabolism were excluded. Universal screening for GDM using a two-hour 75 g OGTT was performed for all pregnant women at 24-28 weeks of gestational age from March 30, 2018 to January 4, 2019. Additionally, women with risk factors for GDM repeated the test at 32-36 weeks if OGTT results were negative at regular tests and the GDM diagnosis confirmed by the second test. The detailed methods of the study were explained earlier (14). This follow up study was conducted on 131 women diagnosed with GDM out of 1027 participants who were completed the OGTT. All women with GDM invited to participate in this study and had their glucose status evaluated at 6–12 weeks after delivery. The post-partum glucose test evaluation was carried out from February to June 2019.

Data collection

All consenting women evaluated for post-partum glucose at the selected public health facilities after fasting for at least eight hours before their appointment. In addition, the women were encouraged to return for follow-up for post-partum glucose tolerance test by direct phone contact. All baseline data (14) collected earlier for each participant were linked to this study data. The data included; demographic profile, obstetric history such as gravidity, anthropometric measurements, type of treatment of GDM in the index pregnancy (diet or insulin), behavioral factors (exposure to alcohol use and coffee intake), lifestyle parameters (dietary diversity and physical activity),

antenatal depression status, blood glucose value (FPG and OGTT). Details of the data collection process are provided elsewhere (14). All participants had FPG and 2hr OGTT blood tests performed.

Laboratory assessment

As the detailed laboratory assessment was described earlier (14), the universal screening for GDM using a two-hour 75 g OGTT was performed for all pregnant women by capillary glucose testing, using a standard plasma-calibrated glucometer (HemoCue Glucose B-201+ (A¨ngelholm AB, Sweden)).This corresponded to the latest consensus recommendations of the International Federation of Gynecology and Obstetrics (FIGO) initiative for GDM diagnosis in settings where close-by laboratories or facilities for proper storage and transport of blood samples to distant laboratories are not available (15). The updated diagnostic criteria (WHO and ADA) uses to diagnosis GDM based on one or more of the values of plasma glucose level were met (fasting: ≥ 92 mg/dL, 1 h: ≥180 mg/dL; 2 h: ≥ 153 mg/dL) (16, 17). Similarly, post-partum glucose tolerance status was evaluated by means of a standard FPG and 75 g 2-hour oral glucose tolerance test at 6–12 weeks after delivery, using a similar test procedure but a higher cut off point for the classification of post-partum glucose intolerance (16, 17).

Outcome measures

The primary outcome was the diagnosis of postpartum pre-diabetes (impaired fasting glucose (IFG): FPG 100- 125 mg/dL; impaired glucose tolerance (IGT) 2-h plasma glucose in the 75-g OGTT 140-199 mg/dL) or diabetes (FPG ≥ 126 mg/dL or 2-h plasma glucose ≥ 200 mg/dL in the OGTT, or random plasma glucose ≥ 200 mg/dL) (16, 17). Subjects were divided into two groups: the GI group, which consisted of IGT and IFG patients, and the normal group according to 75 g OGTT at 6-12 weeks after delivery.

Data processing and statistical analysis

All data were entered into Epi Info™ 7 software and exported to R statistical programming language version 3.6.0 for analysis. Descriptive statistics (mean, median, standard deviations (SD), inter-quartile range (IQR), percentages, and rates) were computed. Differences in the distributions of categorical variables were analyzed with a chi-square test. The Shapiro-Wilk test was used to verify if continuous variables were normally distributed. Parametric continuous and non-parametric variables were evaluated with the T-test and Mann-Whitney test, respectively.

Glycemias on diagnostic OGTT were correlated to postpartum OGTT using the Spearman correlation test. We performed a univariate analysis using logistic regression to obtain insight into the association of each potential determinant with post-partum glucose intolerance and to select potential predictors for the multivariate analysis. We fitted all variables with p-value ≤ 0.2 in the univariate analysis to the multivariate model to be more liberal. Then we used a stepwise backward elimination technique with p-value < 0.10 for the likelihood ratio test to fit the reduced model of easily obtainable characteristics. In this study, the most significant factors have been defined as variables with p < values 0.05 in the multivariate logistic regression analysis.

For the discriminative power of predictable variables for postpartum glucose intolerance and to check model accuracy, we computed the area under the ROC curve (discrimination) and calibration plot (calibration) using '*classifierplots' and 'givitiR'* packages of R, respectively (18) and estimated as the area under the curve (AUC) with 95% confidence interval. The AUC ranged from 0.5 (discrimination no better than chance) to 1 (perfect discrimination). To construct an easily applicable postpartum glucose intolerance prediction score, we transformed each coefficient from the model to a round number by dividing to the lowest coefficient. The number of points was subsequently rounded to the nearest integer. We determined the total score for everyone by assigning the points to each variable present and adding them up. In addition, sensitivity, specificity, likelihood ratios and post-test probability of FPG at diagnosis with 95% confidence intervals were calculated by using the optimal cut-offs of levels.

Patient and public involvement

Patients and public were not invited to comment on study design or conduction of the study. However, they will be informed of the study results through publications.

Results

Characteristics of the study group

A prospective cohort study on 1027 women tested for GDM with a 75 g OGTT, where 131(12.8%) of the participants were diagnosed GDM. Of all the women with GDM, 112 (85.5%) attended the postpartum 75 g OGTT at 6-12 weeks after delivery. The overall incidence of early postpartum glucose intolerance was 21.4% (95% CI: 14.3–28.4) inclusive of 18.7% (95% CI: 11.5–25.3) prediabetes and 2.7 % (95% CI: 0.9–6.4) diabetes.

The median age of the cohort was 31 (27-36) years, 20.5% had family history of diabetes mellitus, 33.8% had a previous history of GDM, 18.3 % were anemic, 36.6 % overweight and /or obese at the first prenatal visit. A higher proportion of overweight and/ or obesity ($p < 0.001$), maternal age (≥35 years) ($p=0.025$), and antenatal depression ($p=0.033$) were seen among women with postpartum glucose intolerance than those with normal glucose profile (**Table 1).**

A significant correlation was observed between the OGTT FPG during pregnancy with postpartum FPG and postpartum FPG ($r = 0.424$, $p < 0.001$). There also was also a positive correlation between the 2-h OGTT during pregnancy and the 2-hr postpartum glucose ($r = 0.213$, $p=0.024$).

Table 1. Characteristics of GDM patients according to postpartum glucose test results

Variables	Women with OGTT postpartum (n =112)	GI (n=24)	NGT (n=88)	P value
Maternal age (years)	31 (27-36)	33.5 (30-36.25)	30 (26-34)	0.007
<35	81 (72.3)	13 (54.2)	68 (77.3)	0.025
≥35	31 (27.7)	11 (45.8)	20 (22.7)	
Gravidity	2 (1-3)	3 (2-4)	2 (1-3)	0.000
Primigravida	37 (33)	4 (16.7)	33 (37.5)	0.054
Multigravida	75 (67)	20 (83.3)	55 (62.5)	
Previous history GDM*(n=74)				
Yes	25 (33.8)	8 (40)	17 (31.5)	0.49
No	49 (66.2)	12 (60)	37 (68.5)	
Family history of DM				
Yes	23 (20.5)	7 (29.2)	16 (18.2)	0.238
No	89 (79.5)	17 (70.8)	72 (81.8)	
MUAC	26 (24-29)	29 (25.75-30)	25 (24-28)	0.003
MUAC < 28 cm	71 (63.4)	7 (29.2)	64 (72.7)	0.000
MUAC ≥ 28 cm	41 (36.6)	17 (70.8)	24 (27.3)	
Blood pressure (mmHg)				
Systolic blood pressure	110 (104-120)	110 (100-120)	110 (104.75-120)	0.000
Diastolic blood pressure	70 (69.75- 80)	70 (70-80)	70 (69-80)	0.000
Hemoglobin (g/dl) **	12.6 (11-13.6)	13 (12-14)	12.3 (11-13,6)	0.000
Normal (Hb ≥ 11 g/dl)	89 (81.7)	22 (91.7)	67 (78.8)	0.2328*
Anemia (Hb < 11 g/dl)	20 (18.3)	2 (8.3)	18 (21.2)	
Blood glucose level at diagnosis (mg/dL)				
FPG– GDM diagnosis OGTT	105 (94- 116)	117 (107.75-120.25)	101.5 (92-114)	0.0004
1-h PG – GDM diagnosis OGTT	170 (150.8 – 178)	170.5 (161.5- 179)	170 (150-178)	0.2635
2-h PG – GDM diagnosis OGTT	144.5 (129 -158)	143.5 (132-153.5)	145.5 (128.75-158)	0.7577
Gestational age of diagnosis (weeks)	26 (25-27)	26 (24-27)	26 (25-27)	
24-28 weeks	99 (88.4)	20 (83.3)	79 (89.8)	
≥ 32 weeks	13 (11.6)	4 (16.7)	9 (10.2)	
Level of physical activity				
High	18 (16.1)	5 (20.8)	13 (14.8)	0.590
Moderate	28 (25)	7 (29.2)	21 (23.9)	
Low	66 (58.9)	12 (50)	54 (61.4)	
Dietary diversity status				
Adequate	24 (21.4)	2 (8.3)	22 (25)	0.05973*
Inadequate	88 (78.6)	22 (91.7)	66 (75)	
Antenatal depression				
Yes	28 (25)	10 (41.7)	18 (20.5)	0.033
No	84 (75)	14 (58.3)	70 (79.5)	
Insulin treated GDM				
Yes	7 (6.3)	2 (8.3)	5 (5.7)	0.641*
No	105 (93.8)	22 (91.7)	83 (94.3)	

Data were presented by n (%) or median (IQR). *P value of Fisher exact test; * (n=74) **= 3 participants had no Hgb value (n=109) IQR=Interquartile range GI=Glucose intolerance NGT=Normal glucose tolerance GDM=gestational diabetes mellitus h=hour Hb=hemoglobin g/dl= gram per deciliter mg/dl=milligram deciliter mmHg=millimeter of mercury OGTT=oral glucose tolerance test MUAC=Mid upper arm circumference

A prediction model for postpartum glucose intolerance

After review of literature, 13 demographic, obstetric, and clinical characteristics of mothers collected during the prenatal visits or baseline survey were considered to predict postpartum glucose intolerance. On the univariate analysis (maternal age, gravidity, maternal obesity and\or overweight, FPG at GDM diagnosis, and antenatal depression) variables were found to have significant association. However, in the final multivariable regression analysis and the reduced model four predictors of progression, such as age of mother (≥35 years) during pregnancy (AOR=4.04; 95%:1.23, 14.33), maternal obesity and\or overweight (AOR=3.92; 95%: 1.13, 15.04), FPG at GDM diagnosis (AOR=1.08; 95%: 1.04, 1.15), and antenatal depression (AOR=5.90 ; 95%: 1.66, 23.47) remained significant. Using the results, a prediction model was developed and the equation for the prediction model was obtained **(Table 2).**

The area under the ROC curve (AUC) of the final reduced model was 0.884 (95% CI: 0.821 to 0.939). The calibration test had a p-value of 0.759, indicating the model does not misrepresent the data (**Fig 1).**

Table 2. Multiple logistic regressions for predicting post-partum glucose intolerance among women with GDM.

Predictor variables	OR (95% CI)			Simplified risk score
	Univariate	Multivariate	P value	
Maternal age (≥35 years)	2.88 (1.11, 1.7.46)	4.04 (1.23, 14.33)	0.02380	**4**
Gravidity (multigravida) *	3.00 (1.027, 10.989)	1.75 (0.39, 8.66)	0.47196	-
Previous history GDM	1.45 (0.45, 4.19)	NA		
Family history of DM	1.85 (0.63, 5.11)	NA		
MUAC (≥ 28 cm)	6.48 (2.474, 18.61)	3.92 (1.13,15.04)	0.03617	**4**
Blood pressure (mmHg)				
Systolic blood pressure	0.998 (0.976, 1.054)	NA		
Diastolic blood pressure	1.015 (0.976, 1.053)	NA		
Anemia (Hb < 11 g/dl)	0.34 (0.05, 1.30)	NA		
Blood glucose level at diagnosis (mg/dL)				
FPG– GDM diagnosis OGTT	1.07 (1.03, 1.13)	1.08 (1.04, 1.15)	0.00171	**1**
1-h PG – GDM diagnosis OGTT	1.014 (0.99, 1.03)	NA		
2-h PG – GDM diagnosis OGTT	0.99(0.97, 1.02)	NA		
Gestational age of diagnosis (weeks)	1.03 (0.89, 1.18)	NA		
Level of physical activity				
High	1			
Moderate	0.87 (0.23, 3.47)	NA		
Low	0.57 (0.18, 2.07)			
Dietary diversity status (Inadequate)*	3.66 (0.97, 24.03)	3.07(0.58, 24,45)	0.22031	-
Antenatal depression	2.78 (1.05, 7.29)	5.90 (1.66, 23.47)	0.00770	**5**
Insulin treated GDM	1.51 (0.21, 7.54)	NA		

GDM =gestational diabetes mellitus h=hour Hb=hemoglobin g/dl= gram per deciliter mg/dl=milligram deciliter mmHg=millimeter of mercury OGTT=oral glucose tolerance test MUAC=Mid upper arm circumference

NA - not included to the multivariate analysis *Variables were also retained in the reduced model using likelihood ratio test are; gravidity and dietary diversity status. Both backward and forward selection showed same results. ORs after internal validation with bootstrapping are shown.

In addition, to verify whether any antepartum trait was used as a specific predictor of postpartum glucose intolerance we performed ROC analysis. The analysis indicated that FPG at GDM diagnosis [AUC= 0.736 (95% CI: 0.616-0.845), P < 0.001)], overweight and/or obesity [AUC = 0.718 (95% CI: 0.614 - 0.814), P=0.0284)], maternal age (≥ 35 years) [AUC = 0.616 (95% CI: 0.506 – 0.722), P < 0.001)], and antennal depression [AUC = 0.606 (95% CI: 0.506 - 0.718), P=0.0375] emerged as better predictors of postpartum glucose intolerance **(Fig 2).** Moreover, the AUC for the combined predictors of FPG at diagnosis and MUAC was 0.822 (95% CI:0.722-0.907); FPG at diagnosis and antenatal depression was 0.793 (95% CI:0.698- 0.876), and MUAC and antenatal depression was 0.759 (95% CI: 0.646- 0.856)] (**Fig 3**). The evaluation of the sensitivity across different FPG level thresholds showed that FPG ≥ 105 mg/dl during pregnancy had the optimal sensitivity of 79% (95% CI 58%– 93 %) with a specificity of 56% (95% CI 45%–66%) to predict glucose intolerance postpartum **(Table 3).**

Table 3: Sensitivity and specificity of the FPG test for postpartum glucose intolerance

Threshold FPG (mg/dl)	**Sensitivity**	**Specificity**	**LR+**	**LR–**	**Positive Post-test Probability**	**Negative Post-test Probability**
	% (95% CI)	% (95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
≥ 116	54 (33, 74)	78 (68,86)	2.51 (1.46, 4.31)	0.58 (0.37, 0.92)	41 (24,59)	86 (77,93)
≥ 105	79 (58, 93)	56 (45, 66)	1.79 (1.31, 2.44)	0.37 (0.17, 0.83)	33 (21, 46)	91 (80, 97)
≥ 94	88 (68, 97)	27 (18, 38)	1.20 (0.99, 1.47)	0.46 (0.15, 1.39)	25 (16, 35)	89 (71, 98)

Discussion

Overall, the prevalence of post-partum glucose intolerance observed in this study was 21.4%. The major predictors of developing glucose intolerance were advanced maternal age, overweight and/or obesity, high fasting plasma glucose level at the diagnosis, and antenatal depression during prenatal time. To the best of our knowledge, this is the first study reporting glucose intolerance prevalence and predictors in 6-12 weeks after delivery among postpartum women in Ethiopia. Women with a history of gestational diabetes mellitus (GDM) have more risk for developing postpartum hyperglycemia. Thus, it requires close clinical follow-up for diagnosis and appropriate treatment of patients who develop diabetes early in the postpartum period. Identifying the potential predictors of the future progression of pre-diabetes and/or diabetes in women with gestational diabetes is crucial for managing future disease risks and establishing or maintaining lifestyle changes that decrease the risk of type 2 diabetes later in life or delaying its onset.

Our study showed that more than one-fifth of the women in the cohort had glucose intolerance at 6–12 weeks of delivery. This rate was consistent with the results of studies in Australia (19), Belgium (12), Japan (13), and Brazilin (11). However, the finding was much lower compared with the two existing evidences in Saudi Arabia, where the prevalence of glucose intolerance was 38.6% (20) and 56% (21) and Belgium (43.7%) (22). This difference might have arisen due to the use of different screening and diagnostic methods. We used the universal, one-step approach with a 75g OGTT and the updated diagnostic criteria. Whereas, the other studies used the universal two-step screening strategy for GDM (22). The two-step screening strategy with a glucose challenge test (GCT), therefore, has the potential to limit the number of OGTTs to screen for GDM based on the 2013 WHO criteria and at the same time identify a high-risk group for postpartum glucose intolerance.

