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# BMJ Open

## 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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3 1 **Predictors of postpartum glucose intolerance in women with gestational diabetes mellitus: A**  
4 **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

### 1 **Strengths and limitation of the study**

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

### 9 **Introduction**

10 Gestational diabetes mellitus (GDM) is defined as “hyperglycemia first detected during pregnancy

11 that is clearly not preexisting or overt diabetes” (1). Although GDM normally disappears after a

12 birth, women previously diagnosed with the disease are at high risk of developing long-term

13 metabolic disorders such as type 2 diabetes (2-5).

14 Postprandial hyperglycemia is common among women with GDM, more than half develop type 2

15 diabetes 5 years after delivery (6, 7). Literature showed that the occurrence of diabetes ranged

16 from 2.6% to over 70% corresponds to 6 weeks to 28 years of postpartum. The prospect of incident

17 was also high at subsequent pregnancies with GDM (8).

18 Even though international guidelines recommend early screening to explore post-partum pre-

19 diabetes or diabetes in women with gestational diabetes at 6–12 weeks of delivery (9, 10), evidence

20 based on the updated GDM diagnostic criteria are limited. In resource-limited settings, pregnancy

21 often marks the first formal exposure to healthcare. The identification of potential future

22 progression predictors of pre-diabetes and/or diabetes in women with GDM could improve

23 accurate risk stratification of patients during pregnancy. This provides an opportunity for

24 appropriate, cost-effective, and priority intervention programs of high-risk group. If the persistence

25 risk can be estimated accurately, treatment may be tailored to individual patient needs. Low

26 persistence risk warrants adoption of a watchful waiting policy, while a high persistence risk may

27 call for immediate and possibly more aggressive treatment (e.g., life style modification and

28 behavioral change in combination with drug treatment).

29 The few available studies on risk factors for persistent diabetes mellitus, present don't allow

30 predictions of the absolute risk in individual patients in daily practices (11-13). Setting a prognosis

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2  
3 1 in individual cases with GDM, however, is notoriously difficult and a lack of empirical evidence  
4  
5 2 has already occurred earlier. We sought to (1) identify the prevalence of post-partum glucose  
6  
7 3 intolerance; and (2) develop a prediction model to enable objective estimations of outcome  
8  
9 4 probabilities (risks) according to different combinations of predictor values for women with GDM  
10  
11 5 in the Ethiopian context by using the updated international diagnostic criteria. We hypothesized  
12  
13 6 that using antenatal clinical characteristics would improve identification of women with GDM at  
14  
15 7 high risk for post-partum glucose intolerance.

## 16 8 **Materials and methods**

### 17 9 **Study design and population**

18  
19 10 A prospective cohort study was conducted among pregnant women recruited at the antenatal care  
20  
21 11 (ANC) clinics of selected health facilities of Gondar town and followed till 6-12 weeks after  
22  
23 12 delivery. Women were enrolled if they were aged 18 years or more with 20 - 23<sup>+6</sup> weeks of  
24  
25 13 gestational age and singleton pregnancy. Pregnant women who had pre-existing diabetes mellitus  
26  
27 14 or overt DM, chronic diseases, medications that may affect glucose metabolism were excluded.  
28  
29 15 Universal screening for GDM using a two-hour 75 g OGTT was performed for all pregnant women  
30  
31 16 at 24-28 weeks of gestational age from March 30, 2018 to January 4, 2019. Additionally, women  
32  
33 17 with risk factors for GDM repeated the test at 32-36 weeks if OGTT results were negative at  
34  
35 18 regular tests and the GDM diagnosis confirmed by the second test. The detailed methods of the  
36  
37 19 study were explained earlier (14). This follow up study was conducted on 131 women diagnosed  
38  
39 20 with GDM out of 1027 participants who were completed the OGTT. All women with GDM invited  
40  
41 21 to participate in this study and had their glucose status evaluated at 6–12 weeks after delivery. The  
42  
43 22 post-partum glucose test evaluation was carried out from February to June 2019.

### 44 23 **Data collection**

45 24 All consenting women evaluated for post-partum glucose at the selected public health facilities  
46  
47 25 after fasting for at least eight hours before their appointment. In addition, the women were  
48  
49 26 encouraged to return for follow-up for post-partum glucose tolerance test by direct phone contact.  
50  
51 27 All baseline data (14) collected earlier for each participant were linked to this study data. The data  
52  
53 28 included; demographic profile, obstetric history such as gravidity, anthropometric measurements,  
54  
55 29 type of treatment of GDM in the index pregnancy (diet or insulin), behavioral factors (exposure to  
56  
57 30 alcohol use and coffee intake), lifestyle parameters (dietary diversity and physical activity),

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

#### 4 **Laboratory assessment**

5 As the detailed laboratory assessment was described earlier (14), the universal screening for GDM  
6 using a two-hour 75 g OGTT was performed for all pregnant women by capillary glucose testing,  
7 using a standard plasma-calibrated glucometer (HemoCue Glucose B-201+ (A`ngelholm AB,  
8 Sweden)). This corresponded to the latest consensus recommendations of the International  
9 Federation of Gynecology and Obstetrics (FIGO) initiative for GDM diagnosis in settings where  
10 close-by laboratories or facilities for proper storage and transport of blood samples to distant  
11 laboratories are not available (15). The updated diagnostic criteria (WHO and ADA) uses to  
12 diagnosis GDM based on one or more of the values of plasma glucose level were met (fasting:  $\geq$   
13 92 mg/dL, 1 h:  $\geq$ 180 mg/dL; 2 h:  $\geq$  153 mg/dL) (16, 17). Similarly, post-partum glucose tolerance  
14 status was evaluated by means of a standard FPG and 75 g 2-hour oral glucose tolerance test at 6–  
15 12 weeks after delivery, using a similar test procedure but a higher cut off point for the  
16 classification of post-partum glucose intolerance (16, 17).

#### 17 **Outcome measures**

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

#### 24 **Data processing and statistical analysis**

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



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3 1 Glycemias on diagnostic OGTT were correlated to postpartum OGTT using the Spearman  
4 2 correlation test. We performed a univariate analysis using logistic regression to obtain insight into  
5 3 the association of each potential determinant with post-partum glucose intolerance and to select  
6 4 potential predictors for the multivariate analysis. We fitted all variables with p-value  $\leq 0.2$  in the  
7 5 univariate analysis to the multivariate model to be more liberal. Then we used a stepwise backward  
8 6 elimination technique with p-value  $< 0.10$  for the likelihood ratio test to fit the reduced model of  
9 7 easily obtainable characteristics. In this study, the most significant factors have been defined as  
10 8 variables with p < values 0.05 in the multivariate logistic regression analysis.  
11 9 For the discriminative power of predictable variables for postpartum glucose intolerance and to  
12 10 check model accuracy, we computed the area under the ROC curve (discrimination) and  
13 11 calibration plot (calibration) using '*classifierplots*' and '*givitiR*' packages of R, respectively (18)  
14 12 and estimated as the area under the curve (AUC) with 95% confidence interval. The AUC ranged  
15 13 from 0.5 (discrimination no better than chance) to 1 (perfect discrimination). To construct an easily  
16 14 applicable postpartum glucose intolerance prediction score, we transformed each coefficient from  
17 15 the model to a round number by dividing to the lowest coefficient. The number of points was  
18 16 subsequently rounded to the nearest integer. We determined the total score for everyone by  
19 17 assigning the points to each variable present and adding them up. In addition, sensitivity,  
20 18 specificity, likelihood ratios and post-test probability of FPG at diagnosis with 95% confidence  
21 19 intervals were calculated by using the optimal cut-offs of levels.