As can be expected, women with GDM who developed glucose intolerance in early postpartum were more insulin resistant and had impaired beta-cell function compared to NGT women after delivery. During pregnancy, insulin sensitivity and beta-cell dysfunction were not significantly different between both groups. However, women who often develop GDM, have a subclinical metabolic dysfunction prior to conception compared with NGT women (23).This finding highlights the importance of adherence to postpartum screening and lifestyle modifications to prevent or delay the onset of type 2 diabetes in these women.

The analysis of our cohort of women with GDM has shown that antenatal factors are modestly predictive of the development of glucose intolerance at 6–12 weeks of postpartum. Our study identified that FPG at GDM diagnosis, MUAC, and antenatal depression or the combined as the good predictors for glucose intolerance.

Our study showed that a measured fasting plasma glucose level at GDM diagnosis was the strongest predictor of glucose intolerance at post-partum period. This was in line with our finding that showed most women with glucose intolerance had high levels of fasting plasma at diagnosis and it was found to be a strong predictor (13, 24). There is also evidence that elevated fasting glucose during pregnancy has been a consistent predictor on developing type 2 DM among women with GDM(25).The reasonable explanation to this finding is that the presence of gestational diabetes identifies women with defects in β-cell function in whom insulin secretion does not increase adequately in response to the insulin resistant state of pregnancy. The same defect in β-cell function predisposes some women to overt diabetes in the ensuing years (26). Thus, the diagnosis of GDM represents a window of opportunity for implementing these interventions for those with high blood glucose level at prenatal visits to prevent subsequent diabetes mellitus. This estimate should be used by clinicians to assist their counselling of pregnant women and by policy-makers to target these women for screening and prevention. Therefore, the high fasting BGL on the diagnostic OGTT in pregnancy is well known to be associated with an increased risk for subsequent diabetes.

We found that advanced maternal age (≥35 years) during pregnancy was associated with four-fold increase of abnormal glucose tolerance risk at 6–12 weeks postpartum. This was in line with literatures that reported advanced maternal age as a risk factor for persistent diabetes mellitus (24, 27). Therefore, we strongly believe that appropriate prevention as well as strict control of gestational diabetes mellitus parameters should be performed on such groups of patients.

Maternal overweight and/or obesity was associated with nearly four-fold increase of abnormal glucose tolerance risk and it was another strong predictor of the progression to post-partum glucose intolerance. Similarly, studies have demonstrated that pre-pregnancy BMI was predictive of the development of subsequent diabetes(20, 28-30).

Another strong predicting factor for post-partum glucose intolerance was the presence of antenatal depression. Women with antenatal depression had six folds higher chance of developing post-partum glucose intolerance compared to women with non-depressive symptoms during their prenatal period.

Studies strongly agreed that antenatal depression was associated with gestational diabetes mellitus (14, 31, 32). Similarly, a meta-analysis showed depression as a risk factor for the development of type 2 diabetes (33, 34). This could be explained by shared psychosocial and physiological factors for these comorbid situations. Conversely, pregnant women with depression were more likely to practice unhealthy behaviors and poor diabetes self-care, which might be obstacle for management of GDM and progressed to post-partum glucose abnormality (35). Indeed, women with GDM and antenatal depression struggle to cope with the physical and psychological demands of pregnancy and early motherhood. However, current accredited guidelines for the treatment and management of GDM do not provide adequate advice regarding the care of patients with antenatal depression.

Conclusions

This prospective cohort study showed that one-fifth of the women with GDM had glucose intolerance at 6-12 weeks of delivery according to the updated diagnostic criteria. Antenatal factors (advanced maternal age, high FPG at GDM diagnosis, overweight and/or obesity, antenatal depression) were strong predictors of post-partum glucose intolerance. In addition, a risk score calculation based on a combination of antenatal factors was effective but had a lower accuracy than the model-based approach. Our findings highlighted the need for increased awareness among women and their primary care physicians regarding the importance of long-term glucose screening after pregnancies complicated by GDM.

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Authors' contributions

AAM: conceived and designed the study, analyzed the data and prepared the manuscript. OO & YKG: assisted the development of the research idea, the analysis, interpretation and preparation of the manuscript. All authors read and approved the final manuscript

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Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval and consent to participate

The study was conducted after ethical approval was obtained from the Institute for Advanced Medical Research and Training (IAMRAT), College of Medicine, University of Ibadan, Ibadan, Nigeria with the I/UCH EC Registration Number of NHREC/05/01/2008a and UI/UCH Ethics Committee assigned the number UI/EC/17/0435 and the Institutional Review Board (IRB) of the University of Gondar (Ref.No; O/V/P/RCS/05/811/2018). Permission from the Amhara Public Health Institute and the health authorities of the study sites was also received prior to the start of the study. All participants signed (written or thumb-printed) informed consent form, after, they received a face to face explanation about the objectives of the study. The collected information during the course of the research was treated with the utmost confidentiality.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the correspondence author on reasonable request.

References

1. World Health Organization (WHO). Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. World Health Organization; 2013.
2. McIntyre HD, Thomae M, Wong S, Idris N, Callaway LK. Pregnancy in type 2 diabetes mellitus-problems & promises. Current diabetes reviews. 2009;5(3):190-200.
3. Holman N, Young B, Gadsby R. Current prevalence of Type 1 and Type 2 diabetes in adults and children in the UK. Diabetic Medicine. 2015;32(9):1119-20.
4. World Health Organization (WHO). Global report on diabetes: World Health Organization; 2016.
5. Bellamy L, Casas J-P, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. The Lancet. 2009;373(9677):1773-9.
6. Buchanan TA, Metzger BE, Freinkel N, Bergman RN. Insulin sensitivity and B-cell responsiveness to glucose during late pregnancy in lean and moderately obese women with normal glucose tolerance or mild gestational diabetes. American journal of obstetrics and gynecology. 1990;162(4):1008-14.
7. Gerstein HC, Santaguida P, Raina P, Morrison KM, Balion C, Hunt D, et al. Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: a systematic overview and meta-analysis of prospective studies. Diabetes research and clinical practice. 2007;78(3):305-12.
8. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes. Diabetes care. 2002;25(10):1862-8.
9. Metzger BE, Buchanan TA, Coustan DR, De Leiva A, Dunger DB, Hadden DR, et al. Summary and recommendations of the fifth international workshop-conference on gestational diabetes mellitus. Diabetes care. 2007;30(Supplement 2):S251-S60.
10. American Diabetes Association (ADA). Standards of medical care in diabetes—2013. Diabetes care. 2013;36(Supplement 1):S11-S66.
11. Weinert LS, Mastella LS, Oppermann ML, Silveiro SP, Guimaraes LS, Reichelt AJ. Postpartum glucose tolerance status 6 to 12 weeks after gestational diabetes mellitus: a Brazilian cohort. Arquivos brasileiros de endocrinologia e metabologia. 2014;58(2):197-204.
12. Benhalima K, Van Crombrugge P, Moyson C, Verhaeghe J, Vandeginste S, Verlaenen H, et al. Prediction of Glucose Intolerance in Early Postpartum in Women with Gestational Diabetes Mellitus Based on the 2013 WHO Criteria. J Clin Med. 2019;8(3).
13. Kojima N, Tanimura K, Deguchi M, Morizane M, Hirota Y, Ogawa W, et al. Risk factors for postpartum glucose intolerance in women with gestational diabetes mellitus. Gynecological Endocrinology. 2016;32(10):803-6.
14. Muche AA, Olayemi OO, Gete YK. Prevalence of gestational diabetes mellitus and associated factors among women attending antenatal care at Gondar town public health facilities, Northwest Ethiopia. BMC pregnancy and childbirth. 2019;19(1):334.
15. Hod M, Kapur A, Sacks DA, Hadar E, Agarwal M, Di Renzo GC, et al. The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: A pragmatic guide for diagnosis, management, and care#. International Journal of Gynecology & Obstetrics. 2015;131:S173-S211.
16. American Diabetes Association. Classification and diagnosis of diabetes. Diabetes care. 2017 Jan 1;40(Supplement 1):S11-24.
17. World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization Guideline. Diabetes research and clinical practice. 2014;103(3):341-63.
18. Finazzi S, Poole D, Luciani D, Cogo PE, Bertolini G. Calibration Belt for Quality-of-Care Assessment Based on Dichotomous Outcomes. PLOS ONE. 2011;6(2):e16110.

19. Ingram ER, Robertson IK, Ogden KJ, Dennis AE, Campbell JE, Corbould AM. Utility of antenatal clinical factors for prediction of postpartum outcomes in women with gestational diabetes mellitus (GDM). The Australian & New Zealand journal of obstetrics & gynaecology. 2017;57(3):272-9.
20. Wahabi H, Fayed A, Tunkar SM, Bakhsh H, Al-Hazmi AM, Esmaeil S, et al. Incidence and contributing factors of glucose intolerance in Saudi postpartum women: Sub-group analysis from RAHMA study. PloS one. 2019;14(1):e0210024.
21. Wahabi H. Prevalence and Risk Factors for Glucose Intolerance among Saudi Women with Gestational Diabetes. Journal of diabetes research. 2018;2018.
22. Benhalima K, Jegers K, Devlieger R, Verhaeghe J, Mathieu C. Glucose Intolerance after a Recent History of Gestational Diabetes Based on the 2013 WHO Criteria. PloS one. 2016;11(6):e0157272.
23. Catalano PM. Trying to understand gestational diabetes. Diabetic medicine : a journal of the British Diabetic Association. 2014;31(3):273-81.
24. Capula C, Chiefari E, Vero A, Foti DP, Brunetti A, Vero R. Prevalence and predictors of postpartum glucose intolerance in Italian women with gestational diabetes mellitus. Diabetes research and clinical practice. 2014;105(2):223-30.
25. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes care. 2002;25(10):1862-8.
26. Buchanan TA. Pancreatic B-cell defects in gestational diabetes: implications for the pathogenesis and prevention of type 2 diabetes. The Journal of Clinical Endocrinology & Metabolism. 2001;86(3):989-93.
27. Feig DS, Zinman B, Wang X, Hux JE. Risk of development of diabetes mellitus after diagnosis of gestational diabetes. CMAJ : Canadian Medical Association journal. 2008;179(3):229-34.
28. Cheung NW, Helmink D. Gestational diabetes: the significance of persistent fasting hyperglycemia for the subsequent development of diabetes mellitus. Journal of diabetes and its complications. 2006;20(1):21-5.
29. Lobner K, Knopff A, Baumgarten A, Mollenhauer U, Marienfeld S, Garrido-Franco M, et al. Predictors of postpartum diabetes in women with gestational diabetes mellitus. Diabetes.2006;55(3):792-7.
30. ÅBerg AE, Jönsson EK, Eskilsson I, Landin-Olsson M, Frid AH. Predictive factors of developing diabetes mellitus in women with gestational diabetes. Acta obstetricia et gynecologica Scandinavica. 2002;81(1):11-6.
31. Morrison C, McCook JG, Bailey BA. First trimester depression scores predict development of gestational diabetes mellitus in pregnant rural Appalachian women. Journal of Psychosomatic Obstetrics & Gynecology. 2016;37(1):21-5.
32. Byrn M, Penckofer S. The relationship between gestational diabetes and antenatal depression. Journal of obstetric, gynecologic, and neonatal nursing : JOGNN. 2015;44(2):246-55.
33. Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia. 2006;49(5):837-45.
34. Rotella F, Mannucci E. Depression as a risk factor for diabetes: a meta-analysis of longitudinal studies. J Clin Psychiatry. 2013;74(1):31-7.
35. Gonzalez JS, Peyrot M, McCarl LA, Collins EM, Serpa L, Mimiaga MJ, et al. Depression and diabetes treatment nonadherence: a meta-analysis. Diabetes care. 2008;31(12):2398-403.

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Fig 3. ROC curve for the combined predictors of FPG at diagnosis, MUAC and antenatal depression on glucose intolerance.

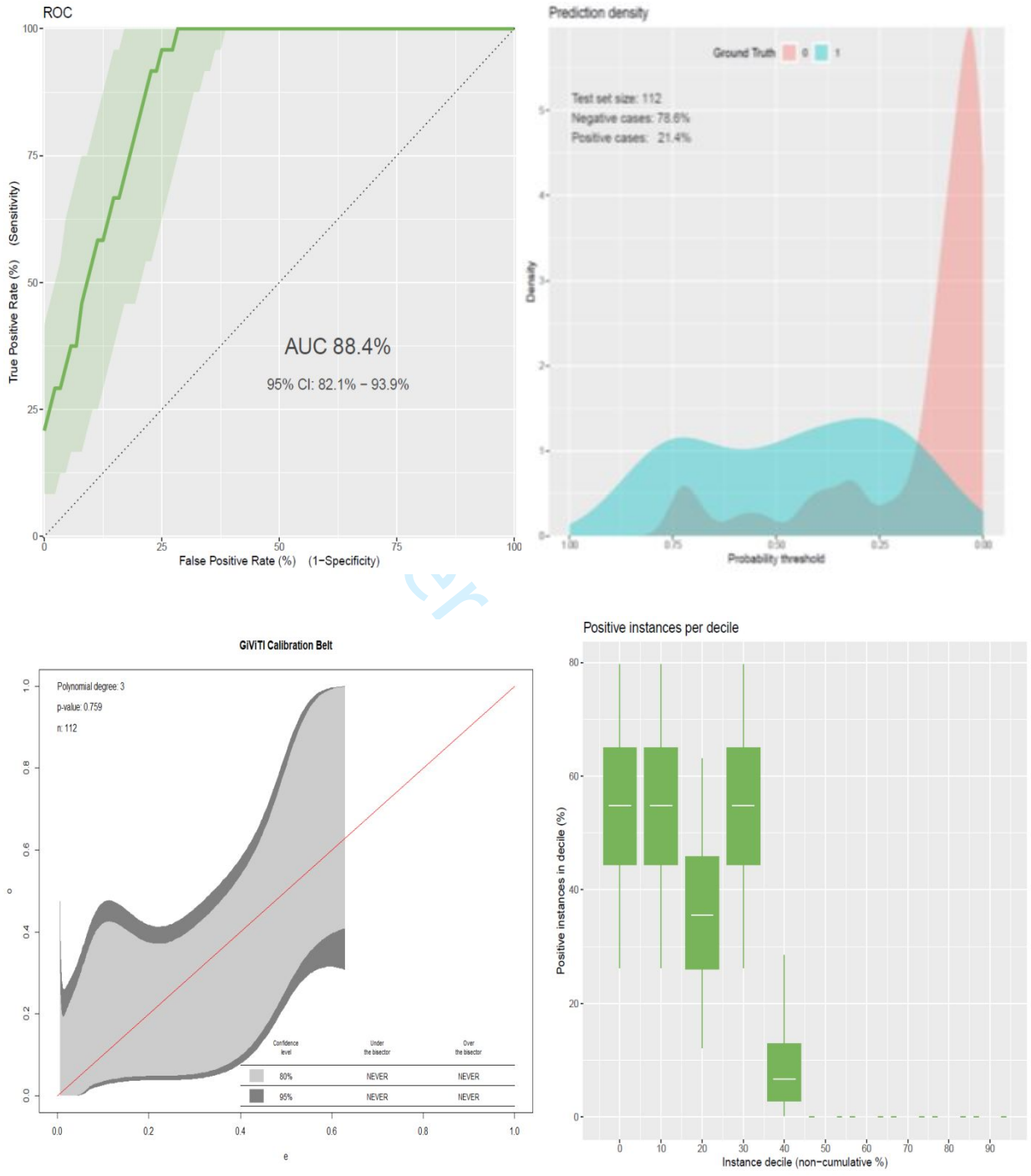
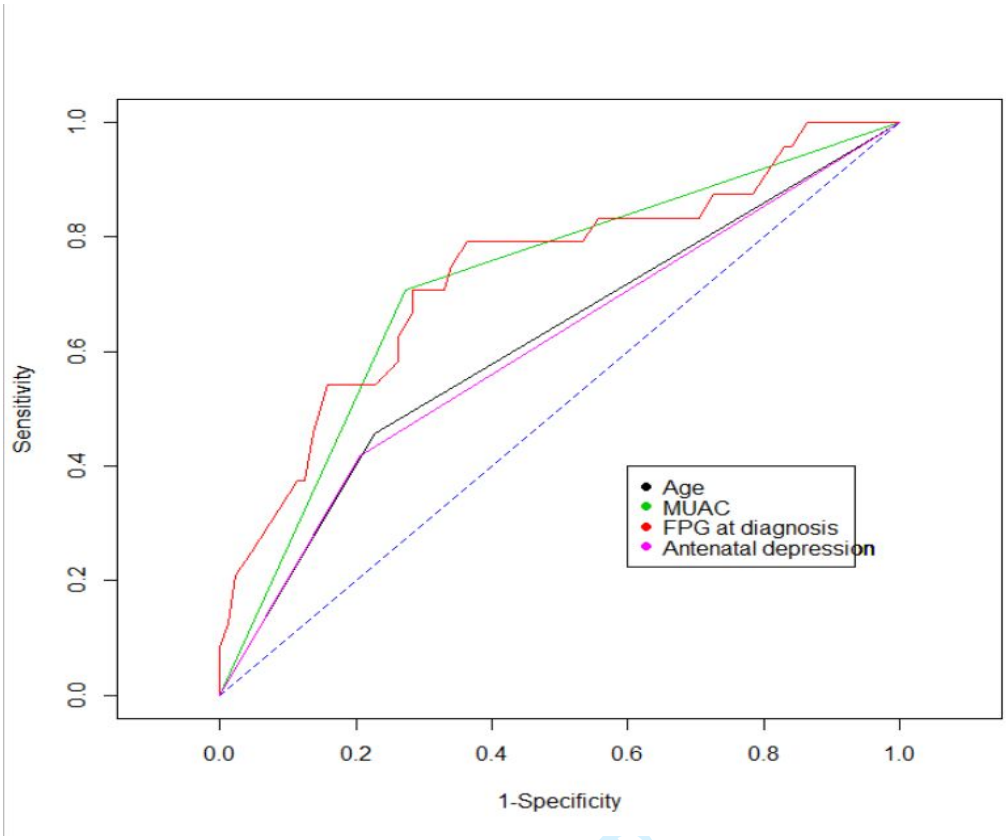


Fig 1: ROC curve (left-up), calibration plot (left-bottom), prediction density (right-up), and positive instances per decile (right-bottom) of a model to predict post-partum glucose intolerance based maternal characteristics. Linear predictors for estimated risk of post-partum glucose intolerance = 1/(1+exp-(-11.87007) + 1.48 x age (≥35 years) + 1.716×overweight and/or obesity (MUAC ≥ 28CM) + 0.081x FPG at diagnosis + 1.637x antenatal depression (yes)



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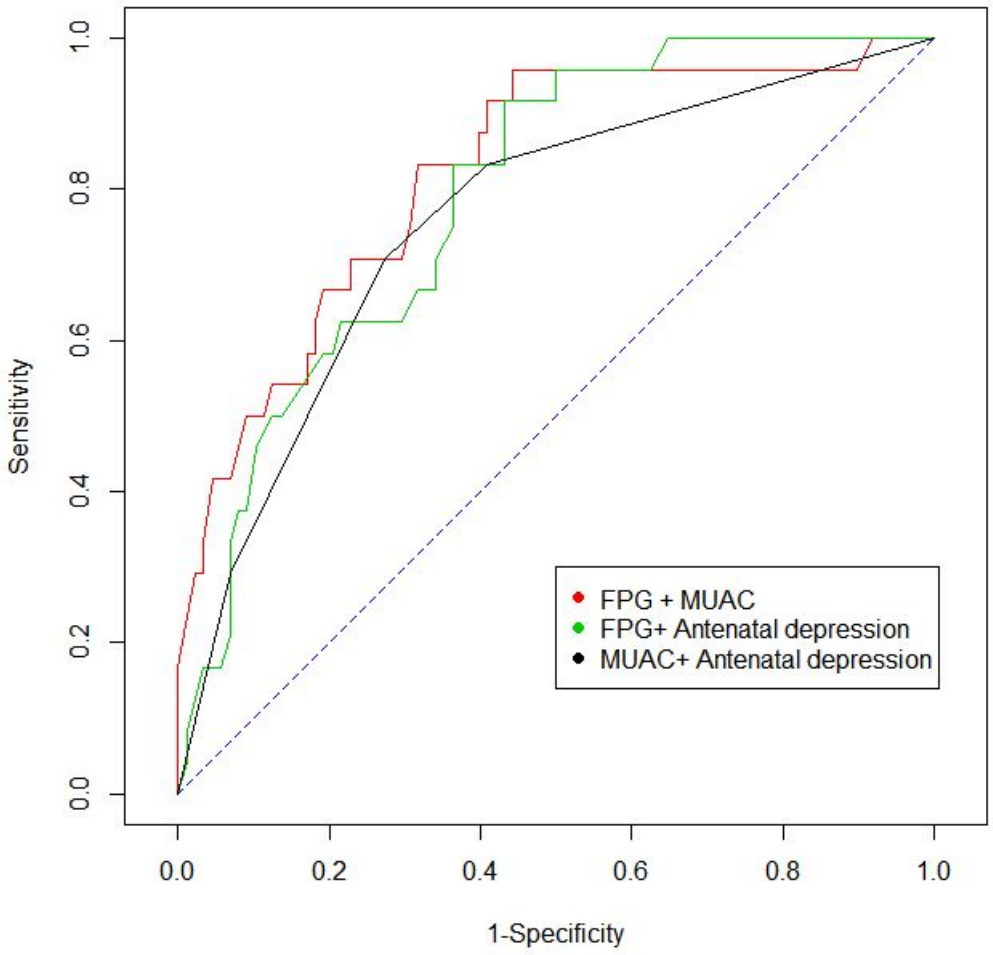

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Predictors of postpartum glucose intolerance in women with gestational diabetes mellitus: A prospective cohort study in Ethiopia based on the updated diagnostic criteria

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Abstract

Objective: This study aimed to identify the prevalence of postpartum glucose intolerance and to develop a prediction model based on antenatal characteristics to predict postpartum glucose intolerance.

Methods: A prospective cohort study was conducted on women with gestational diabetes mellitus (GDM) diagnosed using the updated international diagnostic criteria. All women who had GDM were advised to undergo postpartum oral glucose tolerance test (ppOGTT) at 6-12 weeks of delivery. Predictors of postpartum glucose intolerance were identified using the multivariate analysis. The discriminative power of the predictable variables for postpartum glucose intolerance and the model accuracy were computed by the area under the receiver operating characteristic (ROC) curve and estimated by the area under the curve (AUC) with 95% confidence interval.

Results: Of all women with GDM, 112 (85.5%) attended and completed the ppOGTT. The prevalence of postpartum glucose intolerance was 21.4% (95% CI: 14.3–28.4) inclusive of 18.7% prediabetes and 2.7 % diabetes. Multivariate logistic regression analysis revealed that advanced maternal age, high fasting plasma glucose (FPG) level at diagnosis, overweight and/or obesity, and antenatal depression were predictors for postpartum glucose intolerance. The AUC of the final reduced model to predict postpartum glucose intolerance was 0.884 (95% CI: 0.822 to 0.937). The FPG at GDM diagnosis [AUC= 0.736 (95% CI: 0.616-0.845)] and overweight and/or obesity [AUC = 0.718 (95% CI:0.614- 0.814)] were better predictors of postpartum glucose intolerance**.** Moreover, the AUC for the combined predictors of FPG at diagnosis and mid-upper arm circumference (MUAC) was 0.822 (95% CI:0.722- 0.907), which was the best predictor.

Conclusions: Our finding confirmed the prevalence of postpartum glucose intolerance is high among women with GDM. Antenatal predictors were modestly predicted postpartum glucose intolerance. The findings suggested the ongoing glucose screening is indicated for all women with GDM.

Keywords: gestational diabetes mellitus, post-partum glucose intolerance, prediction

Strengths and limitation of the study

- This prospective cohort study involved GDM patients identified using the updated diagnostic criteria with uniform protocols for all women and followed them till 6-12 weeks of delivery.
- This prognostic risk prediction models showed antenatal factors were modestly predicted post-partum glucose intolerance in women with GDM.
- The study used relatively a small sample size and that ongoing sampling in the future months may change the chances of some variables as significant risk factors and improve a wide range of confidence intervals (CI) in the multivariate analysis.

Introduction

Gestational diabetes mellitus (GDM) is defined as "hyperglycemia first detected during pregnancy that is clearly not preexisting or overt diabetes" (1). Although GDM normally disappears after birth, women previously diagnosed with the disease are at high risk of developing long-term metabolic disorders such as type 2 diabetes (2-5).

Postprandial hyperglycemia is common among women with GDM, more than half develop type 2 diabetes 5 years after delivery (6, 7). A systematic review conducted by Kim et al (8) disclosed that the cumulative incidence of type 2 diabetes among women with prior GDM ranged from 2.6% to 70%. Similarly, the prospect of incident of diabetes was also high at succeeding pregnancies with GDM (8).

Even though international guidelines recommend early screening to explore postpartum pre-diabetes or diabetes in women with gestational diabetes at 6–12 weeks of delivery (9, 10), evidence based on the updated GDM diagnostic criteria is limited. In resource-limited settings, pregnancy often marks the first formal exposure to healthcare. The identification of potential future progression predictors of pre-diabetes and/or diabetes in women with GDM could improve the accurate risk stratification of patients during pregnancy. This provides an opportunity for appropriate, cost-effective, and priority intervention programs of high-risk groups. If the persistence risk can be estimated accurately, treatment may be tailored to individual patient needs. Low persistence risk warrants adoption of a watchful waiting policy, while a high persistence risk may call for immediate and possibly more appropriate management (e.g., lifestyle modification and behavioral change in combination with drug treatment).

Though few studies available to determine the risk factors of postpartum glucose intolerance, presently don't allow predictions of the absolute risk in individual patients in daily practices (11-14). It is anticipated that in our setting could use such model to predict postpartum glucose intolerance risks for women with GDM and refer patients early. Implementation of predictive models could help prospectively evaluated to determine the presence of the outcome, caregivers to guide the best treatment choices per individual patient promptly and be more cost-effective by identifying high-risk patients who benefit most from certain interventions. We sought to (1) identify the prevalence of postpartum glucose intolerance; and (2) develop a prediction model to enable objective estimations of outcome probabilities (risks) according to different combinations of predictor values for women with GDM in the Ethiopian context by using the updated international diagnostic criteria. We hypothesized that using antenatal clinical characteristics would improve the identification of women with GDM at high risk for postpartum glucose intolerance.

Methods and Materials

Study design and population

This prospective cohort study was conducted in five selected public health facilities of Gondar town namely University of Gondar comprehensive specialized hospital, Gondar health center, Woleka health center, Azezo health center, and Maraki health center from 30th March, 2018 to 26th March, 2019. Pregnant women were enrolled if they were 18 years or older, had singleton pregnancy and 20 -23^{+6} weeks of gestation during commencement time, then followed them until at 6–12 weeks after delivery. Whereas, pregnant women who had pre-existing or overt diabetes, chronic diseases, or on medication that might affect their glucose metabolism (steroids, β-adrenergic agonists, anti-psychotic drugs) at commencement were excluded. All pregnant women are screened for overt diabetes in the first antenatal care visit. If the test at the first visit is normal, a two-hour 75 g OGTT is performed for all pregnant women at 24-28 weeks' gestation to screened GDM. In high-risk patients, the 75 g OGTT is repeated at 32-36 weeks, if the result normal at 24-28 weeks' gestation. The detailed methods of the study were explained earlier (15). This follow up study was conducted on 131 women diagnosed with GDM out of 1027 participants who were completed the OGTT. All women with GDM invited to participate in this study and evaluated their glucose status at 6–12 weeks of postpartum.

Data collection

All women who had GDM encouraged to return for postpartum glucose tolerance test by direct phone contact. All baseline data (15) collected earlier for each participant were linked to this study data. The data included; demographic profile, obstetric history such as gravidity, anthropometric measurements, type of treatment of GDM in the index pregnancy (diet or insulin), behavioral factors (exposure to alcohol use and coffee intake), lifestyle parameters (dietary diversity and physical activity), antenatal depression status, blood glucose value (FPG and OGTT). Details of the data collection process are provided elsewhere (15). All participants had FPG and 2hr OGTT blood tests performed at 6–12 weeks after delivery.

Laboratory assessment

As the detailed laboratory assessment was described earlier (15), the universal screening for GDM using a two-hour 75 g OGTT was performed for all pregnant women by capillary glucose testing, using a standard plasma-calibrated glucometer (HemoCue Glucose B-201+ (A¨ngelholm AB, Sweden)).This corresponded to the latest consensus recommendations of the International Federation of Gynecology and Obstetrics (FIGO) initiative for GDM diagnosis in settings where close-by laboratories or facilities for proper storage and transport of blood samples to distant laboratories are not available (16). After capillary blood samples were taken the whole blood capillary values were converted to plasma venous values by multiplying a constant factor of 1.11 (17). The updated diagnostic criteria for GDM diagnosis was made by using the 2017 American Diabetes Association (ADA) (18) or 2013 WHO (1) or modified International Association of the Diabetes and Pregnancy Study Groups (IADPSG) (19). The diagnosis of GDM is made when one or more of the values of plasma glucose level was met (fasting: ≥ 92 mg/dL, 1 h: ≥180 mg/dL; 2 h: ≥ 153 mg/dL). Similarly, postpartum glucose tolerance status was evaluated by means of a standard FPG and 75 g 2-hour oral glucose tolerance test, using a similar test procedure but a higher cut off point for the classification of postpartum glucose intolerance (1, 18)

Outcome measures

The primary outcome was the diagnosis of postpartum pre-diabetes (impaired fasting glucose (IFG): FPG 100- 125 mg/dL; impaired glucose tolerance (IGT) 2-h plasma glucose in the 75-g OGTT 140-199 mg/dL) or diabetes (FPG ≥ 126 mg/dL or 2-h plasma glucose ≥ 200 mg/dL in the OGTT, or random plasma glucose ≥ 200 mg/dL) (1, 18). Subjects were divided into two groups: the glucose intolerance group, which consisted of IGT and IFG patients, and the normal group.

Data processing and statistical analysis

All data were entered into Epi Info™ 7 software and exported to R statistical programming language version 3.6.0 for analysis. Descriptive statistics (mean, median, standard deviations (SD), inter-quartile range (IQR), percentages, and rates) were computed. Differences in the distributions of categorical variables were analyzed with a chi-square test. The Shapiro-Wilk test was used to verify if continuous variables were normally distributed. Normally distributed and non-normally distributed variables were evaluated with the T-test and Mann-Whitney test, respectively. Glycemia on diagnostic OGTT was correlated to postpartum OGTT using the Spearman correlation test. We performed a univariate analysis using logistic regression to obtain insight into the association of each potential determinant with postpartum glucose intolerance and to select potential predictors for the multivariate analysis. We fitted all variables with p-value ≤ 0.2 in the univariate analysis to the multivariate model to be more liberal. Then we used a stepwise backward elimination technique with p-value < 0.10 for the likelihood ratio test to fit the reduced model of easily obtainable characteristics. In this study, the significant factors have been defined as variables with p < values 0.05 in the multivariate logistic regression analysis.

For the discriminative power of predictable variables for postpartum glucose intolerance and to check model accuracy, we computed the area under the ROC curve (discrimination) and calibration plot (calibration) using '*classifierplots' and 'givitiR'* packages of R, respectively (20) and estimated as the area under the curve (AUC) with 95% confidence interval. The AUC ranged from 0.5 (discrimination no better than chance) to 1 (perfect discrimination). To construct an easily applicable postpartum glucose intolerance prediction score, we transformed each coefficient from the model to a round number by dividing to the lowest coefficient. The number of points was subsequently rounded to the nearest integer. We determined the total score for everyone by assigning the points to each variable present and adding them up. In addition, sensitivity, specificity, likelihood ratios, and post-test probability of FPG at diagnosis with 95% confidence intervals were calculated by using the optimal cut-offs of levels.

Patient and public involvement

Patients and public were not invited to comment on study design or conduction of the study. However, they will be informed of the study results through publications.

Results

Characteristics of the study group

A prospective cohort study on 1027 women tested for GDM with a 75 g OGTT, where 131(12.8%) of the participants were diagnosed GDM. Of all the women with GDM, 112 (85.5%) attended the postpartum 75 g OGTT at 6-12 weeks after delivery. The overall incidence of early postpartum glucose intolerance was 21.4% (95% CI: 14.3–28.4) inclusive of 18.7% (95% CI: 11.5–25.3) prediabetes and 2.7 % (95% CI: 0.9–6.4) diabetes.

The median age of the cohort was 31 (27-36) years, 20.5% had a family history of diabetes mellitus, 33.8% had a previous history of GDM, 18.3 % were anemic, 36.6 % overweight and /or obese at the first prenatal visit. A higher proportion of overweight and/ or obesity ($p < 0.001$), maternal age (≥35 years) ($p=0.025$), and antenatal depression ($p=0.033$) were seen among women with postpartum glucose intolerance than those with normal glucose profile (**Table 1).**

There was a positive correlation between FPG during pregnancy and postpartum FPG ($r = 0.424$, $p < 0.001$). There also was also a positive correlation between the 2-h plasma glucose level during pregnancy and the 2-hr postpartum plasma glucose level ($r = 0.213$, $p=0.024$).