## 20 **Patient and public involvement**

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

### 2 **Characteristics of the study group**

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

8 The median age of the cohort was 31 (27-36) years, 20.5% had family history of diabetes mellitus,  
9 33.8% had a previous history of GDM, 18.3 % were anemic, 36.6 % overweight and /or obese at  
10 the first prenatal visit. A higher proportion of overweight and/ or obesity ( $p < 0.001$ ), maternal age  
11 ( $\geq 35$  years) ( $p=0.025$ ), and antenatal depression ( $p=0.033$ ) were seen among women with  
12 postpartum glucose intolerance than those with normal glucose profile (**Table 1**).

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

1 **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)	

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

## 1 A prediction model for postpartum glucose intolerance

2 After review of literature, 13 demographic, obstetric, and clinical characteristics of mothers  
3 collected during the prenatal visits or baseline survey were considered to predict postpartum  
4 glucose intolerance. On the univariate analysis (maternal age, gravidity, maternal obesity and/or  
5 overweight, FPG at GDM diagnosis, and antenatal depression) variables were found to have  
6 significant association. However, in the final multivariable regression analysis and the reduced  
7 model four predictors of progression, such as age of mother ( $\geq 35$  years) during pregnancy  
8 (AOR=4.04; 95%:1.23, 14.33), maternal obesity and/or overweight (AOR=3.92; 95%: 1.13,  
9 15.04), FPG at GDM diagnosis (AOR=1.08; 95%: 1.04, 1.15), and antenatal depression  
10 (AOR=5.90 ; 95%: 1.66, 23.47) remained significant. Using the results, a prediction model was  
11 developed and the equation for the prediction model was obtained (**Table 2**).

12 The area under the ROC curve (AUC) of the final reduced model was 0.884 (95% CI: 0.821 to  
13 0.939). The calibration test had a p-value of 0.759, indicating the model does not misrepresent the  
14 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 ( $\geq 35$ years)	2.88 (1.11, 1.7.46)	4.04 (1.23, 14.33)	0.02380	<b>4</b>
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 ( $\geq 28$ cm)	6.48 (2.474, 18.61)	3.92 (1.13,15.04)	0.03617	<b>4</b>
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	<b>1</b>
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	<b>5</b>
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 ( $\geq 35$  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 (**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  $\geq 105$  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)
$\geq 116$	54 (33, 74)	78 (68,86)	2.51 (1.46, 4.31)	0.58 (0.37, 0.92)	41 (24,59)	86 (77,93)
$\geq 105$	79 (58, 93)	56 (45, 66)	1.79 (1.31, 2.44)	0.37 (0.17, 0.83)	33 (21, 46)	91 (80, 97)
$\geq 94$	88 (68, 97)	27 (18, 38)	1.20 (0.99, 1.47)	0.46 (0.15, 1.39)	25 (16, 35)	89 (71, 98)

## 1 Discussion

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

13 Our study showed that more than one-fifth of the women in the cohort had glucose intolerance at  
14 6–12 weeks of delivery. This rate was consistent with the results of studies in Australia (19),  
15 Belgium (12), Japan (13), and Brazil (11). However, the finding was much lower compared with  
16 the two existing evidences in Saudi Arabia, where the prevalence of glucose intolerance was 38.6%  
17 (20) and 56% (21) and Belgium (43.7%) (22). This difference might have arisen due to the use of  
18 different screening and diagnostic methods. We used the universal, one-step approach with a 75g  
19 OGTT and the updated diagnostic criteria. Whereas, the other studies used the universal two-step  
20 screening strategy for GDM (22). The two-step screening strategy with a glucose challenge test  
21 (GCT), therefore, has the potential to limit the number of OGTTs to screen for GDM based on the  
22 2013 WHO criteria and at the same time identify a high-risk group for postpartum glucose  
23 intolerance.

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

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2  
3 1 The analysis of our cohort of women with GDM has shown that antenatal factors are modestly  
4 2 predictive of the development of glucose intolerance at 6–12 weeks of postpartum. Our study  
5 3 identified that FPG at GDM diagnosis, MUAC, and antenatal depression or the combined as the  
6 4 good predictors for glucose intolerance.  
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10  
11 5 Our study showed that a measured fasting plasma glucose level at GDM diagnosis was the  
12 6 strongest predictor of glucose intolerance at post-partum period. This was in line with our finding  
13 7 that showed most women with glucose intolerance had high levels of fasting plasma at diagnosis  
14 8 and it was found to be a strong predictor (13, 24). There is also evidence that elevated fasting  
15 9 glucose during pregnancy has been a consistent predictor on developing type 2 DM among women  
16 10 with GDM(25).The reasonable explanation to this finding is that the presence of gestational  
17 11 diabetes identifies women with defects in  $\beta$ -cell function in whom insulin secretion does not  
18 12 increase adequately in response to the insulin resistant state of pregnancy. The same defect in  $\beta$ -  
19 13 cell function predisposes some women to overt diabetes in the ensuing years (26). Thus, the  
20 14 diagnosis of GDM represents a window of opportunity for implementing these interventions for  
21 15 those with high blood glucose level at prenatal visits to prevent subsequent diabetes mellitus. This  
22 16 estimate should be used by clinicians to assist their counselling of pregnant women and by policy-  
23 17 makers to target these women for screening and prevention. Therefore, the high fasting BGL on  
24 18 the diagnostic OGTT in pregnancy is well known to be associated with an increased risk for  
25 19 subsequent diabetes.  
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37 20 We found that advanced maternal age ( $\geq 35$  years) during pregnancy was associated with four-fold  
38 21 increase of abnormal glucose tolerance risk at 6–12 weeks postpartum. This was in line with  
39 22 literatures that reported advanced maternal age as a risk factor for persistent diabetes mellitus (24,  
40 23 27). Therefore, we strongly believe that appropriate prevention as well as strict control of  
41 24 gestational diabetes mellitus parameters should be performed on such groups of patients.  
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46 25 Maternal overweight and/or obesity was associated with nearly four-fold increase of abnormal  
47 26 glucose tolerance risk and it was another strong predictor of the progression to post-partum glucose  
48 27 intolerance. Similarly, studies have demonstrated that pre-pregnancy BMI was predictive of the  
49 28 development of subsequent diabetes(20, 28-30).  
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3 1 Another strong predicting factor for post-partum glucose intolerance was the presence of antenatal  
4 2 depression. Women with antenatal depression had six folds higher chance of developing post-  
5 3 partum glucose intolerance compared to women with non-depressive symptoms during their  
6 4 prenatal period.

7 5 Studies strongly agreed that antenatal depression was associated with gestational diabetes mellitus  
8 6 (14, 31, 32). Similarly, a meta-analysis showed depression as a risk factor for the development of  
9 7 type 2 diabetes (33, 34). This could be explained by shared psychosocial and physiological factors  
10 8 for these comorbid situations. Conversely, pregnant women with depression were more likely to  
11 9 practice unhealthy behaviors and poor diabetes self-care, which might be obstacle for management  
12 10 of GDM and progressed to post-partum glucose abnormality (35). Indeed, women with GDM and  
13 11 antenatal depression struggle to cope with the physical and psychological demands of pregnancy  
14 12 and early motherhood. However, current accredited guidelines for the treatment and management  
15 13 of GDM do not provide adequate advice regarding the care of patients with antenatal depression.

#### 14 **Conclusions**

15 15 This prospective cohort study showed that one-fifth of the women with GDM had glucose  
16 16 intolerance at 6-12 weeks of delivery according to the updated diagnostic criteria. Antenatal factors  
17 17 (advanced maternal age, high FPG at GDM diagnosis, overweight and/or obesity, antenatal  
18 18 depression) were strong predictors of post-partum glucose intolerance. In addition, a risk score  
19 19 calculation based on a combination of antenatal factors was effective but had a lower accuracy  
20 20 than the model-based approach. Our findings highlighted the need for increased awareness among  
21 21 women and their primary care physicians regarding the importance of long-term glucose screening  
22 22 after pregnancies complicated by GDM.

#### 23 **Acknowledgements**

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2 health facilities and the study participants.