Table 1. Characteristics of GDM patients according to postpartum glucose test results

Variables	Women with OGTT postpartum (n =112)	GI (n=24)	NGT (n=88)	P value
Maternal age (years)	31 (27-36)	33.5 (30-36.25)	30 (26-34)	0.007
<35	81 (72.3)	13 (54.2)	68 (77.3)	0.025
≥35	31 (27.7)	11 (45.8)	20 (22.7)	
Gravidity	2 (1-3)	3 (2-4)	2 (1-3)	0.000
Primigravida	37 (33)	4 (16.7)	33 (37.5)	0.054
Multigravida	75 (67)	20 (83.3)	55 (62.5)	
Previous history GDM*(n=74)				
Yes	25 (33.8)	8 (40)	17 (31.5)	0.49
No	49 (66.2)	12 (60)	37 (68.5)	
Family history of DM				
Yes	23 (20.5)	7 (29.2)	16 (18.2)	0.238
No	89 (79.5)	17 (70.8)	72 (81.8)	
MUAC	26 (24-29)	29 (25.75-30)	25 (24-28)	0.003
MUAC < 28 cm	71 (63.4)	7 (29.2)	64 (72.7)	0.000
MUAC ≥ 28 cm	41 (36.6)	17 (70.8)	24 (27.3)	
Blood pressure (mmHg)				
Systolic blood pressure	110 (104-120)	110 (100-120)	110 (104.75-120)	0.000
Diastolic blood pressure	70 (69.75- 80)	70 (70-80)	70 (69-80)	0.000
Hemoglobin (g/dl) **	12.6 (11-13.6)	13 (12-14)	12.3 (11-13,6)	0.000
Normal (Hb ≥ 11 g/dl)	89 (81.7)	22 (91.7)	67 (78.8)	0.2328*
Anemia (Hb < 11 g/dl)	20 (18.3)	2 (8.3)	18 (21.2)	
Blood glucose level at diagnosis (mg/dL)				
FPG– GDM diagnosis OGTT	105 (94- 116)	117 (107.75-120.25)	101.5 (92-114)	0.0004
1-h PG – GDM diagnosis OGTT	170 (150.8 – 178)	170.5 (161.5- 179)	170 (150-178)	0.2635
2-h PG – GDM diagnosis OGTT	144.5 (129 -158)	143.5 (132-153.5)	145.5 (128.75-158)	0.7577
Gestational age of diagnosis (weeks)	26 (25-27)	26 (24-27)	26 (25-27)	
24-28 weeks	99 (88.4)	20 (83.3)	79 (89.8)	
≥ 32 weeks	13 (11.6)	4 (16.7)	9 (10.2)	
Level of physical activity				
High	18 (16.1)	5 (20.8)	13 (14.8)	0.590
Moderate	28 (25)	7 (29.2)	21 (23.9)	
Low	66 (58.9)	12 (50)	54 (61.4)	
Dietary diversity status				
Adequate	24 (21.4)	2 (8.3)	22 (25)	0.05973*
Inadequate	88 (78.6)	22 (91.7)	66 (75)	
Antenatal depression				
Yes	28 (25)	10 (41.7)	18 (20.5)	0.033
No	84 (75)	14 (58.3)	70 (79.5)	
Insulin treated GDM				
Yes	7 (6.3)	2 (8.3)	5 (5.7)	0.641*
No	105 (93.8)	22 (91.7)	83 (94.3)	

Data were presented by n (%) or median (IQR). *P value of Fisher exact test; * (n=74) **= 3 participants had no Hgb value (n=109) IQR=Interquartile range GI=Glucose intolerance NGT=Normal glucose tolerance GDM=gestational diabetes mellitus h=hour Hb=hemoglobin g/dl= gram per deciliter mg/dl=milligram deciliter mmHg=millimeter of mercury OGTT=oral glucose tolerance test MUAC=Mid upper arm circumference

A prediction model for postpartum glucose intolerance

After review of literatures, 13 demographic, obstetric, and clinical characteristics of mothers collected during the prenatal visits or baseline survey were considered to predict postpartum glucose intolerance. On the univariate analysis (maternal age, gravidity, maternal obesity and\or overweight, FPG at GDM diagnosis, and antenatal depression) variables were found to have a significant association. However, in the final multivariable regression analysis and the reduced model four predictors of progression, such as age of mother (≥35 years) during pregnancy (AOR=4.04; 95%:1.23, 14.33), maternal obesity and\or overweight (AOR=3.92; 95%: 1.13, 15.04), FPG at GDM diagnosis (AOR=1.08; 95%: 1.04, 1.15), and antenatal depression (AOR=5.90; 95%: 1.66, 23.47) remained significant. Using the results, a prediction model was developed and the equation for the prediction model was obtained **(Table 2).**

The area under the ROC curve (AUC) of the final reduced model was 0.884 (95% CI: 0.822 to 0.937). The calibration test had a p-value of 0.759, indicating the model does not misrepresent the data (**Figure 1A).** Rounding of all regression coefficients in the reduced model to 1 point resulted in a simplified prediction score presented in table 2. The AUC of the simplified risk score prediction model was 0.808 (95% CI: 0.705 to 0.90). The calibration test had a p-value of 0.044, indicating the model less represent the data (**Figure 1B).** Since the simplified score had a lower prediction accuracy than the model that used the results of the original β coefficients, we prefer to use the original β coefficients.

Table 2. Multiple logistic regressions for predicting post-partum glucose intolerance among women with GDM.

Predictor variables	OR (95% CI)			Simplified risk score
	Univariate	Multivariate	P value	
Maternal age (≥35 years)	2.88 (1.11, 1.7.46)	4.04 (1.23, 14.33)	0.02380	**4**
Gravidity (multigravida) *	3.00 (1.027, 10.989)	1.75 (0.39, 8.66)	0.47196	-
Previous history GDM	1.45 (0.45, 4.19)	NA		
Family history of DM	1.85 (0.63, 5.11)	NA		
MUAC (≥ 28 cm)	6.48 (2.474, 18.61)	3.92 (1.13,15.04)	0.03617	**4**
Blood pressure (mmHg)				
Systolic blood pressure	0.998 (0.976, 1.054)	NA		
Diastolic blood pressure	1.015 (0.976, 1.053)	NA		
Anemia (Hb < 11 g/dl)	0.34 (0.05, 1.30)	NA		
Blood glucose level at diagnosis (mg/dL)				
FPG– GDM diagnosis OGTT	1.07 (1.03, 1.13)	1.08 (1.04, 1.15)	0.00171	**1**
1-h PG – GDM diagnosis OGTT	1.014 (0.99, 1.03)	NA		
2-h PG – GDM diagnosis OGTT	0.99(0.97, 1.02)	NA		
Gestational age of diagnosis (weeks)	1.03 (0.89, 1.18)	NA		
Level of physical activity				
High	1			
Moderate	0.87 (0.23, 3.47)	NA		
Low	0.57 (0.18, 2.07)			
Dietary diversity status (Inadequate)*	3.66 (0.97, 24.03)	3.07(0.58, 24,45)	0.22031	-
Antenatal depression	2.78 (1.05, 7.29)	5.90 (1.66, 23.47)	0.00770	**5**
Insulin treated GDM	1.51 (0.21, 7.54)	NA		

GDM =gestational diabetes mellitus h=hour Hb=hemoglobin g/dl= gram per deciliter mg/dl=milligram deciliter FPG= Fasting plasma glucose mmHg=millimeter of mercury OGTT=oral glucose tolerance test MUAC=Mid upper arm circumference

NA - not included to the multivariate analysis *Variables were also retained in the reduced model using likelihood ratio test are; gravidity and dietary diversity status. Both backward and forward selection showed same results. ORs after internal validation with bootstrapping are shown.

In addition, to verify whether any antepartum trait was used as a specific predictor of postpartum glucose intolerance we performed ROC analysis. The analysis indicated that FPG at GDM diagnosis [AUC= 0.736 (95% CI: 0.616-0.845), P < 0.001)], overweight and/or obesity [AUC = 0.718 (95% CI: 0.614 - 0.814), P=0.0284)], maternal age (≥ 35 years) [AUC = 0.616 (95% CI: 0.506 – 0.722), P < 0.001)], and antenatal depression [AUC = 0.606 (95% CI: 0.506 - 0.718), P=0.0375] emerged as better predictors of postpartum glucose intolerance **(Figure 2).** Moreover, the AUC for the combined predictors of FPG at diagnosis and MUAC was 0.822 (95% CI:0.722-0.907); FPG at diagnosis and antenatal depression was 0.793 (95% CI:0.698- 0.876), and MUAC and antenatal depression was 0.759 (95% CI: 0.646- 0.856)] (**Figure 3**). The evaluation of the sensitivity across different FPG level thresholds showed that FPG ≥ 105 mg/dl during pregnancy had the optimal sensitivity of 79% (95% CI 58%– 93 %) with a specificity of 56% (95% CI 45%–66%) to predict glucose intolerance postpartum **(Table 3).**

Table 3: Sensitivity and specificity of the FPG test for postpartum glucose intolerance

Threshold FPG (mg/dl)	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR– (95% CI)	Positive Post-test Probability % (95% CI)	Negative Post-test Probability % (95% CI)
≥ 116	54 (33, 74)	78 (68,86)	2.51 (1.46, 4.31)	0.58 (0.37, 0.92)	41 (24,59)	86 (77,93)
≥ 105	79 (58, 93)	56 (45, 66)	1.79 (1.31, 2.44)	0.37 (0.17, 0.83)	33 (21, 46)	91 (80, 97)
≥ 94	88 (68, 97)	27 (18, 38)	1.20 (0.99, 1.47)	0.46 (0.15, 1.39)	25 (16, 35)	89 (71, 98)

FPG= Fasting plasma glucose mg/dl=milligram deciliter LR+= positive likelihood ratio LR–=negative likelihood ratio

Discussion

Overall, the prevalence of postpartum glucose intolerance observed in this study was 21.4%. The major predictors of developing glucose intolerance were advanced maternal age, overweight and/or obesity, high fasting plasma glucose level at the diagnosis, and antenatal depression. Women who had a recent GDM are at higher risk of developing postpartum hyperglycemia (either prediabetes or type 2 diabetes). Taken together, this study suggests the needs of close follow-up women who had GDM and identified the predictors for postpartum glucose intolerance was very crucial to early managing future risks of type 2 diabetes in life or delaying its onset.

Our study showed that more than one-fifth of the women in the cohort had glucose intolerance at 6–12 weeks of delivery. This rate was consistent with the results of studies in Australia (21), Belgium (22), Japan (12), and Brazil (11). However, the finding was much lower compared with the two existing evidences in Saudi Arabia, where the prevalence of glucose intolerance was 38.6% (14) and 56% (23) and Belgium (43.7%) (13). This difference might have arisen due to the use of different screening and diagnostic methods. We used the universal, one-step approach with a 75g OGTT and the updated diagnostic criteria. Whereas, the other studies used the universal two-step screening strategy for GDM (13). The two-step screening strategy with a glucose challenge test (GCT), therefore, has the potential to limit the number of OGTTs to screen for GDM and identified a high-risk group for postpartum glucose intolerance. The tight relationship between GDM and postpartum glucose intolerance suggests that GDM may represent an early stage in the natural history of postpartum glucose intolerance (24, 25). Pregnancy might also constitute a physiological condition of insulin resistance and impaired beta-cell function (26, 27). In addition, the early onset of GDM would be expected to indicate greater pre-existing insulin resistance/pancreatic ß-cell dysfunction and therefore increased risk of postpartum glucose intolerance (28). This finding highlights the importance of adherence to postpartum screening and lifestyle modifications to prevent or delay the onset of type 2 diabetes in these women. Regardless of the screening approach used, research on the efficacy or effectiveness of lifestyle interventions in preventing or delaying the progression to postpartum glucose intolerance in women with GDM in Ethiopia would provide much-needed data.

The finding of our study has shown that antenatal characteristics could modestly predicted the development of postpartum glucose intolerance. FPG at GDM diagnosis, MUAC, and antenatal

depression or the combined as the good predictors for glucose intolerance. The model for combined antenatal predictors showed excellent predictive accuracy with an area under the receiver operating characteristic (ROC) curve of 0.88. This prognostic prediction model provides a powerful tool for the identification of GDM patients at higher occurrence on the progression of postpartum glucose intolerance.

In the present study, the levels of FPG in antepartum OGTT was the strongest predictor of glucose intolerance during the early postpartum period in women with GDM. Similar evidence was obtained in studies conducted in Italy (29), United Kingdom (30), and Sweden (31), reported FPG during OGTT as a predictor of postpartum glucose intolerance. These results suggest that the decline in basal insulin secretion and in early phase glucose-stimulated insulin secretion is strongly related to the pathology of postpartum glucose intolerance. Evidences also revealed that elevated fasting glucose level during pregnancy has been a consistent predictor of development of type 2 diabetes in women with GDM (12, 29, 32). The reasonable explanation to this finding is that the presence of GDM identifies women with defects in β-cell function in whom insulin secretion does not increase adequately in response to the insulin resistant state of pregnancy. The same defect in β-cell function predisposes some women to overt diabetes subsequently (26). Thus, the diagnosis of GDM represents a window of opportunity for implementing these interventions for those with high blood glucose level at prenatal visits to prevent subsequent diabetes mellitus. This estimate should be used by clinicians to assist their counselling of pregnant women and by policymakers to target these women for screening and prevention early.

We found that advanced maternal age (≥35 years) during pregnancy as a predictor of abnormal glucose tolerance risk at 6–12 weeks of postpartum. Similar evidence was obtained in studies conducted in Italy (29), South Africa (33), which described advanced maternal age was predictor of postpartum glucose intolerance. On the contrary, a study conducted in Belgium maternal age was not a predictor for glucose intolerance in early postpartum (34). Postpartum glucose intolerance arose due to the inadequate Pancreatic B cell response to stimulation and be more insulin-resistant in the advanced maternal age (35). Thus, the study suggested that due attention should be given to GDM women with advanced maternal age. By changing their lifestyle after pregnancy can reduce the risk progressing to type 2 diabetes (36). Mainly for women with

advanced age integrating behavioral counseling on nutrition and exercise into ANC services is a low-cost intervention to prevent subsequent diabetes.

Maternal overweight and/or obesity was a strong predictor of abnormal glucose tolerance during postpartum period. Similarly, studies have demonstrated that pre-pregnancy BMI was predictive of the development of subsequent diabetes (14, 37-39). In view of the current high burden of overweight or obesity in the African women and the expected rise in diabetes prevalence, it is imperative to identify populations at elevated risk and introduce risk-lowering interventions such as avoiding sedentary life (40, 41).

Another strong predictor for postpartum glucose intolerance was the presence of antenatal depression. Though study is limited in predictive effect of antenatal depression on postpartum glucose intolerance, there evidences showed the association of antenatal depression with GDM (15, 42, 43). Similarly, depression has been suggested as a risk factor for the development of type 2 diabetes (44, 45). This could be explained by shared psychosocial and physiological factors for these comorbid situations. Besides, GDM women with antenatal depression could practice unhealthy behaviors, and poor glycemic control which leads the progression to abnormal glucose status in post-pregnancy (46). These women also struggle to cope with the physical and psychological demands of pregnancy and early motherhood. Unfortunately, the guidelines for the treatment and management of GDM do not provide adequate advice regarding the care of patients with antenatal depression particularly countries with low resource setting.

The strength of this study was a prospective cohort study involved GDM patients identified using the updated diagnostic criteria with uniform protocols for all women and followed them until 6-12 weeks of delivery. In addition, to the best of our knowledge, this study is the first prospective cohort study to follow postpartum outcomes of GDM and included several antenatal variables to use for the prediction model of postpartum glucose intolerance in Ethiopia. Though, WHO recommends that in settings where laboratories or proper storages and transport of blood samples is not guaranteed, which is the case in resource limited countries like Ethiopia, the use of point of care tests may influence the result (47). However, we used plasma-calibrated hand-held glucometers because of convenience and acceptable reliability. Moreover, the study used a relatively small sample size, limited number of examined cases and that ongoing sampling in future

months may change the chances of some variables as significant risk factors and improve a wide range of confidence intervals (CI) in the multivariate analysis could be the limitations of the study.

Conclusions

This prospective cohort study showed that one-fifth of the women with GDM had glucose intolerance at 6-12 weeks of delivery according to the updated diagnostic criteria. Antenatal characteristics (advanced maternal age, high FPG at GDM diagnosis, overweight and/or obesity, antenatal depression) were strong predictors of post-partum glucose intolerance. This prognostic risk prediction models revealed the utility of antenatal predictors were modestly predicted post-partum glucose intolerance in women with GDM. In addition, a risk score calculation based on a combination of antenatal predictors was effective but had lower accuracy than the model-based approach by original β coefficients. Thus, our findings highlighted the need for increased awareness among women and their primary care physicians regarding the importance of long-term glucose screening after pregnancies complicated by GDM.

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Authors' contributions

AAM: conceived and designed the study, analyzed the data and prepared the manuscript. OO & YKG: assisted the development of the research idea, the analysis, interpretation and preparation of the manuscript. All authors read and approved the final manuscript

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Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval and consent to participate

The study was conducted after ethical approval was obtained from the Institute for Advanced Medical Research and Training (IAMRAT), College of Medicine, University of Ibadan, Ibadan, Nigeria with the I/UCH EC Registration Number of NHREC/05/01/2008a and UI/UCH Ethics Committee assigned the number UI/EC/17/0435 and the Institutional Review Board (IRB) of the University of Gondar (Ref.No; O/V/P/RCS/05/811/2018). Permission from the Amhara Public Health Institute and the health authorities of the study sites was also received prior to the start of the study. All participants signed (written or thumb-printed) informed consent form, after, they received a face to face explanation about the objectives of the study. The collected information during the course of the research was treated with the utmost confidentiality.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the correspondence author on reasonable request.

References

1. World Health Organization (WHO). Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. Available from: http://apps.who.int/iris/bitstream/10665/8597/1/WHO_NMH_MND_13.2_eng.pdf. 2013.
2. McIntyre HD, Thomae M, Wong S, Idris N, Callaway LK. Pregnancy in type 2 diabetes mellitus-problems & promises. Current diabetes reviews. 2009;5(3):190-200.
3. Holman N, Young B, Gadsby R. Current prevalence of Type 1 and Type 2 diabetes in adults and children in the UK. Diabetic Medicine. 2015;32(9):1119-20.
4. World Health Organization (WHO). Global report on diabetes: World Health Organization; 2016.
5. Bellamy L, Casas J-P, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. The Lancet. 2009;373(9677):1773-9.
6. Buchanan TA, Metzger BE, Freinkel N, Bergman RN. Insulin sensitivity and B-cell responsiveness to glucose during late pregnancy in lean and moderately obese women with normal glucose tolerance or mild gestational diabetes. American journal of obstetrics and gynecology. 1990;162(4):1008-14.
7. Gerstein HC, Santaguida P, Raina P, Morrison KM, Balion C, Hunt D, et al. Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: a systematic overview and meta-analysis of prospective studies. Diabetes research and clinical practice. 2007;78(3):305-12.
8. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes. Diabetes care. 2002;25(10):1862-8.
9. Metzger BE, Buchanan TA, Coustan DR, De Leiva A, Dunger DB, Hadden DR, et al. Summary and recommendations of the fifth international workshop-conference on gestational diabetes mellitus. Diabetes care. 2007;30(Supplement 2):S251-S60.
10. American Diabetes Association (ADA). Standards of medical care in diabetes—2013. Diabetes care. 2013;36(Supplement 1):S11-S66.
11. Weinert LS, Mastella LS, Oppermann ML, Silveiro SP, Guimaraes LS, Reichelt AJ. Postpartum glucose tolerance status 6 to 12 weeks after gestational diabetes mellitus: a Brazilian cohort. Arquivos brasileiros de endocrinologia e metabologia. 2014;58(2):197-204.
12. Kojima N, Tanimura K, Deguchi M, Morizane M, Hirota Y, Ogawa W, et al. Risk factors for postpartum glucose intolerance in women with gestational diabetes mellitus. Gynecological Endocrinology. 2016;32(10):803-6.
13. Benhalima K, Jegers K, Devlieger R, Verhaeghe J, Mathieu C. Glucose Intolerance after a Recent History of Gestational Diabetes Based on the 2013 WHO Criteria. PloS one. 2016;11(6):e0157272.
14. Wahabi H, Fayed A, Tunkar SM, Bakhsh H, Al-Hazmi AM, Esmaeil S, et al. Incidence and contributing factors of glucose intolerance in Saudi postpartum women: Sub-group analysis from RAHMA study. PloS one. 2019;14(1):e0210024.
15. Muche AA, Olayemi OO, Gete YK. Prevalence of gestational diabetes mellitus and associated factors among women attending antenatal care at Gondar town public health facilities, Northwest Ethiopia. BMC pregnancy and childbirth. 2019;19(1):334.
16. Hod M, Kapur A, Sacks DA, Hadar E, Agarwal M, Di Renzo GC, et al. The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: A pragmatic guide for diagnosis, management, and care#. International Journal of Gynecology & Obstetrics. 2015;131:S173-S211.
17. D'Orazio P, Burnett RW, Fogh-Andersen N, Jacobs E, Kuwa K, Külpmann WR, et al. Approved IFCC recommendation on reporting results for blood glucose (abbreviated). Clinical chemistry. 2005;51(9):1573-6.
18. American Diabetes Association (ADA). Classification and diagnosis of diabetes. Sec. 2. In Standards ofMedical Care in Diabetesd 2017. Diabetes Care 2017;40(Suppl. 1):S11–S24.

19. International Association of Diabetes and Pregnancy Study Groups (IADPSG). International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes care. 2010;33(3):676-82.
20. Finazzi S, Poole D, Luciani D, Cogo PE, Bertolini G. Calibration Belt for Quality-of-Care Assessment Based on Dichotomous Outcomes. PLOS ONE. 2011;6(2):e16110.
21. Ingram ER, Robertson IK, Ogden KJ, Dennis AE, Campbell JE, Corbould AM. Utility of antenatal clinical factors for prediction of postpartum outcomes in women with gestational diabetes mellitus (GDM). The Australian & New Zealand journal of obstetrics & gynaecology. 2017;57(3):272-9.
22. Benhalima K, Van Crombrugge P, Moyson C, Verhaeghe J, Vandeginste S, Verlaenen H, et al. Prediction of Glucose Intolerance in Early Postpartum in Women with Gestational Diabetes Mellitus Based on the 2013 WHO Criteria. J Clin Med. 2019;8(3).
23. Wahabi H. Prevalence and Risk Factors for Glucose Intolerance among Saudi Women with Gestational Diabetes. Journal of diabetes research. 2018;2018.
24. Ben-Haroush A, Yogev Y, Hod M. Epidemiology of gestational diabetes mellitus and its association with Type 2 diabetes. Diabetic Medicine. 2004;21(2):103-13.
25. Cho YM, Kim T, Lim S, Choi SH, Shin H, Lee H, et al. Type 2 diabetes-associated genetic variants discovered in the recent genome-wide association studies are related to gestational diabetes mellitus in the Korean population. Diabetologia. 2009;52(2):253-61.
26. Buchanan TA. Pancreatic B-cell defects in gestational diabetes: implications for the pathogenesis and prevention of type 2 diabetes. The Journal of Clinical Endocrinology & Metabolism. 2001;86(3):989-93.
27. Ta B. Xiang AH. Gestational diabetes mellitus. J Clin Invest. 2005;115:485-91.
28. Ingram ER, Robertson IK, Ogden KJ, Dennis AE, Campbell JE, Corbould AM. Utility of antenatal clinical factors for prediction of postpartum outcomes in women with gestational diabetes mellitus (GDM). Australian and New Zealand Journal of Obstetrics and Gynaecology. 2017;57(3):272-9.
29. Capula C, Chiefari E, Vero A, Foti DP, Brunetti A, Vero R. Prevalence and predictors of postpartum glucose intolerance in Italian women with gestational diabetes mellitus. Diabetes research and clinical practice. 2014;105(2):223-30.
30. Sivaraman SC, Vinnamala S, Jenkins D. Gestational diabetes and future risk of diabetes. J Clin Med Res. 2013;5(2):92-6.
31. Ekelund M, Shaat N, Almgren P, Groop L, Berntorp K. Prediction of postpartum diabetes in women with gestational diabetes mellitus. Diabetologia. 2010;53(3):452-7.
32. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes care. 2002;25(10):1862-8.
33. Feig DS, Zinman B, Wang X, Hux JE. Risk of development of diabetes mellitus after diagnosis of gestational diabetes. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2008;179(3):229-34.
34. Benhalima K, Lens K, Bosteels J, Chantal M. The Risk for Glucose Intolerance after Gestational Diabetes Mellitus since the Introduction of the IADPSG Criteria: A Systematic Review and Meta-Analysis. Journal of clinical medicine. 2019;8(9):1431.
35. Jolly M, Sebire N, Harris J, Robinson S, Regan L. The risks associated with pregnancy in women aged 35 years or older. Human reproduction. 2000;15(11):2433-7.
36. Chivese T, Norris SA, Levitt NS. Progression to type 2 diabetes mellitus and associated risk factors after hyperglycemia first detected in pregnancy: A cross-sectional study in Cape Town, South Africa. PLoS medicine. 2019;16(9):e1002865-e.
37. Cheung NW, Helmink D. Gestational diabetes: the significance of persistent fasting hyperglycemia for the subsequent development of diabetes mellitus. Journal of diabetes and its complications. 2006;20(1):21-5.

38. Lobner K, Knopff A, Baumgarten A, Mollenhauer U, Marienfeld S, Garrido-Franco M, et al. Predictors of postpartum diabetes in women with gestational diabetes mellitus. Diabetes. 2006;55(3):792-7.

39. ÅBerg AE, Jönsson EK, Eskilsson I, Landin-Olsson M, Frid AH. Predictive factors of developing diabetes mellitus in women with gestational diabetes. Acta obstetricia et gynecologica Scandinavica. 2002;81(1):11-6.

40. NCD Risk Factor Collaboration– Africa Working Group .Trends in obesity and diabetes across Africa from 1980 to 2014: an analysis of pooled population-based studies. International journal of epidemiology. 2017;46(5):1421-32.

41. Puoane T, Steyn K, Bradshaw D, Laubscher R, Fourie J, Lambert V, et al. Obesity in South Africa: the South African demographic and health survey. Obesity research. 2002;10(10):1038-48.

42. Morrison C, McCook JG, Bailey BA. First trimester depression scores predict development of gestational diabetes mellitus in pregnant rural Appalachian women. Journal of Psychosomatic Obstetrics & Gynecology. 2016;37(1):21-5.

43. Byrn M, Penckofer S. The relationship between gestational diabetes and antenatal depression. Journal of obstetric, gynecologic, and neonatal nursing : JOGNN. 2015;44(2):246-55.

44. Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia. 2006;49(5):837-45.

45. Rotella F, Mannucci E. Depression as a risk factor for diabetes: a meta-analysis of longitudinal studies. J Clin Psychiatry. 2013;74(1):31-7.

46. Gonzalez JS, Peyrot M, McCarl LA, Collins EM, Serpa L, Mimiaga MJ, et al. Depression and diabetes treatment nonadherence: a meta-analysis. Diabetes care. 2008;31(12):2398-403.

47. Hod M, Kapur A, Sacks DA, Hadar E, Agarwal M, Di Renzo GC, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on gestational diabetes mellitus: a pragmatic guide for diagnosis, management, and care. International Journal of Gynecology & Obstetrics. 2015;131:S173-S211.

List of figures

Figure 1. ROC curve for prediction of postpartum glucose intolerance using different models

Figure 2. ROC curves of antepartum parameters for the prediction of postpartum glucose intolerance

Figure 3. ROC curve for the combined predictors of FPG at diagnosis, MUAC and antenatal depression on glucose intolerance

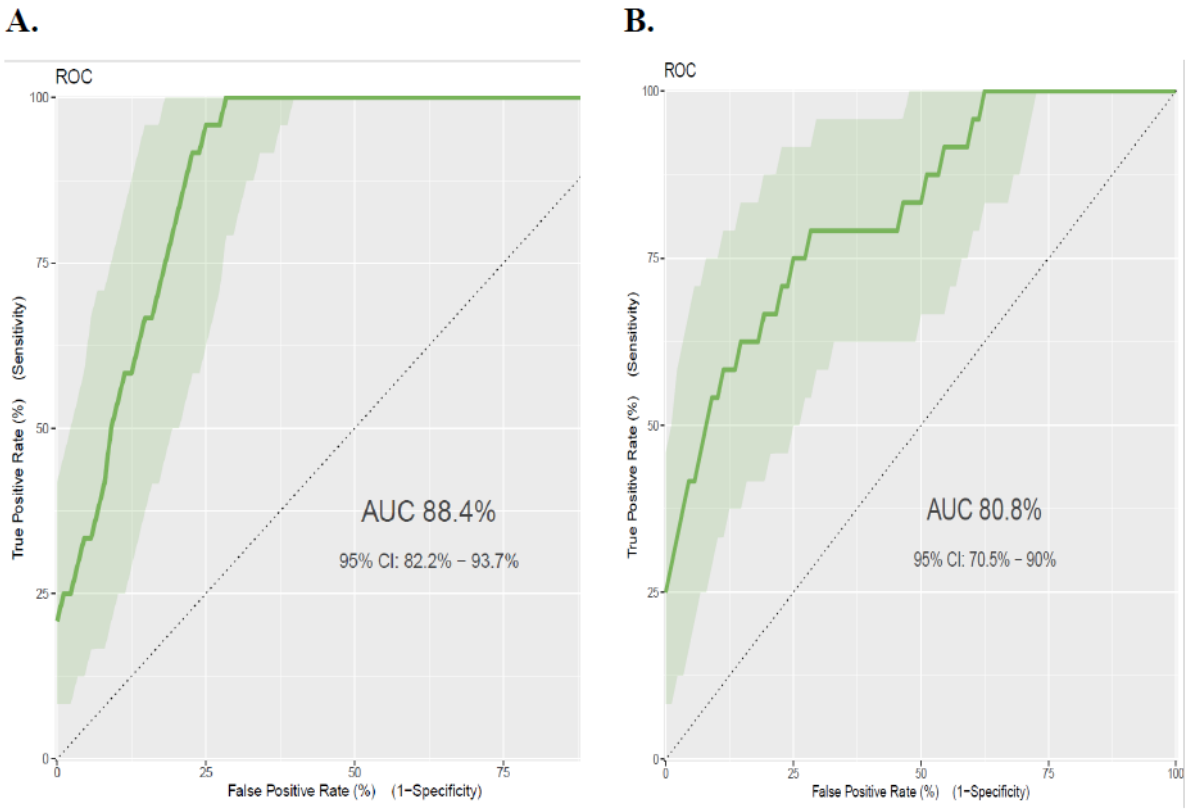

Figure 1. ROC curve for prediction of postpartum glucose intolerance using different models:
A. Linear predictor model for estimated risk of postpartum glucose intolerance = 1/(1+exp-(-11.8 7007) +1.48 * age (≥35 years)+1.716*overweight and/or obesity (MUAC ≥ 28CM) + 0.081* FPG at diagnosis + 1.637* antenatal depression (yes)
B. Simplified risk score predictor model for estimated risk of postpartum glucose intolerance = (age ≥35 years***4**) + (overweight and/or obesity (MUAC ≥ 28CM)* **4**) + (FPG at diagnosis***1**) + (antenatal depression***5**)

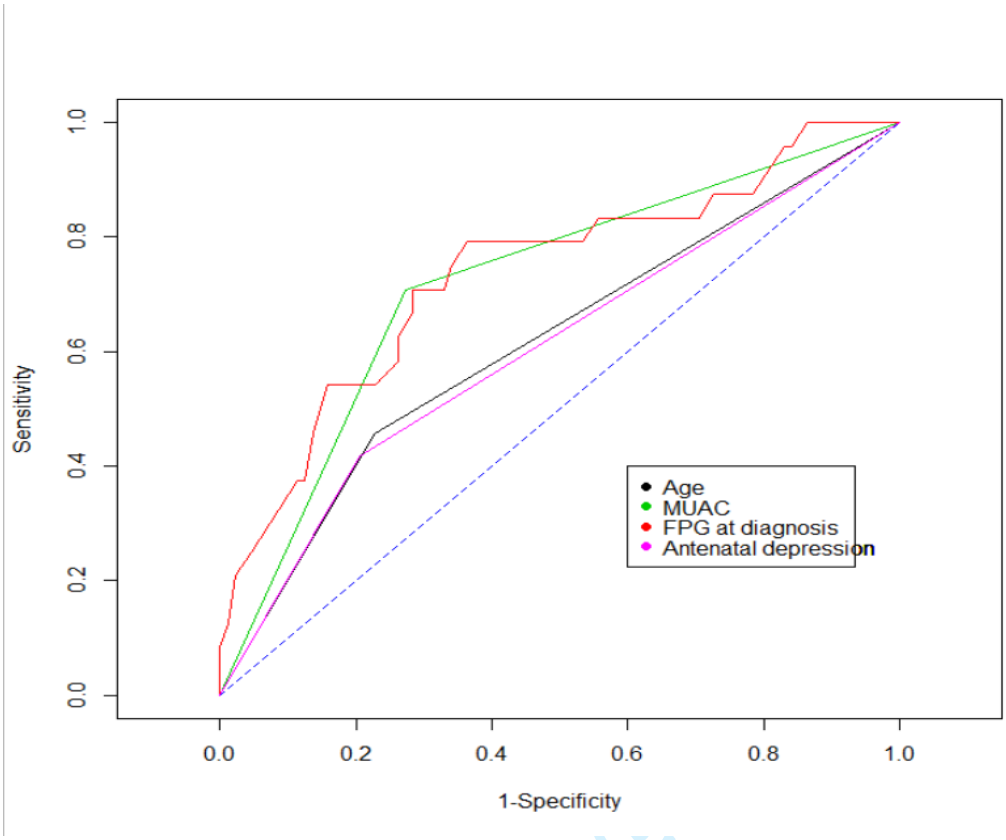

Figure 2. ROC curves of antepartum parameters for the prediction of postpartum glucose intolera nce