### 3 **Authors' contributions**

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

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11 role in the design, data collection, analysis, interpretation of data and preparation of the manuscript  
12 of the study.

### 13 **Competing interests**

14 None declared.

### 15 **Patient consent for publication**

16 Not required.

### 17 **Ethics approval and consent to participate**

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

### 27 **Availability of data and materials**

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

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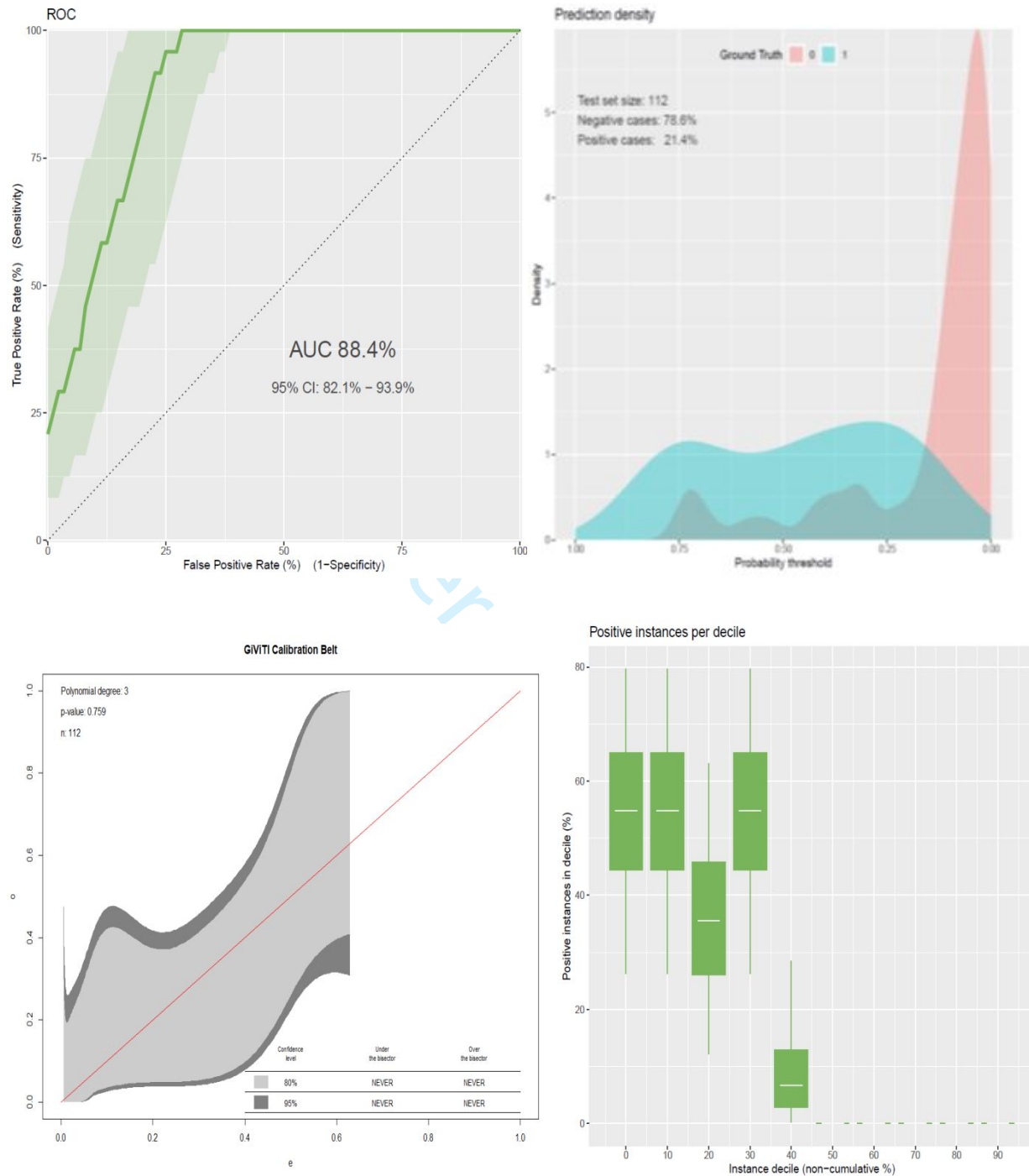
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#### List of figures

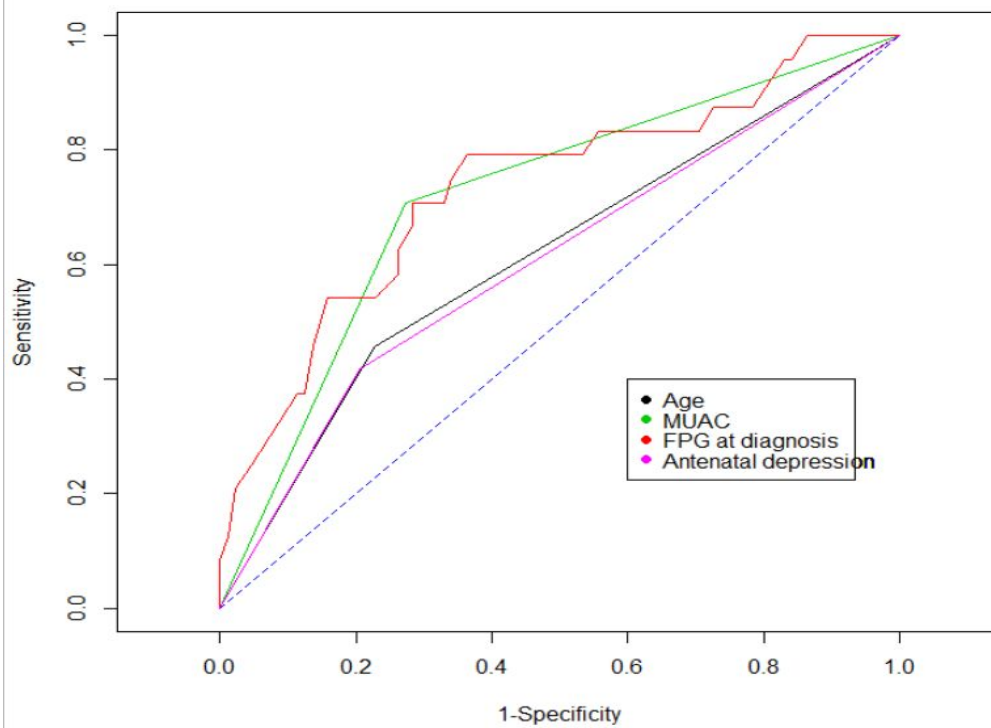
**Fig 1.** ROC curve (left-up), calibration plot (left-bottom), prediction density (right-up), and positive instances per decile (right-bottom) of a model to predict post-partum glucose intolerance