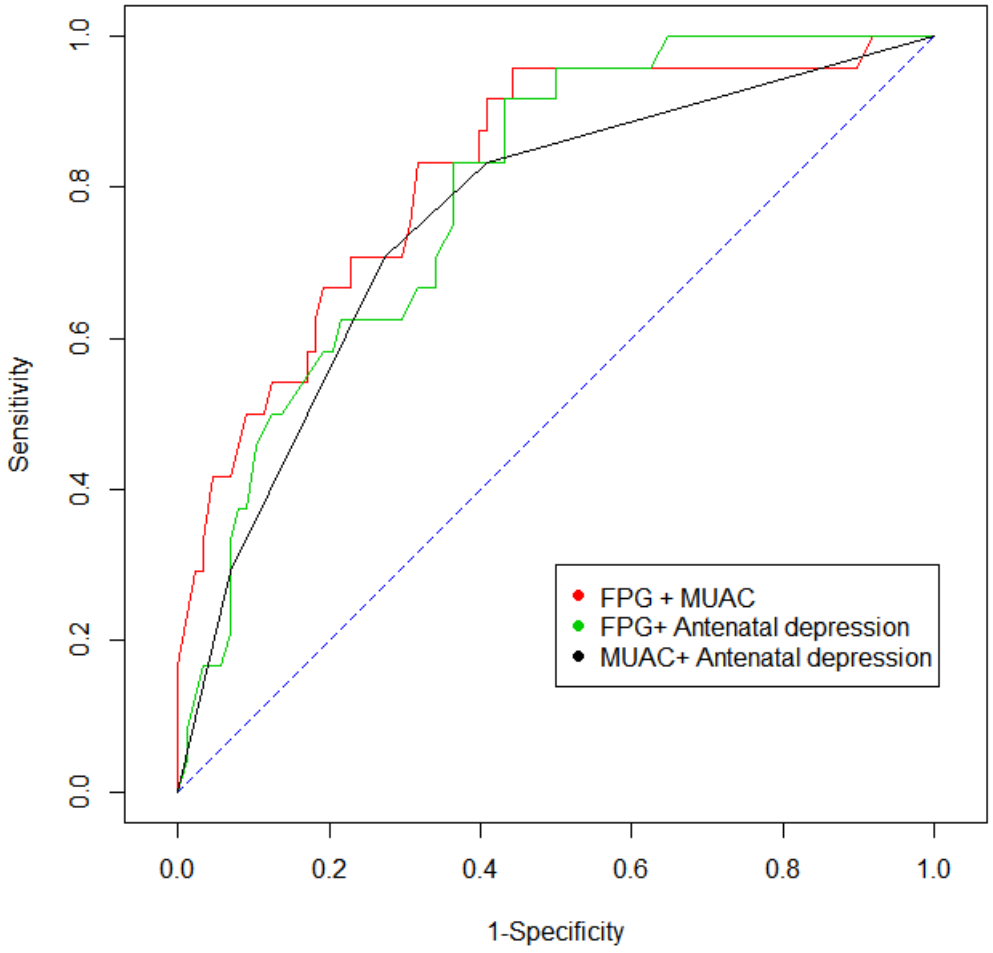

Figure 3. ROC curve for the combined predictors of FPG at diagnosis, MUAC and antenatal depression on glucose intolerance.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4,5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	--
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	4, 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5, 6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	4, 7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9, 10
		(*b*) Report category boundaries when continuous variables were categorized	10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10, 11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Predictors of postpartum glucose intolerance in women with gestational diabetes mellitus: A prospective cohort study in Ethiopia based on the updated diagnostic criteria

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Abstract

Objective: To identify the incidence of postpartum glucose intolerance and develop a prediction model based on antenatal characteristics to predict postpartum glucose intolerance.

Design: Prospective cohort study

Setting: Gondar town public health facilities, Northwest Ethiopia.

Participants: Women who had gestational diabetes mellitus were advised to undergo postpartum oral glucose tolerance test at 6-12 weeks of delivery**.**

Main outcome: Postpartum glucose intolerance.

Data analysis: Predictors of postpartum glucose intolerance were identified using the multivariable logistic regression analysis. The discriminative power of the predictable variables for postpartum glucose intolerance and the model accuracy were computed by the area under the receiver operating characteristic (ROC) curve and estimated by the area under the curve (AUC) with 95% confidence interval.

Results: A total of 112 (85.5%) of women with gestational diabetes mellitus were returned and completed the postpartum oral glucose tolerance test. The incidence of postpartum glucose intolerance was 21.4% (95% CI: 14.3 - 28.4) inclusive of 18.7% prediabetes and 2.7 % diabetes. Multivariable logistic regression analysis revealed that advanced maternal age, high fasting plasma glucose level at diagnosis, overweight and/or obesity, and antenatal depression were predictors for postpartum glucose intolerance. The AUC of the final reduced model to predict postpartum glucose intolerance was 0.884 (95% CI: 0.822 - 0.937). The fasting plasma glucose at gestational diabetes mellitus diagnosis [AUC= 0.736 (95% CI: 0.616 - 0.845)] and overweight and/or obesity [AUC = 0.718 (95% CI:0.614 - 0.814)] were better predictors of postpartum glucose intolerance**.** Moreover, the AUC for the combined predictors of fasting plasma glucose at diagnosis and mid-upper arm circumference was 0.822 (95% CI:0.722 - 0.907), which was the best predictor.

Conclusions: The incidence of postpartum glucose intolerance was high among women with gestational diabetes mellitus. Antenatal predictors were modestly predicted postpartum glucose intolerance. The findings suggested the ongoing glucose screening is indicated for all women with gestational diabetes mellitus.

Keywords: gestational diabetes mellitus, post-partum glucose intolerance, prediction

Strengths and limitation of the study

- This prospective cohort study involved women with gestational diabetes mellitus diagnosed using the updated diagnostic criteria and followed them till 6-12 weeks of delivery.
- The prediction model is constructed from easily obtainable antenatal characteristics that make it applicable in low resource settings
- The study used relatively a small sample size.

Introduction

Gestational diabetes mellitus (GDM) is defined as "hyperglycemia first detected during pregnancy that is clearly not preexisting or overt diabetes" (1). Although GDM normally disappears after birth, women previously diagnosed with the disease are at high risk of developing long-term metabolic disorders such as type 2 diabetes (2-5).

Postprandial hyperglycemia is common among women with GDM, thereby more than half develop type 2 diabetes 5 years after delivery (6, 7). A systematic review conducted by Kim et al. (8) disclosed that the incidence of type 2 diabetes among women with prior GDM ranged from 2.6% to 70%. Similarly, the prospect of incident of diabetes was also high at succeeding pregnancies with GDM (8).

The international guidelines recommend that women with GDM should be screened for persistent diabetes at 6–12 weeks of postpartum (9, 10). Indeed, the identification of those women who are at the highest risk of progressing to postpartum glucose intolerance in our setting remains limited. In resource-limited settings, pregnancy often marks the first formal exposure to healthcare. The identification of potential future progression predictors of pre-diabetes and/or diabetes in women with GDM could improve the accurate risk stratification of patients during pregnancy. This provides an opportunity for appropriate, cost-effective, and priority intervention programs of high-risk groups. If the persistence risk can be estimated accurately, treatment may be tailored to individual patient needs. Low persistence risk warrants adoption of a watchful waiting policy, while a high persistence risk may call for immediate and possibly more appropriate management (e.g., lifestyle modification and behavioral change in combination with drug treatment).

Though few studies available to determine the risk factors of postpartum glucose intolerance, presently don't allow predictions of the absolute risk in individual patients in daily practices (11-14). It is anticipated that our setting could use such model to predict postpartum glucose intolerance

risks for women with GDM and refer patients early. This predictive model could help prospectively evaluated to determine the presence of persistent diabetes, caregivers to guide the best treatment choices per individual patient promptly and be more cost-effective by identifying high-risk patients who benefit most from certain interventions. We sought to (1) identify the incidence of postpartum glucose intolerance, and (2) develop a prediction model to enable objective estimations of outcome probabilities (risks) according to different combinations of predictor values for women with GDM in the Ethiopian context by using the updated international diagnostic criteria. We hypothesized that using antenatal clinical characteristics would improve the identification of women with GDM at high risk for postpartum glucose intolerance.

Methods and Materials

This prospective cohort study was part of a larger project, where similar methodology was used in previous published article elsewhere (15).

Study design and population

This study was conducted in five selected public health facilities of Gondar town namely University of Gondar Comprehensive Specialized Hospital and Health Centers (Gondar, Woleka, Azezo, and Maraki) from 30th March, 2018 to 26th March, 2019. Pregnant women were enrolled if they were 18 years or older, had singleton pregnancy and 20-23^{+6} weeks of gestation during commencement time, then followed them until at 6-12 weeks after delivery. Whereas pregnant women who had pre-existing or overt diabetes, chronic diseases, or on medication that might affect their glucose metabolism (steroids, β-adrenergic agonists, anti-psychotic drugs) at commencement were excluded. All pregnant women were screened for overt diabetes in the first antenatal care visit. If the test at the first visit is normal, a two-hour 75 g oral glucose tolerance test (OGTT) is performed for all pregnant women at 24-28 weeks gestation to screened GDM. High risk women were advised to repeat the test at 32-36 weeks even if their OGTT results were normal at 24-28 weeks gestation. As described earlier among 1,027 pregnant women, 131 (12.8%) were diagnosed with GDM (15). All women with GDM invited to participate in this study and evaluated their glucose status at 6-12 weeks of postpartum.

Data collection

All women who had GDM encouraged to return for postpartum glucose tolerance test. The baseline data of each participants was linked to this study data. The data included; demographic profile,

obstetric history, anthropometric measurements, type of treatment of GDM (diet or insulin), behavioral factors (alcohol use and coffee intake), lifestyle parameters (dietary diversity and physical activity), antenatal depression status, blood glucose value (FPG and OGTT). All participants also had FPG and 2hr OGTT blood tests performed at 6–12 weeks after delivery.

Laboratory assessment

The universal screening for GDM using a two-hour 75 g OGTT was performed for all pregnant women by capillary glucose testing, using a standard plasma-calibrated glucometer (HemoCue Glucose B-201+ (A¨ngelholm AB, Sweden)).This corresponded to the latest consensus recommendations of the International Federation of Gynecology and Obstetrics (FIGO) initiative for GDM diagnosis in settings where close-by laboratories or facilities for proper storage and transport of blood samples to distant laboratories are not available (16). After capillary blood samples taken, the whole blood capillary values were converted to plasma venous values by multiplying a constant factor of 1.11 (17). The updated diagnostic criteria for GDM diagnosis was made by using the 2017 American Diabetes Association (ADA) (18) or 2013 WHO (1) or modified International Association of the Diabetes and Pregnancy Study Groups (IADPSG) (19). The diagnosis of GDM is made when one or more of the values of plasma glucose level was met (fasting: ≥ 92 mg/dL, 1 hr.: ≥180 mg/dL; 2 hr.: ≥ 153 mg/dL). Similarly, postpartum glucose tolerance status was evaluated by a standard FPG and 75 g 2-hr OGTT, using a similar test procedure but a higher cut off point for the classification of postpartum glucose intolerance (1, 18).

Outcome measures

The primary outcome was the diagnosis of postpartum pre-diabetes (impaired fasting glucose (IFG): FPG 100-125 mg/dL; impaired glucose tolerance (IGT) 2-hr plasma glucose in the 75-g OGTT 140-199 mg/dL) or diabetes (FPG ≥ 126 mg/dL or 2-hr plasma glucose ≥ 200 mg/dL in the OGTT, or random plasma glucose ≥ 200 mg/dL) (1, 18). Subjects were divided into two groups: the glucose intolerance group, which consisted of IGT and IFG patients, and the normal group.

Data processing and statistical analysis

All data were entered into Epi Info™ 7 software and exported to R statistical programming language version 3.6.0 for analysis. Descriptive statistics (mean, median, standard deviations (SD), inter-quartile range (IQR), percentages, and rates) were computed. Differences in the distributions

of categorical variables were analyzed with a chi-square test. The Shapiro-Wilk test was used to verify if continuous variables were normally distributed. Normally distributed and non-normally distributed variables were evaluated with the t-test and Mann-Whitney test, respectively. Glycemia on diagnostic OGTT was correlated to postpartum OGTT using the Spearman correlation test. We performed a univariable analysis using logistic regression to obtain insight into the association of each potential determinant with postpartum glucose intolerance and to select potential predictors for the multivariable analysis. We fitted all variables with p-value ≤ 0.2 in the univariable analysis to the multivariable model to be more liberal. Then we used a stepwise backward elimination technique with p-value < 0.10 for the likelihood ratio test to fit the reduced model of easily obtainable characteristics. In this study, the significant factors have been defined as variables with p-value < 0.05 in the multivariable logistic regression analysis.

For discriminative power of predictable variables of postpartum glucose intolerance and to check model accuracy, we computed the area under the ROC curve (discrimination) and calibration plot (calibration) using '*classifierplots' and 'givitiR'* packages of R, respectively (20) and estimated as the area under the curve (AUC) with 95% confidence interval. The AUC ranged from 0.5 (no predictive ability) to 1 (perfect discrimination). To construct an easily applicable postpartum glucose intolerance prediction score, we transformed each coefficient from the model to a round number by dividing to the lowest coefficient. The number of points was subsequently rounded to the nearest integer. We determined the total score for everyone by assigning the points to each variable present and adding them up. In addition, sensitivity, specificity, likelihood ratios, and post-test probability of FPG at diagnosis with 95% confidence intervals were calculated by using the optimal cut-offs of levels.

Patient and public involvement

Patients and public were not invited to comment on study design or conduction of the study. However, they will be informed of the study results through publications.

Results

Characteristics of the study group

Of all 131 women with GDM, 112 (85.5%) returned and completed the postpartum OGTT at 6-12 weeks after delivery. The incidence of early postpartum glucose intolerance was 21.4% (95% CI: 14.3 - 28.4) inclusive of 18.7% (95% CI: 11.5 - 25.3) prediabetes and 2.7 % (95% CI: 0.9 - 6.4) diabetes.

The median age of women was 31 (IQR:27-36) years, 20.5% had family history of diabetes mellitus, 33.8% had previous history of GDM, 18.3 % were anemic, 36.6 % overweight and /or obese at the first prenatal visit. A higher proportion of overweight and/ or obesity ($p < 0.001$), maternal age (≥35 years) ($p=0.025$), and antenatal depression ($p=0.033$) were seen among women with postpartum glucose intolerance than those with normal glucose profile (**Table 1).**

There was a positive correlation between FPG during pregnancy and postpartum FPG ($r = 0.424$, $p < 0.001$). There also was also a positive correlation between 2-hr plasma glucose level during pregnancy and 2-hr postpartum plasma glucose level ($r = 0.213$, $p=0.024$).