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

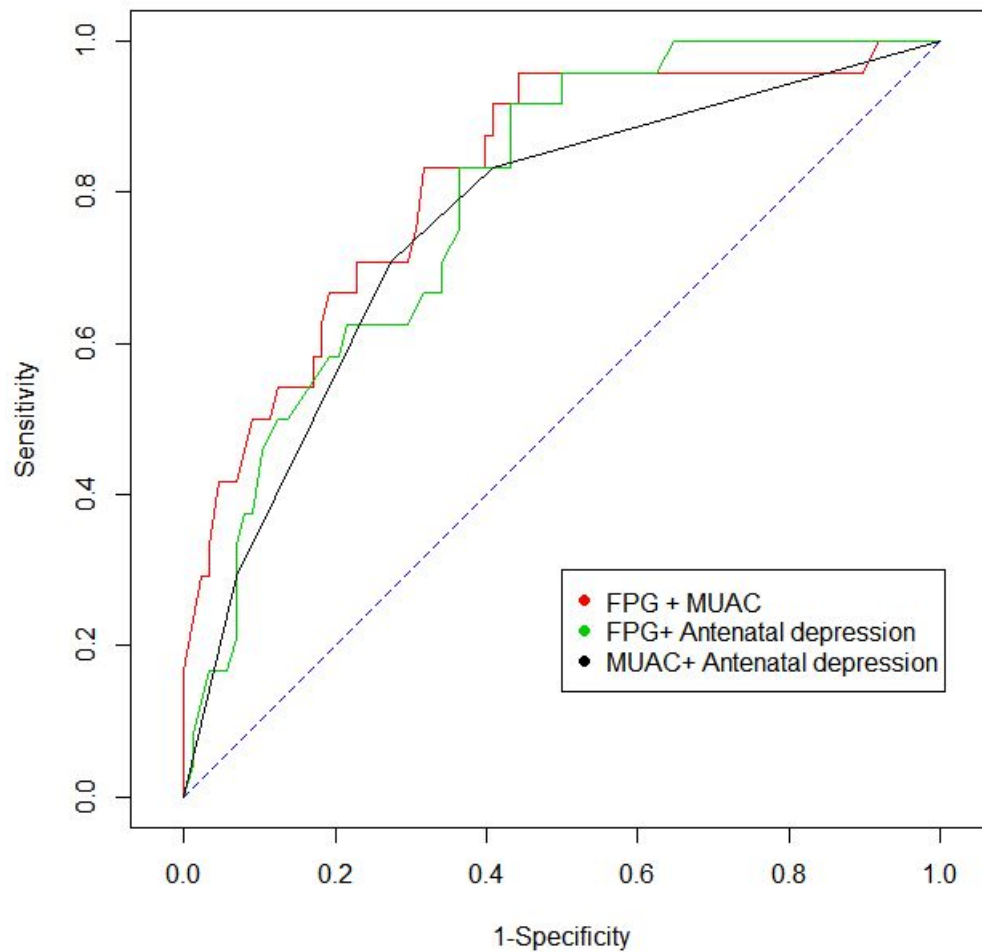
**Fig 3.** ROC curve for the combined predictors of FPG at diagnosis, MUAC and antenatal depression on glucose intolerance.



**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 =  $1/(1+\exp(-11.87007)) + 1.48 \times \text{age} (\geq 35 \text{ years}) + 1.716 \times \text{overweight and/or obesity (MUAC} \geq 28\text{CM)} + 0.081 \times \text{FPG at diagnosis} + 1.637 \times \text{antenatal depression (yes)}$



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



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

# BMJ Open

## 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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3 1 Predictors of postpartum glucose intolerance in women with gestational diabetes mellitus: A  
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5 2 prospective cohort study in Ethiopia based on the updated diagnostic criteria  
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10 5 Achenef Asmamaw Muche <sup>1,2\*</sup>, Oladapo O. Olayemi<sup>3</sup>, Yigzaw Kebede Gete<sup>2</sup>

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## 1 **Abstract**

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

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

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

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

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

### 1 **Strengths and limitation of the study**

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

### 9 **Introduction**

10 Gestational diabetes mellitus (GDM) is defined as “hyperglycemia first detected during pregnancy

11 that is clearly not preexisting or overt diabetes” (1). Although GDM normally disappears after

12 birth, women previously diagnosed with the disease are at high risk of developing long-term

13 metabolic disorders such as type 2 diabetes (2-5).

14 Postprandial hyperglycemia is common among women with GDM, more than half develop type 2

15 diabetes 5 years after delivery (6, 7). A systematic review conducted by Kim et al (8) disclosed

16 that the cumulative incidence of type 2 diabetes among women with prior GDM ranged from 2.6%

17 to 70%. Similarly, the prospect of incident of diabetes was also high at succeeding pregnancies

18 with GDM (8).

19 Even though international guidelines recommend early screening to explore postpartum pre-

20 diabetes or diabetes in women with gestational diabetes at 6–12 weeks of delivery (9, 10), evidence

21 based on the updated GDM diagnostic criteria is limited. In resource-limited settings, pregnancy

22 often marks the first formal exposure to healthcare. The identification of potential future

23 progression predictors of pre-diabetes and/or diabetes in women with GDM could improve the

24 accurate risk stratification of patients during pregnancy. This provides an opportunity for

25 appropriate, cost-effective, and priority intervention programs of high-risk groups. If the

26 persistence risk can be estimated accurately, treatment may be tailored to individual patient needs.

27 Low persistence risk warrants adoption of a watchful waiting policy, while a high persistence risk

28 may call for immediate and possibly more appropriate management (e.g., lifestyle modification

29 and behavioral change in combination with drug treatment).

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3 1 Though few studies available to determine the risk factors of postpartum glucose intolerance,  
4 2 presently don't allow predictions of the absolute risk in individual patients in daily practices (11-  
5 3 14). It is anticipated that in our setting could use such model to predict postpartum glucose  
6 4 intolerance risks for women with GDM and refer patients early. Implementation of predictive  
7 5 models could help prospectively evaluated to determine the presence of the outcome, caregivers  
8 6 to guide the best treatment choices per individual patient promptly and be more cost-effective by  
9 7 identifying high-risk patients who benefit most from certain interventions. We sought to (1)  
10 8 identify the prevalence of postpartum glucose intolerance; and (2) develop a prediction model to  
11 9 enable objective estimations of outcome probabilities (risks) according to different combinations  
12 10 of predictor values for women with GDM in the Ethiopian context by using the updated  
13 11 international diagnostic criteria. We hypothesized that using antenatal clinical characteristics  
14 12 would improve the identification of women with GDM at high risk for postpartum glucose  
15 13 intolerance.

## 14 **Methods and Materials**

### 15 **Study design and population**

16 This prospective cohort study was conducted in five selected public health facilities of Gondar  
17 town namely University of Gondar comprehensive specialized hospital, Gondar health center,  
18 Woleka health center, Azezo health center, and Maraki health center from 30<sup>th</sup> March, 2018 to  
19 26<sup>th</sup> March, 2019. Pregnant women were enrolled if they were 18 years or older, had singleton  
20 pregnancy and 20 -23<sup>+6</sup> weeks of gestation during commencement time, then followed them until  
21 at 6–12 weeks after delivery. Whereas, pregnant women who had pre-existing or overt diabetes,  
22 chronic diseases, or on medication that might affect their glucose metabolism (steroids,  $\beta$ -  
23 adrenergic agonists, anti-psychotic drugs) at commencement were excluded. All pregnant women  
24 are screened for overt diabetes in the first antenatal care visit. If the test at the first visit is normal,  
25 a two-hour 75 g OGTT is performed for all pregnant women at 24-28 weeks' gestation to screened  
26 GDM. In high-risk patients, the 75 g OGTT is repeated at 32-36 weeks, if the result normal at  
27 24-28 weeks' gestation. The detailed methods of the study were explained earlier (15). This follow  
28 up study was conducted on 131 women diagnosed with GDM out of 1027 participants who were  
29 completed the OGTT. All women with GDM invited to participate in this study and evaluated their  
30 glucose status at 6–12 weeks of postpartum.

31

## 1 **Data collection**

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

## 10 **Laboratory assessment**

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

## 26 **Outcome measures**

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

## 1 **Data processing and statistical analysis**

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

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

## 27 **Patient and public involvement**

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

30

## 1 **Results**

### 2 **Characteristics of the study group**

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

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

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



1 **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)	

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

## 1 A prediction model for postpartum glucose intolerance

2 After review of literatures, 13 demographic, obstetric, and clinical characteristics of mothers  
3 collected during the prenatal visits or baseline survey were considered to predict postpartum  
4 glucose intolerance. On the univariate analysis (maternal age, gravidity, maternal obesity and/or  
5 overweight, FPG at GDM diagnosis, and antenatal depression) variables were found to have a  
6 significant association. However, in the final multivariable regression analysis and the reduced  
7 model four predictors of progression, such as age of mother ( $\geq 35$  years) during pregnancy  
8 (AOR=4.04; 95%:1.23, 14.33), maternal obesity and/or overweight (AOR=3.92; 95%: 1.13,  
9 15.04), FPG at GDM diagnosis (AOR=1.08; 95%: 1.04, 1.15), and antenatal depression  
10 (AOR=5.90; 95%: 1.66, 23.47) remained significant. Using the results, a prediction model was  
11 developed and the equation for the prediction model was obtained (**Table 2**).