Table 1. Characteristics of GDM patients according to postpartum glucose test results

Variables	Women with OGTT postpartum (n =112)	GI (n=24)	NGT (n=88)	P value
Maternal age (years)	31 (27-36)	33.5 (30-36.25)	30 (26-34)	0.007
<35	81 (72.3)	13 (54.2)	68 (77.3)	0.025
≥35	31 (27.7)	11 (45.8)	20 (22.7)	
Gravidity	2 (1-3)	3 (2-4)	2 (1-3)	< 0.001
Primigravida	37 (33)	4 (16.7)	33 (37.5)	0.054
Multigravida	75 (67)	20 (83.3)	55 (62.5)	
Previous history GDM*(n=74)				
Yes	25 (33.8)	8 (40)	17 (31.5)	0.49
No	49 (66.2)	12 (60)	37 (68.5)	
Family history of DM				
Yes	23 (20.5)	7 (29.2)	16 (18.2)	0.238
No	89 (79.5)	17 (70.8)	72 (81.8)	
MUAC	26 (24-29)	29 (25.75-30)	25 (24-28)	0.003
MUAC < 28 cm	71 (63.4)	7 (29.2)	64 (72.7)	< 0.001
MUAC ≥ 28 cm	41 (36.6)	17 (70.8)	24 (27.3)	
Blood pressure (mmHg)				
Systolic blood pressure	110 (104-120)	110 (100-120)	110 (104.75-120)	< 0.001
Diastolic blood pressure	70 (69.75- 80)	70 (70-80)	70 (69-80)	< 0.001
Hemoglobin (g/dl) **	12.6 (11-13.6)	13 (12-14)	12.3 (11-13,6)	< 0.001
Normal (Hb ≥ 11 g/dl)	89 (81.7)	22 (91.7)	67 (78.8)	0.2328*
Anemia (Hb < 11 g/dl)	20 (18.3)	2 (8.3)	18 (21.2)	
Blood glucose level at diagnosis (mg/dL)				
FPG– GDM diagnosis OGTT	105 (94- 116)	117 (107.75-120.25)	101.5 (92-114)	0.0004
1-h PG – GDM diagnosis OGTT	170 (150.8 – 178)	170.5 (161.5- 179)	170 (150-178)	0.2635
2-h PG – GDM diagnosis OGTT	144.5 (129 -158)	143.5 (132-153.5)	145.5 (128.75-158)	0.7577
Gestational age of diagnosis (weeks)	26 (25-27)	26 (24-27)	26 (25-27)	
24-28 weeks	99 (88.4)	20 (83.3)	79 (89.8)	
≥ 32 weeks	13 (11.6)	4 (16.7)	9 (10.2)	
Level of physical activity				
High	18 (16.1)	5 (20.8)	13 (14.8)	0.590
Moderate	28 (25)	7 (29.2)	21 (23.9)	
Low	66 (58.9)	12 (50)	54 (61.4)	
Dietary diversity status				
Adequate	24 (21.4)	2 (8.3)	22 (25)	0.05973*
Inadequate	88 (78.6)	22 (91.7)	66 (75)	
Antenatal depression				
Yes	28 (25)	10 (41.7)	18 (20.5)	0.033
No	84 (75)	14 (58.3)	70 (79.5)	
Insulin treated GDM				
Yes	7 (6.3)	2 (8.3)	5 (5.7)	0.641*
No	105 (93.8)	22 (91.7)	83 (94.3)	

Data were presented by n (%) or median (IQR). *P value of Fisher exact test; * (n=74) **= 3 participants had no Hgb value (n=109) IQR=Interquartile range GI=Glucose intolerance NGT=Normal glucose tolerance GDM=gestational diabetes mellitus h=hour Hb=hemoglobin g/dl= gram per deciliter mg/dl=milligram deciliter mmHg=millimeter of mercury OGTT=oral glucose tolerance test MUAC=Mid upper arm circumference

A prediction model for postpartum glucose intolerance

Different demographic, obstetric, and clinical characteristics of mothers were collected during prenatal visits and considered to predict postpartum glucose intolerance. On univariable analysis (maternal age, gravidity, maternal obesity and\or overweight, FPG at GDM diagnosis, and antenatal depression) variables were found to have a significant association. However, in the final multivariable regression analysis and the reduced model four predictors of progression, such as age of mother (≥35 years) during pregnancy [AOR=4.04 (95%: 1.23, 14.33)], maternal obesity and\or overweight [AOR=3.92 (95%: 1.13, 15.04)], FPG at GDM diagnosis [AOR=1.08 (95%: 1.04, 1.15)], and antenatal depression [AOR=5.90 (95%: 1.66, 23.47)] remained significant. Using the results, a prediction model was developed and the equation for the prediction model was obtained **(Table 2).**

The area under the ROC curve (AUC) of the final reduced model was 0.884 (95% CI: 0.822 - 0.937). The calibration test had a p-value of 0.759, indicating the model does not misrepresent the data (**Figure 1A).** Rounding of all regression coefficients in the reduced model to 1 point resulted in a simplified prediction score presented in table 2. The AUC of the simplified risk score prediction model was 0.808 (95% CI: 0.705 - 0.90). The calibration test had a p-value of 0.044, indicating the model less represent the data (**Figure 1B).** Since the simplified score had a lower prediction accuracy than the model that used results of original β coefficients, we prefer to use the original β coefficients.

Table 2. Multiple logistic regressions for predicting post-partum glucose intolerance among women with GDM.

Predictor variables	Univariable analysis	Multivariable analysis		Simplified risk score
	COR (95% CI)	AOR (95% CI)	P value	
Maternal age (≥35 years)	2.88 (1.11, 1.7.46)	4.04 (1.23, 14.33)	0.02380	**4**
Gravidity (multigravida) *	3.00 (1.027, 10.989)	1.75 (0.39, 8.66)	0.47196	-
Previous history GDM	1.45 (0.45, 4.19)	NA		
Family history of DM	1.85 (0.63, 5.11)	NA		
MUAC (≥ 28 cm)	6.48 (2.474, 18.61)	3.92 (1.13,15.04)	0.03617	**4**
Blood pressure (mmHg)				
Systolic blood pressure	0.998 (0.976, 1.054)	NA		
Diastolic blood pressure	1.015 (0.976, 1.053)	NA		
Anemia (Hb < 11 g/dl)	0.34 (0.05, 1.30)	NA		
Blood glucose level (mg/dL)				
FPG at GDM diagnosis	1.07 (1.03, 1.13)	1.08 (1.04, 1.15)	0.00171	**1**
1-hr PG at GDM diagnosis	1.014 (0.99, 1.03)	NA		
2-hr PG at GDM diagnosis	0.99(0.97, 1.02)	NA		
Gestational age of diagnosis (weeks)	1.03 (0.89, 1.18)	NA		
Level of physical activity				
High	1			
Moderate	0.87 (0.23, 3.47)	NA		
Low	0.57 (0.18, 2.07)			
Inadequate dietary diversity*	3.66 (0.97, 24.03)	3.07(0.58, 24,45)	0.22031	-
Antenatal depression	2.78 (1.05, 7.29)	5.90 (1.66, 23.47)	0.00770	**5**
Insulin treated GDM	1.51 (0.21, 7.54)	NA		

GDM =gestational diabetes mellitus hr=hour Hb=hemoglobin g/dl= gram per deciliter mg/dl=milligram deciliter FPG= Fasting plasma glucose mmHg=millimeter of mercury OGTT=oral glucose tolerance test MUAC=Mid upper arm circumference COR = Crude Odds Ratio AOR = Adjusted Odds Ratio CI = Confidence Interval.

NA - not included to the multivariate analysis *Variables were also retained in the reduced model using likelihood ratio test are; gravidity and dietary diversity status. Both backward and forward selection showed same results. ORs after internal validation with bootstrapping are shown.

In addition, to verify whether any antepartum trait was used as a specific predictor of postpartum glucose intolerance we performed ROC analysis. The analysis indicated that FPG at GDM diagnosis [AUC= 0.736 (95% CI: 0.616 - 0.845), P < 0.001)], overweight and/or obesity [AUC = 0.718 (95% CI: 0.614 - 0.814), P=0.0284)], maternal age (≥ 35 years) [AUC = 0.616 (95% CI: 0.506 - 0.722), P < 0.001)], and antenatal depression [AUC = 0.606 (95% CI: 0.506 - 0.718), P=0.0375] emerged as better predictors of postpartum glucose intolerance **(Figure 2).** Moreover, the AUC for the combined predictors of FPG at diagnosis and mid-upper arm circumference (MUAC) was 0.822 (95% CI:0.722 - 0.907); FPG at diagnosis and antenatal depression was 0.793 (95% CI:0.698 - 0.876), and MUAC and antenatal depression was 0.759 (95% CI: 0.646 - 0.856)] (**Figure 3**). The evaluation of the sensitivity across different FPG level thresholds showed that FPG ≥ 105 mg/dl during pregnancy had the optimal sensitivity of 79% (95% CI: 58% - 93 %) with a specificity of 56% (95% CI: 45% - 66%) to predict postpartum glucose intolerance **(Table 3).**

Table 3: Sensitivity and specificity of the FPG test for postpartum glucose intolerance

Threshold FPG (mg/dl)	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR– (95% CI)	Positive Post-test Probability % (95% CI)	Negative Post-test Probability % (95% CI)
≥ 116	54 (33, 74)	78 (68,86)	2.51 (1.46, 4.31)	0.58 (0.37, 0.92)	41 (24,59)	86 (77,93)
≥ 105	79 (58, 93)	56 (45, 66)	1.79 (1.31, 2.44)	0.37 (0.17, 0.83)	33 (21, 46)	91 (80, 97)
≥ 94	88 (68, 97)	27 (18, 38)	1.20 (0.99, 1.47)	0.46 (0.15, 1.39)	25 (16, 35)	89 (71, 98)

FPG= Fasting plasma glucose mg/dl=milligram deciliter LR+= positive likelihood ratio LR–=negative likelihood ratio

Discussion

This prospective study aimed to identify glucose status at an early postpartum stage after diagnosis of GDM and the predictors of postpartum glucose intolerance. Based on recent guideline, 21.4% women with GDM had postpartum glucose intolerance at 6–12 weeks after delivery. The major predictors of developing glucose intolerance were advanced maternal age, overweight and/or obesity, high FPG at GDM diagnosis, and antenatal depression. Women recently diagnosed with GDM were at higher risk of developing postpartum hyperglycemia. Accordingly, this study suggested close follow-up for women who had GDM and identification of the postpartum glucose intolerance predictors as a crucial way to early manage the future risks of type 2 diabetes in life or to delay its onset.

Our study showed that more than one-fifth of women with GDM developed early postpartum glucose intolerance. This rate was consistent with the studies from Australia (21), Belgium (22), Japan (12), and Brazil (11). However, it was lower than two existing evidence in Saudi Arabia, where the prevalence of glucose intolerance was 38.6% (14) and 56% (23) and Belgium (43.7%) (13). This difference might be due to the use of different screening and diagnostic methods. We used the universal, one-step approach with a 75g OGTT and the updated diagnostic criteria. Whereas, the other studies used the universal two-step screening strategy for GDM (13). The two-step screening strategy with a glucose challenge test, therefore, it has the potential to limit number of OGTTs to screen for GDM and identified a high-risk group for postpartum glucose intolerance. The strong association between GDM and postpartum glucose intolerance indicates the course of the disease developed at early stage (24, 25). Pregnancy by itself caused an insulin resistance and hyperglycemia can occur as a result of its metabolic change (26, 27). In addition, the early onset of GDM indicated the presence pregestational insulin resistance and/or pancreatic ß-cell dysfunction which lead to the higher risk for postpartum glucose abnormality (21). This finding highlights the importance of improving the uptake of checking blood glucose and lifestyle modifications before the onset of type 2 diabetes. Regardless of which screening approach used, research on the efficacy or effectiveness of lifestyle interventions for preventing or delaying the progression to postpartum glucose intolerance after GDM in our setting would provide much-needed data.

This study has shown antenatal characteristics modestly predicted the development of postpartum glucose intolerance. FPG at GDM diagnosis, MUAC, and antenatal depression or the combined

were good predictors of postpartum glucose intolerance. The model for combined antenatal predictors results in AUC of 0.88, which is best predictive ability. This prognostic prediction model provides a powerful tool for identification of GDM patients at higher occurrence on the progression of postpartum glucose intolerance.

Similar to the findings of previous studies in Italy (28), United Kingdom (29), and Sweden (30), the current study has shown that FPG level in antepartum OGTT was the strongest predictor of early postpartum glucose intolerance. Evidences also revealed that elevated fasting glucose level during pregnancy has been a consistent predictor of development of type 2 diabetes in women with GDM (12, 28, 31). This suggested that β-cell dysfunction in the presence of insulin resistance is a common feature of GDM. Later, the same β-cell failure might complicate the tendency to persistent diabetes (26). Thus, the diagnosis of GDM represents a window of opportunity for implementing interventions for women with high blood glucose level during antenatal visits to prevent subsequent diabetes mellitus. Moreover, this estimate could use for clinical utility to target these women for early screening and prevention subsequent diabetes.

We found that advanced maternal age during pregnancy as a predictor of abnormal glucose tolerance risk at 6–12 weeks of postpartum. Similar evidence was found in Italy (28), South Africa (32), which described advanced maternal age was predictor of postpartum glucose intolerance. On the contrary, a study conducted in Belgium showed maternal age was not a predictor for early postpartum glucose intolerance (22). The presence of higher risk of insulin resistance and inadequate pancreatic β-cell response occurred due to advanced maternal age, which lead to succeeding diabetes progression (33). This finding suggested that due attention should be given to GDM women with advanced maternal age. Positive lifestyle change during pregnancy could reduce the risk of GDM to type 2 diabetes progression (34). As a low-cost intervention to prevent subsequent diabetes for women with advanced age, integrating behavioral counseling on nutrition and exercise into ANC services is recommended.

In our study, overweight and/or obesity was a strong predictor for early postpartum glucose intolerance occurrence. Similar studies have demonstrated that pre-pregnancy BMI was predictive of subsequent diabetes (14, 35-37). Due to the current and ongoing high burden of overweight or obesity among the African women, increased prevalence of diabetes is expected. Therefore, it is

imperative to identify populations at elevated risk and introduce risk-lowering interventions such as reducing obesity and avoiding sedentary life (38, 39).

Another strong predictor for postpartum glucose intolerance was the presence of antenatal depression. Though study is limited in predictive effect of antenatal depression on postpartum glucose intolerance, the existing evidence shows there is association between antenatal depression and GDM (15, 40, 41). Previous studies also revealed depression increased the risk of type 2 diabetes (42, 43).The existence of comorbid problem of antenatal depression can lead women to poor lifestyle decisions, such as unhealthy eating, poor exercise, weight gain, and poor glycemic control which primes the progression to postpartum diabetes (44). Unfortunately, the guidelines for the treatment and management of GDM don't provide adequate evidence regarding the care of patients with comorbid situations of antenatal depression in low resource setting.

The strength of this study was being a prospective cohort study involving GDM patients identified using the updated diagnostic criteria with uniform protocols for all women and followed them until 6-12 weeks of delivery. In addition, our prediction model is constructed from easily obtainable antenatal characteristics that make it applicable in low resource settings. Though WHO recommend that in settings where laboratories or proper storage and transport of blood samples is not guaranteed, the use of point of care tests may influence the result (16). However, we used plasma-calibrated hand-held glucometers because of convenience and acceptable reliability. Moreover, the study used a relatively small sample size could be the limitations of the study.

Conclusions

Based on the updated diagnostic criteria, the high incidence rate of early postpartum glucose intolerance has been identified among women who had GDM. Antenatal characteristics (advanced maternal age, high FPG at GDM diagnosis, overweight and/or obesity, antenatal depression) were strong predictors of postpartum glucose intolerance. This prognostic risk prediction models revealed the utility of antenatal predictors were modestly predicted post-partum glucose intolerance in women with GDM. In addition, a risk score calculation based on a combination of antenatal predictors was effective but had lower accuracy than the model-based approach by original β coefficients. Thus, our findings highlighted the need for increased awareness among women and their primary care providers regarding the importance of long-term glucose screening after pregnancies complicated by GDM.

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Authors' contributions

AAM: conceived and designed the study, analyzed the data and prepared the manuscript. OO & YKG: assisted the development of the research idea, the analysis, interpretation and preparation of the manuscript. All authors read and approved the final manuscript

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Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval and consent to participate

The study was conducted after ethical approval was obtained from the Institute for Advanced Medical Research and Training (IAMRAT), College of Medicine, University of Ibadan, Ibadan, Nigeria with the I/UCH EC Registration Number of NHREC/05/01/2008a and UI/UCH Ethics Committee assigned the number UI/EC/17/0435 and the Institutional Review Board (IRB) of the University of Gondar (Ref.No; O/V/P/RCS/05/811/2018). Permission from the Amhara Public Health Institute and the health authorities of the study sites was also received prior to the start of

the study. All participants signed (written or thumb-printed) informed consent form, after, they received a face to face explanation about the objectives of the study. The collected information during the course of the research was treated with the utmost confidentiality.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the correspondence author on reasonable request.

References

1. World Health Organization (WHO). Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. Available from: http://apps.who.int/iris/bitstream/10665/8597/1/WHO_NMH_MND_13.2_eng.pdf. 2013.
2. McIntyre HD, Thomae M, Wong S, Idris N, Callaway LK. Pregnancy in type 2 diabetes mellitus-problems & promises. Current diabetes reviews. 2009;5(3):190-200.
3. Holman N, Young B, Gadsby R. Current prevalence of Type 1 and Type 2 diabetes in adults and children in the UK. Diabetic Medicine. 2015;32(9):1119-20.
4. World Health Organization (WHO). Global report on diabetes: World Health Organization; 2016.
5. Bellamy L, Casas J-P, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. The Lancet. 2009;373(9677):1773-9.
6. Buchanan TA, Metzger BE, Freinkel N, Bergman RN. Insulin sensitivity and B-cell responsiveness to glucose during late pregnancy in lean and moderately obese women with normal glucose tolerance or mild gestational diabetes. American journal of obstetrics and gynecology. 1990;162(4):1008-14.
7. Gerstein HC, Santaguida P, Raina P, Morrison KM, Balion C, Hunt D, et al. Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: a systematic overview and meta-analysis of prospective studies. Diabetes research and clinical practice. 2007;78(3):305-12.
8. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes. Diabetes care. 2002;25(10):1862-8.
9. Metzger BE, Buchanan TA, Coustan DR, De Leiva A, Dunger DB, Hadden DR, et al. Summary and recommendations of the fifth international workshop-conference on gestational diabetes mellitus. Diabetes care. 2007;30(Supplement 2):S251-S60.
10. American Diabetes Association (ADA). Standards of medical care in diabetes—2013. Diabetes care. 2013;36(Supplement 1):S11-S66.
11. Weinert LS, Mastella LS, Oppermann ML, Silveiro SP, Guimaraes LS, Reichelt AJ. Postpartum glucose tolerance status 6 to 12 weeks after gestational diabetes mellitus: a Brazilian cohort. Arquivos brasileiros de endocrinologia e metabologia. 2014;58(2):197-204.
12. Kojima N, Tanimura K, Deguchi M, Morizane M, Hirota Y, Ogawa W, et al. Risk factors for postpartum glucose intolerance in women with gestational diabetes mellitus. Gynecological Endocrinology. 2016;32(10):803-6.
13. Benhalima K, Jegers K, Devlieger R, Verhaeghe J, Mathieu C. Glucose Intolerance after a Recent History of Gestational Diabetes Based on the 2013 WHO Criteria. PloS one. 2016;11(6):e0157272.
14. Wahabi H, Fayed A, Tunkar SM, Bakhsh H, Al-Hazmi AM, Esmaeil S, et al. Incidence and contributing factors of glucose intolerance in Saudi postpartum women: Sub-group analysis from RAHMA study. PloS one. 2019;14(1):e0210024.
15. Muche AA, Olayemi OO, Gete YK. Prevalence of gestational diabetes mellitus and associated factors among women attending antenatal care at Gondar town public health facilities, Northwest Ethiopia. BMC pregnancy and childbirth. 2019;19(1):334.

16. Hod M, Kapur A, Sacks DA, Hadar E, Agarwal M, Di Renzo GC, et al. The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: A pragmatic guide for diagnosis, management, and care#. International Journal of Gynecology & Obstetrics. 2015;131:S173-S211.
17. D'Orazio P, Burnett RW, Fogh-Andersen N, Jacobs E, Kuwa K, Külpmann WR, et al. Approved IFCC recommendation on reporting results for blood glucose (abbreviated). Clinical chemistry. 2005;51(9):1573-6.
18. American Diabetes Association (ADA). Classification and diagnosis of diabetes. Sec. 2. In Standards ofMedical Care in Diabetesd 2017. Diabetes Care 2017;40(Suppl. 1):S11–S24.
19. International Association of Diabetes and Pregnancy Study Groups (IADPSG). International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes care. 2010;33(3):676-82.
20. Finazzi S, Poole D, Luciani D, Cogo PE, Bertolini G. Calibration Belt for Quality-of-Care Assessment Based on Dichotomous Outcomes. PLOS ONE. 2011;6(2):e16110.
21. Ingram ER, Robertson IK, Ogden KJ, Dennis AE, Campbell JE, Corbould AM. Utility of antenatal clinical factors for prediction of postpartum outcomes in women with gestational diabetes mellitus (GDM). The Australian & New Zealand journal of obstetrics & gynaecology. 2017;57(3):272-9.
22. Benhalima K, Van Crombrugge P, Moyson C, Verhaeghe J, Vandeginste S, Verlaenen H, et al. Prediction of glucose intolerance in early postpartum in women with gestational diabetes mellitus based on the 2013 WHO Criteria. Journal of clinical medicine. 2019;8(3):383.
23. Wahabi H. Prevalence and Risk Factors for Glucose Intolerance among Saudi Women with Gestational Diabetes. Journal of diabetes research. 2018;2018.
24. Ben-Haroush A, Yogev Y, Hod M. Epidemiology of gestational diabetes mellitus and its association with Type 2 diabetes. Diabetic Medicine. 2004;21(2):103-13.
25. Cho YM, Kim T, Lim S, Choi SH, Shin H, Lee H, et al. Type 2 diabetes-associated genetic variants discovered in the recent genome-wide association studies are related to gestational diabetes mellitus in the Korean population. Diabetologia. 2009;52(2):253-61.
26. Buchanan TA. Pancreatic B-cell defects in gestational diabetes: implications for the pathogenesis and prevention of type 2 diabetes. The Journal of Clinical Endocrinology & Metabolism. 2001;86(3):989-93.
27. Ta B. Xiang AH. Gestational diabetes mellitus. J Clin Invest. 2005;115:485-91.
28. Capula C, Chiefari E, Vero A, Foti DP, Brunetti A, Vero R. Prevalence and predictors of postpartum glucose intolerance in Italian women with gestational diabetes mellitus. Diabetes research and clinical practice. 2014;105(2):223-30.
29. Sivaraman SC, Vinnamala S, Jenkins D. Gestational diabetes and future risk of diabetes. J Clin Med Res. 2013;5(2):92-6.
30. Ekelund M, Shaat N, Almgren P, Groop L, Berntorp K. Prediction of postpartum diabetes in women with gestational diabetes mellitus. Diabetologia. 2010;53(3):452-7.
31. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes care. 2002;25(10):1862-8.
32. Feig DS, Zinman B, Wang X, Hux JE. Risk of development of diabetes mellitus after diagnosis of gestational diabetes. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2008;179(3):229-34.
33. Jolly M, Sebire N, Harris J, Robinson S, Regan L. The risks associated with pregnancy in women aged 35 years or older. Human reproduction. 2000;15(11):2433-7.
34. Chivese T, Norris SA, Levitt NS. Progression to type 2 diabetes mellitus and associated risk factors after hyperglycemia first detected in pregnancy: A cross-sectional study in Cape Town, South Africa. PLoS medicine. 2019;16(9):e1002865-e.

35. Cheung NW, Helmink D. Gestational diabetes: the significance of persistent fasting hyperglycemia for the subsequent development of diabetes mellitus. Journal of diabetes and its complications. 2006;20(1):21-5.
36. Lobner K, Knopff A, Baumgarten A, Mollenhauer U, Marienfeld S, Garrido-Franco M, et al. Predictors of postpartum diabetes in women with gestational diabetes mellitus. Diabetes. 2006;55(3):792-7.
37. ÅBerg AE, Jönsson EK, Eskilsson I, Landin-Olsson M, Frid AH. Predictive factors of developing diabetes mellitus in women with gestational diabetes. Acta obstetricia et gynecologica Scandinavica. 2002;81(1):11-6.
38. NCD Risk Factor Collaboration-Africa Working Group. Trends in obesity and diabetes across Africa from 1980 to 2014: an analysis of pooled population-based studies. International journal of epidemiology. 2017;46(5):1421-32.
39. Puoane T, Steyn K, Bradshaw D, Laubscher R, Fourie J, Lambert V, et al. Obesity in South Africa: the South African demographic and health survey. Obesity research. 2002;10(10):1038-48.
40. Morrison C, McCook JG, Bailey BA. First trimester depression scores predict development of gestational diabetes mellitus in pregnant rural Appalachian women. Journal of Psychosomatic Obstetrics & Gynecology. 2016;37(1):21-5.
41. Byrn M, Penckofer S. The relationship between gestational diabetes and antenatal depression. Journal of obstetric, gynecologic, and neonatal nursing : JOGNN. 2015;44(2):246-55.
42. Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia. 2006;49(5):837-45.
43. Rotella F, Mannucci E. Depression as a risk factor for diabetes: a meta-analysis of longitudinal studies. J Clin Psychiatry. 2013;74(1):31-7.
44. Gonzalez JS, Peyrot M, McCarl LA, Collins EM, Serpa L, Mimiaga MJ, et al. Depression and diabetes treatment nonadherence: a meta-analysis. Diabetes care. 2008;31(12):2398-403.

List of figures

Figure 1. ROC curve for prediction of postpartum glucose intolerance using different models

Figure 2. ROC curves of antepartum parameters for the prediction of postpartum glucose intolerance

Figure 3. ROC curve for the combined predictors of FPG at diagnosis, MUAC and antenatal depression on glucose intolerance

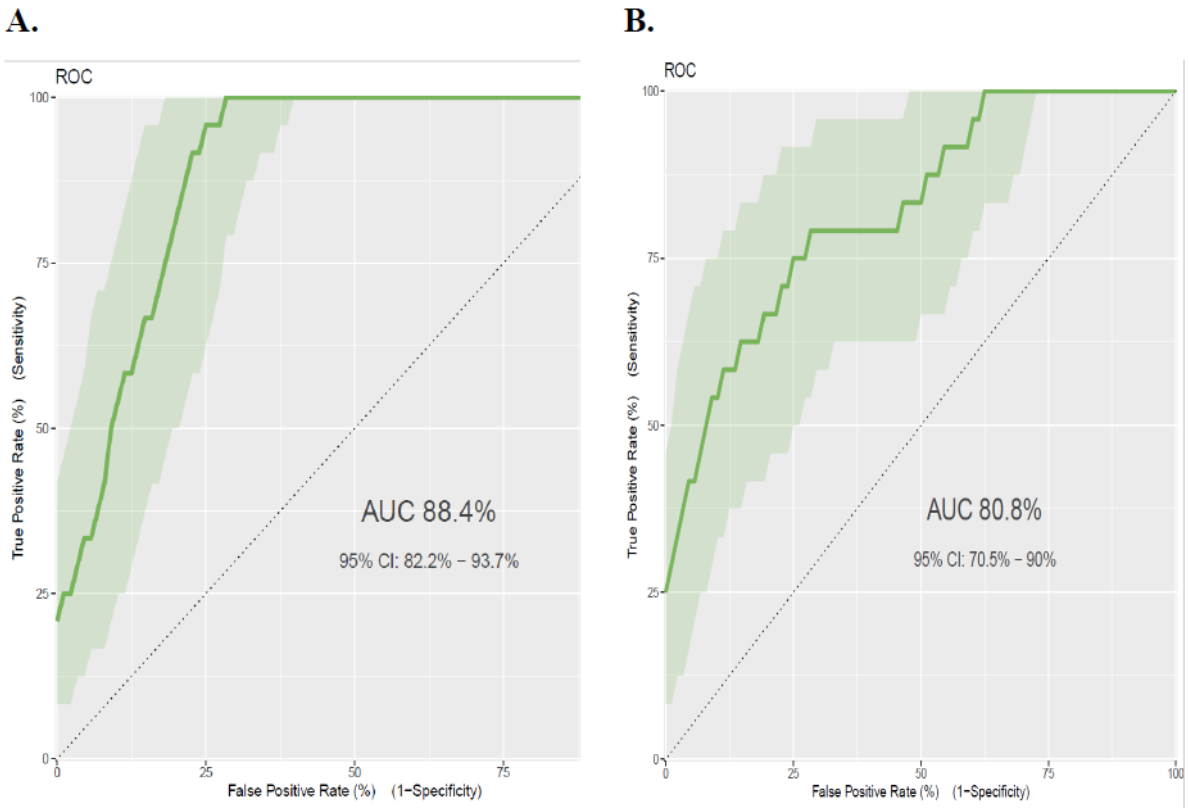

Figure 1. ROC curve for prediction of postpartum glucose intolerance using different models:
A. Linear predictor model for estimated risk of postpartum glucose intolerance = 1/(1+exp-(-11.8 7007) +1.48 * age (≥35 years)+1.716*overweight and/or obesity (MUAC ≥ 28CM) + 0.081* FPG at diagnosis + 1.637* antenatal depression (yes)
B. Simplified risk score predictor model for estimated risk of postpartum glucose intolerance = (age ≥35 years***4**) + (overweight and/or obesity (MUAC ≥ 28CM)* **4**) + (FPG at diagnosis***1**) + (antenatal depression***5**)

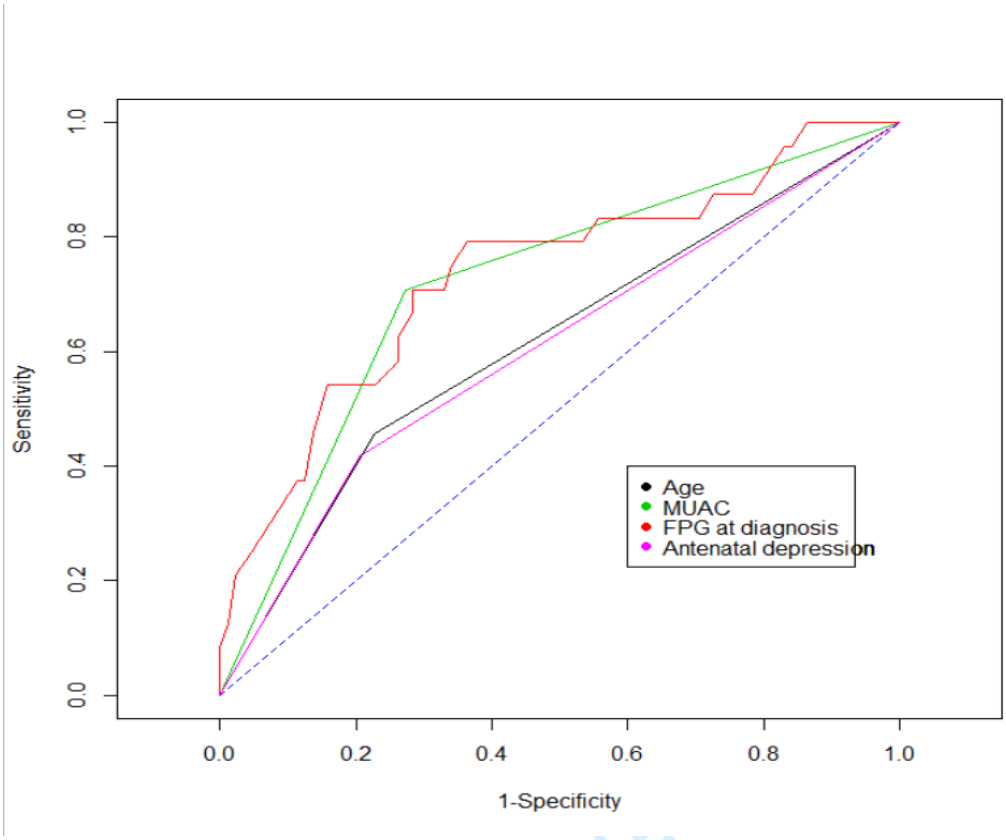

Figure 2. ROC curves of antepartum parameters for the prediction of postpartum glucose intolera nce

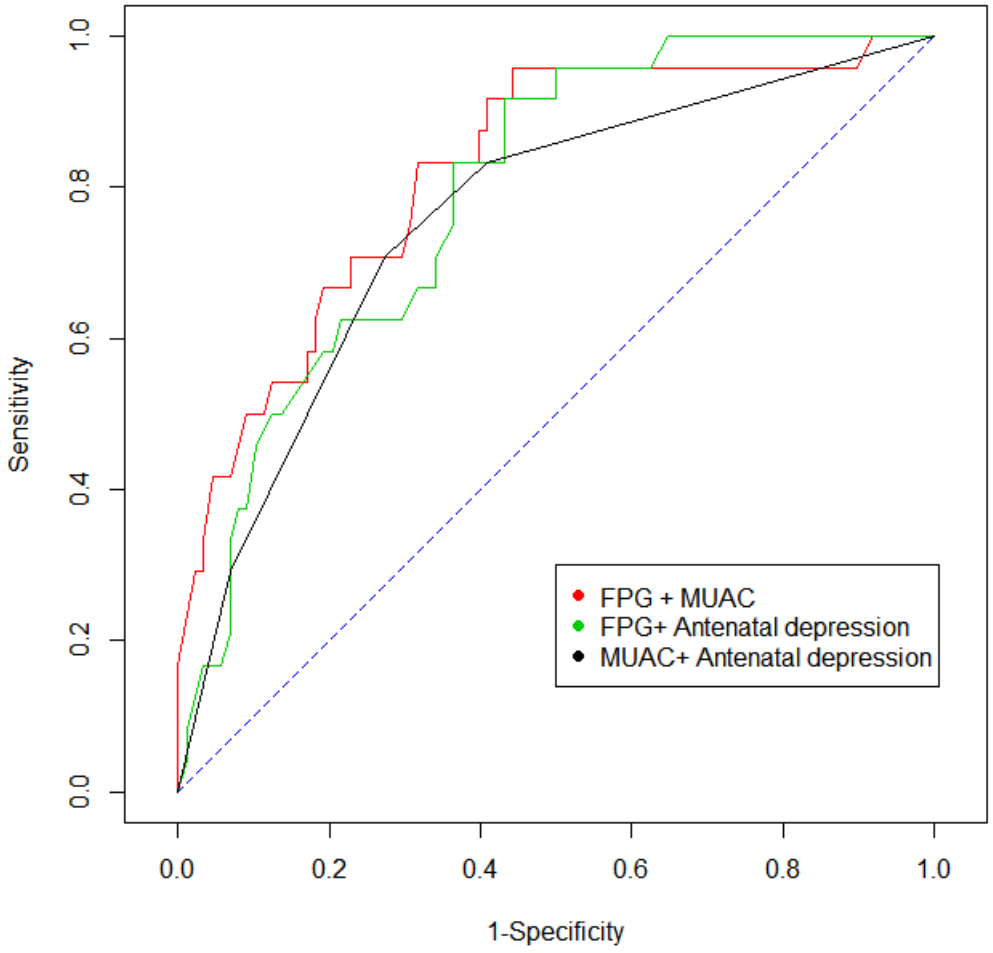

Figure 3. ROC curve for the combined predictors of FPG at diagnosis, MUAC and antenatal depression on glucose intolerance.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4,5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	--
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	4, 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5, 6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	4, 7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9, 10
		(*b*) Report category boundaries when continuous variables were categorized	10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10, 11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.