12 The area under the ROC curve (AUC) of the final reduced model was 0.884 (95% CI: 0.822 to  
13 0.937). The calibration test had a p-value of 0.759, indicating the model does not misrepresent the  
14 data (**Figure 1A**). Rounding of all regression coefficients in the reduced model to 1 point resulted  
15 in a simplified prediction score presented in table 2. The AUC of the simplified risk score  
16 prediction model was 0.808 (95% CI: 0.705 to 0.90). The calibration test had a p-value of 0.044,  
17 indicating the model less represent the data (**Figure 1B**). Since the simplified score had a lower  
18 prediction accuracy than the model that used the results of the original  $\beta$  coefficients, we prefer to  
19 use the original  $\beta$  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 ( $\geq 35$ years)	2.88 (1.11, 1.7.46)	4.04 (1.23, 14.33)	0.02380	<b>4</b>
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 ( $\geq 28$ cm)	6.48 (2.474, 18.61)	3.92 (1.13,15.04)	0.03617	<b>4</b>
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	<b>1</b>
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	<b>5</b>
Insulin treated GDM	1.51 (0.21, 7.54)	NA		

3 GDM =gestational diabetes mellitus h=hour Hb=hemoglobin g/dl= gram per deciliter mg/dl=milligram deciliter  
4 FPG= Fasting plasma glucose mmHg=millimeter of mercury OGTT=oral glucose tolerance test MUAC=Mid upper  
5 arm circumference  
6 NA - not included to the multivariate analysis \*Variables were also retained in the reduced model using likelihood  
7 ratio test are; gravidity and dietary diversity status. Both backward and forward selection showed same results. ORs  
8 after internal validation with bootstrapping are shown.  
9  
10  
11

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 ( $\geq 35$  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  $FPG \geq 105$  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)
$\geq 116$	54 (33, 74)	78 (68,86)	2.51 (1.46, 4.31)	0.58 (0.37, 0.92)	41 (24,59)	86 (77,93)
$\geq 105$	79 (58, 93)	56 (45, 66)	1.79 (1.31, 2.44)	0.37 (0.17, 0.83)	33 (21, 46)	91 (80, 97)
$\geq 94$	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

## 1 Discussion

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

9 Our study showed that more than one-fifth of the women in the cohort had glucose intolerance at  
10 6–12 weeks of delivery. This rate was consistent with the results of studies in Australia (21),  
11 Belgium (22), Japan (12), and Brazil (11). However, the finding was much lower compared with  
12 the two existing evidences in Saudi Arabia, where the prevalence of glucose intolerance was 38.6%  
13 (14) and 56% (23) and Belgium (43.7%) (13). This difference might have arisen due to the use of  
14 different screening and diagnostic methods. We used the universal, one-step approach with a 75g  
15 OGTT and the updated diagnostic criteria. Whereas, the other studies used the universal two-step  
16 screening strategy for GDM (13). The two-step screening strategy with a glucose challenge test  
17 (GCT), therefore, has the potential to limit the number of OGTTs to screen for GDM and identified  
18 a high-risk group for postpartum glucose intolerance. The tight relationship between GDM and  
19 postpartum glucose intolerance suggests that GDM may represent an early stage in the natural  
20 history of postpartum glucose intolerance (24, 25). Pregnancy might also constitute a physiological  
21 condition of insulin resistance and impaired beta-cell function (26, 27). In addition, the early onset  
22 of GDM would be expected to indicate greater pre-existing insulin resistance/pancreatic  $\beta$ -cell  
23 dysfunction and therefore increased risk of postpartum glucose intolerance (28). This finding  
24 highlights the importance of adherence to postpartum screening and lifestyle modifications to  
25 prevent or delay the onset of type 2 diabetes in these women. Regardless of the screening approach  
26 used, research on the efficacy or effectiveness of lifestyle interventions in preventing or delaying  
27 the progression to postpartum glucose intolerance in women with GDM in Ethiopia would provide  
28 much-needed data.

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

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

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

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

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3 1 advanced age integrating behavioral counseling on nutrition and exercise into ANC services is a  
4 2 low-cost intervention to prevent subsequent diabetes.

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7 3 Maternal overweight and/or obesity was a strong predictor of abnormal glucose tolerance during  
8 4 postpartum period. Similarly, studies have demonstrated that pre-pregnancy BMI was predictive  
9 5 of the development of subsequent diabetes (14, 37-39). In view of the current high burden of  
10 6 overweight or obesity in the African women and the expected rise in diabetes prevalence, it is  
11 7 imperative to identify populations at elevated risk and introduce risk-lowering interventions such  
12 8 as avoiding sedentary life (40, 41).

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18 9 Another strong predictor for postpartum glucose intolerance was the presence of antenatal  
19 10 depression. Though study is limited in predictive effect of antenatal depression on postpartum  
20 11 glucose intolerance, there evidences showed the association of antenatal depression with GDM  
21 12 (15, 42, 43). Similarly, depression has been suggested as a risk factor for the development of type  
22 13 2 diabetes (44, 45). This could be explained by shared psychosocial and physiological factors for  
23 14 these comorbid situations. Besides, GDM women with antenatal depression could practice  
24 15 unhealthy behaviors, and poor glycemic control which leads the progression to abnormal glucose  
25 16 status in post-pregnancy (46). These women also struggle to cope with the physical and  
26 17 psychological demands of pregnancy and early motherhood. Unfortunately, the guidelines for the  
27 18 treatment and management of GDM do not provide adequate advice regarding the care of patients  
28 19 with antenatal depression particularly countries with low resource setting.

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38 20 The strength of this study was a prospective cohort study involved GDM patients identified using  
39 21 the updated diagnostic criteria with uniform protocols for all women and followed them until 6-12  
40 22 weeks of delivery. In addition, to the best of our knowledge, this study is the first prospective  
41 23 cohort study to follow postpartum outcomes of GDM and included several antenatal variables to  
42 24 use for the prediction model of postpartum glucose intolerance in Ethiopia. Though, WHO  
43 25 recommends that in settings where laboratories or proper storages and transport of blood samples  
44 26 is not guaranteed, which is the case in resource limited countries like Ethiopia, the use of point of  
45 27 care tests may influence the result (47). However, we used plasma-calibrated hand-held  
46 28 glucometers because of convenience and acceptable reliability. Moreover, the study used a  
47 29 relatively small sample size, limited number of examined cases and that ongoing sampling in future

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

### 3 **Conclusions**

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

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### 24 **Authors' contributions**

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

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1  
2  
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4 2 role in the design, data collection, analysis, interpretation of data and preparation of the manuscript  
5 3 of the study.

#### 8 **Competing interests**

9  
10 5 None declared.

#### 11 **Patient consent for publication**

12 6  
13 7 Not required.

#### 14 **Ethics approval and consent to participate**

15 8  
16 9 The study was conducted after ethical approval was obtained from the Institute for Advanced  
17 10 Medical Research and Training (IAMRAT), College of Medicine, University of Ibadan, Ibadan,  
18 11 Nigeria with the I/UCH EC Registration Number of NHREC/05/01/2008a and UI/UCH Ethics  
19 12 Committee assigned the number UI/EC/17/0435 and the Institutional Review Board (IRB ) of the  
20 13 University of Gondar (Ref.No; O/V/P/RCS/05/811/2018). Permission from the Amhara Public  
21 14 Health Institute and the health authorities of the study sites was also received prior to the start of  
22 15 the study. All participants signed (written or thumb-printed) informed consent form, after, they  
23 16 received a face to face explanation about the objectives of the study. The collected information  
24 17 during the course of the research was treated with the utmost confidentiality.

#### 25 **Availability of data and materials**

26 18  
27 19 The datasets used and/or analyzed during the current study are available from the correspondence  
28 20 author on reasonable request.  
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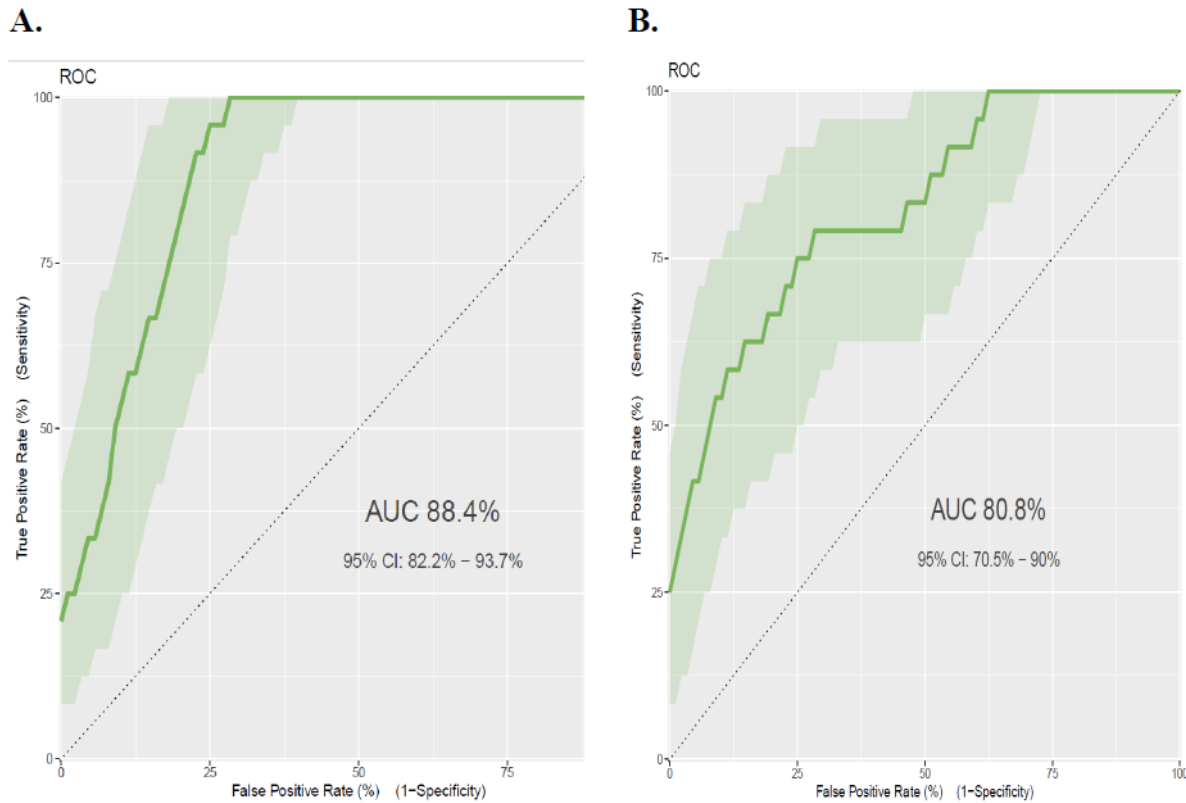
## 27 **List of figures**

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

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

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

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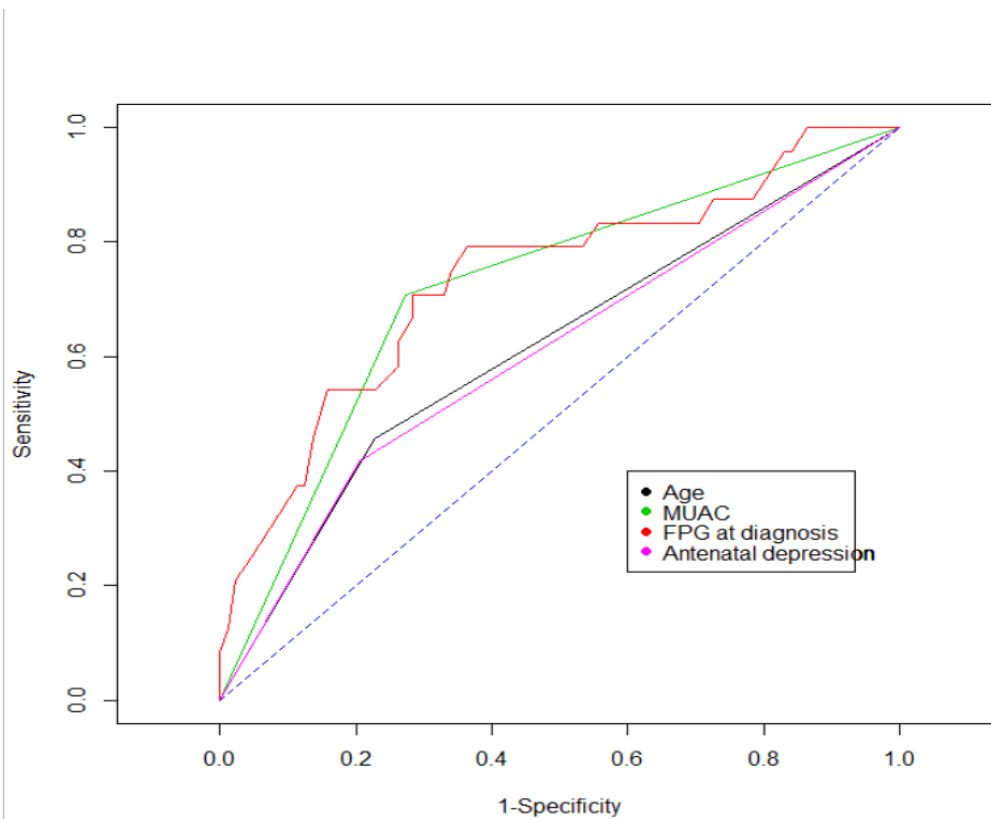


31 **Figure 1.** ROC curve for prediction of postpartum glucose intolerance using different models:

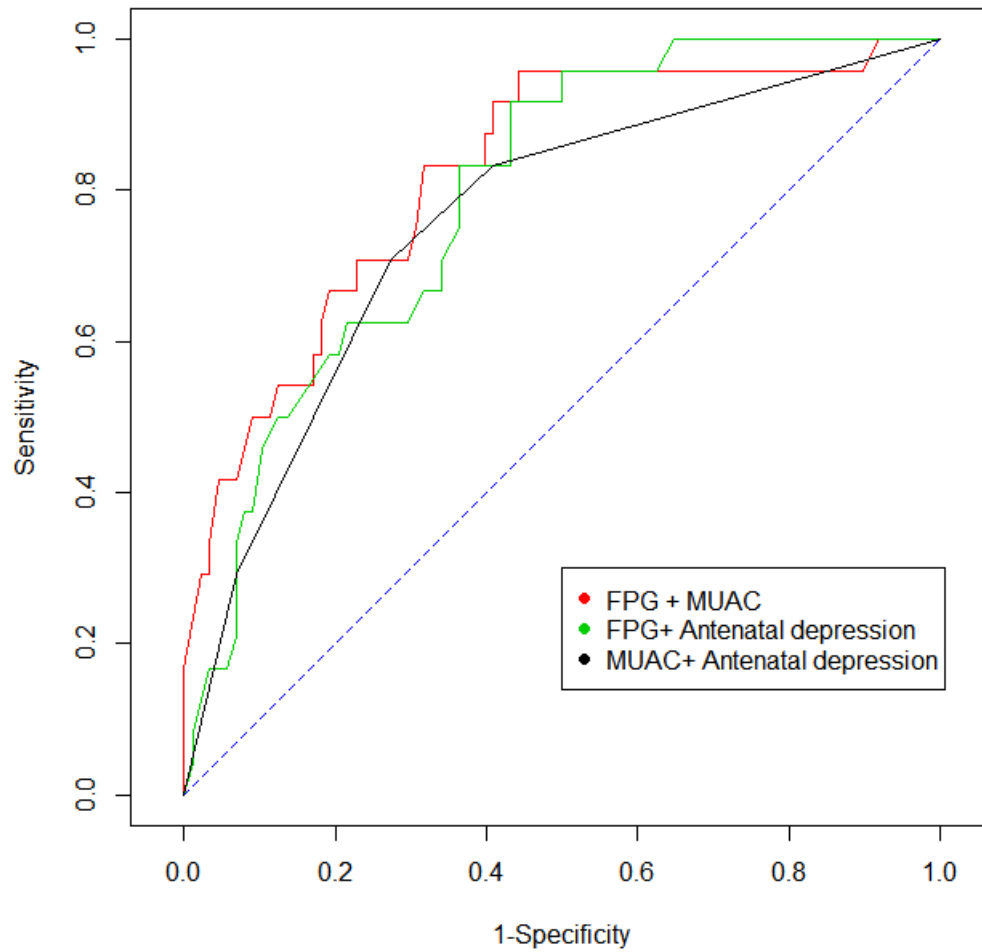
32 **A.** Linear predictor model for estimated risk of postpartum glucose intolerance =  $1/(1+\exp(-11.87007 + 1.48 * \text{age} (\geq 35 \text{ years}) + 1.716 * \text{overweight and/or obesity (MUAC} \geq 28\text{CM)} + 0.081 * \text{FPG at diagnosis} + 1.637 * \text{antenatal depression (yes)}$ )

33  
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35 **B.** Simplified risk score predictor model for estimated risk of postpartum glucose intolerance =  $(\text{age} \geq 35 \text{ years} * 4) + (\text{overweight and/or obesity (MUAC} \geq 28\text{CM)} * 4) + (\text{FPG at diagnosis} * 1) + (\text{antenatal depression} * 5)$





**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.

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

Section/Topic	Item #	Recommendation	Reported on page #
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			



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
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	12-14
<b>Limitations</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).

# BMJ Open

## 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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3 1 Predictors of postpartum glucose intolerance in women with gestational diabetes mellitus: A  
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5 2 prospective cohort study in Ethiopia based on the updated diagnostic criteria  
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10 5 Achenef Asmamaw Muche <sup>1,2\*</sup>, Oladapo O. Olayemi<sup>3</sup>, Yigzaw Kebede Gete<sup>2</sup>

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## 1 **Abstract**

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

4 **Design:** Prospective cohort study

5 **Setting:** Gondar town public health facilities, Northwest Ethiopia.

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

8 **Main outcome:** Postpartum glucose intolerance.

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

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

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

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

### 1 **Strengths and limitation of the study**

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

### 7 **Introduction**

8 Gestational diabetes mellitus (GDM) is defined as “hyperglycemia first detected during pregnancy

9 that is clearly not preexisting or overt diabetes” (1). Although GDM normally disappears after

10 birth, women previously diagnosed with the disease are at high risk of developing long-term

11 metabolic disorders such as type 2 diabetes (2-5).

12 Postprandial hyperglycemia is common among women with GDM, thereby more than half develop

13 type 2 diabetes 5 years after delivery (6, 7). A systematic review conducted by Kim et al. (8)

14 disclosed that the incidence of type 2 diabetes among women with prior GDM ranged from 2.6%

15 to 70%. Similarly, the prospect of incident of diabetes was also high at succeeding pregnancies

16 with GDM (8).

17 The international guidelines recommend that women with GDM should be screened for persistent

18 diabetes at 6–12 weeks of postpartum (9, 10). Indeed, the identification of those women who are

19 at the highest risk of progressing to postpartum glucose intolerance in our setting remains limited.

20 In resource-limited settings, pregnancy often marks the first formal exposure to healthcare. The

21 identification of potential future progression predictors of pre-diabetes and/or diabetes in women

22 with GDM could improve the accurate risk stratification of patients during pregnancy. This

23 provides an opportunity for appropriate, cost-effective, and priority intervention programs of high-

24 risk groups. If the persistence risk can be estimated accurately, treatment may be tailored to

25 individual patient needs. Low persistence risk warrants adoption of a watchful waiting policy,

26 while a high persistence risk may call for immediate and possibly more appropriate management

27 (e.g., lifestyle modification and behavioral change in combination with drug treatment).

28 Though few studies available to determine the risk factors of postpartum glucose intolerance,

29 presently don't allow predictions of the absolute risk in individual patients in daily practices (11-

30 14). It is anticipated that our setting could use such model to predict postpartum glucose intolerance

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

## 10 **Methods and Materials**

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

### 13 **Study design and population**

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

### 28 **Data collection**

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

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3 1 obstetric history, anthropometric measurements, type of treatment of GDM (diet or insulin),  
4 behavioral factors (alcohol use and coffee intake), lifestyle parameters (dietary diversity and  
5 2 physical activity), antenatal depression status, blood glucose value (FPG and OGTT). All  
6 3 participants also had FPG and 2hr OGTT blood tests performed at 6–12 weeks after delivery.  
7 4

### 10 5 **Laboratory assessment**

11 6 The universal screening for GDM using a two-hour 75 g OGTT was performed for all pregnant  
12 7 women by capillary glucose testing, using a standard plasma-calibrated glucometer (HemoCue  
13 8 Glucose B-201+ (Ångelholm AB, Sweden)). This corresponded to the latest consensus  
14 9 recommendations of the International Federation of Gynecology and Obstetrics (FIGO) initiative  
15 10 for GDM diagnosis in settings where close-by laboratories or facilities for proper storage and  
16 11 transport of blood samples to distant laboratories are not available (16). After capillary blood  
17 12 samples taken, the whole blood capillary values were converted to plasma venous values by  
18 13 multiplying a constant factor of 1.11 (17). The updated diagnostic criteria for GDM diagnosis was  
19 14 made by using the 2017 American Diabetes Association (ADA) (18) or 2013 WHO (1) or modified  
20 15 International Association of the Diabetes and Pregnancy Study Groups (IADPSG) (19). The  
21 16 diagnosis of GDM is made when one or more of the values of plasma glucose level was met  
22 17 (fasting:  $\geq 92$  mg/dL, 1 hr.:  $\geq 180$  mg/dL; 2 hr.:  $\geq 153$  mg/dL). Similarly, postpartum glucose  
23 18 tolerance status was evaluated by a standard FPG and 75 g 2-hr OGTT, using a similar test  
24 19 procedure but a higher cut off point for the classification of postpartum glucose intolerance (1,  
25 20 18).

### 21 21 **Outcome measures**

22 22 The primary outcome was the diagnosis of postpartum pre-diabetes (impaired fasting glucose  
23 23 (IFG): FPG 100-125 mg/dL; impaired glucose tolerance (IGT) 2-hr plasma glucose in the 75-g  
24 24 OGTT 140-199 mg/dL) or diabetes (FPG  $\geq 126$  mg/dL or 2-hr plasma glucose  $\geq 200$  mg/dL in the  
25 25 OGTT, or random plasma glucose  $\geq 200$  mg/dL) (1, 18). Subjects were divided into two groups:  
26 26 the glucose intolerance group, which consisted of IGT and IFG patients, and the normal group.

### 27 27 **Data processing and statistical analysis**

28 28 All data were entered into Epi Info™ 7 software and exported to R statistical programming  
29 29 language version 3.6.0 for analysis. Descriptive statistics (mean, median, standard deviations (SD),  
30 30 inter-quartile range (IQR), percentages, and rates) were computed. Differences in the distributions



1 of categorical variables were analyzed with a chi-square test. The Shapiro-Wilk test was used to  
2 verify if continuous variables were normally distributed. Normally distributed and non-normally  
3 distributed variables were evaluated with the t-test and Mann-Whitney test, respectively. Glycemia  
4 on diagnostic OGTT was correlated to postpartum OGTT using the Spearman correlation test. We  
5 performed a univariable analysis using logistic regression to obtain insight into the association of  
6 each potential determinant with postpartum glucose intolerance and to select potential predictors  
7 for the multivariable analysis. We fitted all variables with p-value  $\leq 0.2$  in the univariable analysis  
8 to the multivariable model to be more liberal. Then we used a stepwise backward elimination  
9 technique with p-value  $< 0.10$  for the likelihood ratio test to fit the reduced model of easily  
10 obtainable characteristics. In this study, the significant factors have been defined as variables with  
11 p-value  $< 0.05$  in the multivariable logistic regression analysis.  
12 For discriminative power of predictable variables of postpartum glucose intolerance and to check  
13 model accuracy, we computed the area under the ROC curve (discrimination) and calibration plot  
14 (calibration) using '*classifierplots*' and '*givitiR*' packages of R, respectively (20) and estimated as  
15 the area under the curve (AUC) with 95% confidence interval. The AUC ranged from 0.5 (no  
16 predictive ability) to 1 (perfect discrimination). To construct an easily applicable postpartum  
17 glucose intolerance prediction score, we transformed each coefficient from the model to a round  
18 number by dividing to the lowest coefficient. The number of points was subsequently rounded to  
19 the nearest integer. We determined the total score for everyone by assigning the points to each  
20 variable present and adding them up. In addition, sensitivity, specificity, likelihood ratios, and  
21 post-test probability of FPG at diagnosis with 95% confidence intervals were calculated by using  
22 the optimal cut-offs of levels.

### 23 **Patient and public involvement**

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

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29

## 1 **Results**

### 2 **Characteristics of the study group**

3 Of all 131 women with GDM, 112 (85.5%) returned and completed the postpartum OGTT at 6-12  
4 weeks after delivery. The incidence of early postpartum glucose intolerance was 21.4% (95% CI:  
5 14.3 - 28.4) inclusive of 18.7% (95% CI: 11.5 - 25.3) prediabetes and 2.7 % (95% CI: 0.9 - 6.4)  
6 diabetes.

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

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

1 **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)	

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

## 1 A prediction model for postpartum glucose intolerance

2 Different demographic, obstetric, and clinical characteristics of mothers were collected during  
3 prenatal visits and considered to predict postpartum glucose intolerance. On univariable analysis  
4 (maternal age, gravidity, maternal obesity and/or overweight, FPG at GDM diagnosis, and antenatal  
5 depression) variables were found to have a significant association. However, in the final  
6 multivariable regression analysis and the reduced model four predictors of progression, such as  
7 age of mother ( $\geq 35$  years) during pregnancy [AOR=4.04 (95%: 1.23, 14.33)], maternal obesity  
8 and/or overweight [AOR=3.92 (95%: 1.13, 15.04)], FPG at GDM diagnosis [AOR=1.08 (95%:  
9 1.04, 1.15)], and antenatal depression [AOR=5.90 (95%: 1.66, 23.47)] remained significant. Using  
10 the results, a prediction model was developed and the equation for the prediction model was  
11 obtained (**Table 2**).

12 The area under the ROC curve (AUC) of the final reduced model was 0.884 (95% CI: 0.822 -  
13 0.937). The calibration test had a p-value of 0.759, indicating the model does not misrepresent the  
14 data (**Figure 1A**). Rounding of all regression coefficients in the reduced model to 1 point resulted  
15 in a simplified prediction score presented in table 2. The AUC of the simplified risk score  
16 prediction model was 0.808 (95% CI: 0.705 - 0.90). The calibration test had a p-value of 0.044,  
17 indicating the model less represent the data (**Figure 1B**). Since the simplified score had a lower  
18 prediction accuracy than the model that used results of original  $\beta$  coefficients, we prefer to use the  
19 original  $\beta$  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 ( $\geq 35$ years)	2.88 (1.11, 1.7.46)	4.04 (1.23, 14.33)	0.02380	<b>4</b>
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 ( $\geq 28$ cm)	6.48 (2.474, 18.61)	3.92 (1.13,15.04)	0.03617	<b>4</b>
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	<b>1</b>
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	<b>5</b>
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 ( $\geq 35$  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  $\geq 105$  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)
$\geq 116$	54 (33, 74)	78 (68,86)	2.51 (1.46, 4.31)	0.58 (0.37, 0.92)	41 (24,59)	86 (77,93)
$\geq 105$	79 (58, 93)	56 (45, 66)	1.79 (1.31, 2.44)	0.37 (0.17, 0.83)	33 (21, 46)	91 (80, 97)
$\geq 94$	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

## 1 Discussion

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

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

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

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

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

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

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



1  
2  
3 1 imperative to identify populations at elevated risk and introduce risk-lowering interventions such  
4  
5 2 as reducing obesity and avoiding sedentary life (38, 39).  
6

7 3 Another strong predictor for postpartum glucose intolerance was the presence of antenatal  
8  
9 4 depression. Though study is limited in predictive effect of antenatal depression on postpartum  
10  
11 5 glucose intolerance, the existing evidence shows there is association between antenatal depression  
12  
13 6 and GDM (15, 40, 41). Previous studies also revealed depression increased the risk of type 2  
14  
15 7 diabetes (42, 43). The existence of comorbid problem of antenatal depression can lead women to  
16  
17 8 poor lifestyle decisions, such as unhealthy eating, poor exercise, weight gain, and poor glycemic  
18  
19 9 control which primes the progression to postpartum diabetes (44). Unfortunately, the guidelines  
20  
21 10 for the treatment and management of GDM don't provide adequate evidence regarding the care of  
22  
23 11 patients with comorbid situations of antenatal depression in low resource setting.

24 12 The strength of this study was being a prospective cohort study involving GDM patients identified  
25  
26 13 using the updated diagnostic criteria with uniform protocols for all women and followed them until  
27  
28 14 6-12 weeks of delivery. In addition, our prediction model is constructed from easily obtainable  
29  
30 15 antenatal characteristics that make it applicable in low resource settings. Though WHO  
31  
32 16 recommend that in settings where laboratories or proper storage and transport of blood samples is  
33  
34 17 not guaranteed, the use of point of care tests may influence the result (16). However, we used  
35  
36 18 plasma-calibrated hand-held glucometers because of convenience and acceptable reliability.  
37  
38 19 Moreover, the study used a relatively small sample size could be the limitations of the study.

## 38 20 **Conclusions**

39  
40 21 Based on the updated diagnostic criteria, the high incidence rate of early postpartum glucose  
41  
42 22 intolerance has been identified among women who had GDM. Antenatal characteristics (advanced  
43  
44 23 maternal age, high FPG at GDM diagnosis, overweight and/or obesity, antenatal depression) were  
45  
46 24 strong predictors of postpartum glucose intolerance. This prognostic risk prediction models  
47  
48 25 revealed the utility of antenatal predictors were modestly predicted post-partum glucose  
49  
50 26 intolerance in women with GDM. In addition, a risk score calculation based on a combination of  
51  
52 27 antenatal predictors was effective but had lower accuracy than the model-based approach by  
53  
54 28 original  $\beta$  coefficients. Thus, our findings highlighted the need for increased awareness among  
55  
56 29 women and their primary care providers regarding the importance of long-term glucose screening  
57  
58 30 after pregnancies complicated by GDM.

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## 11 **Authors' contributions**

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

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## 21 **Competing interests**

22 None declared.

## 23 **Patient consent for publication**

24 Not required.

## 25 **Ethics approval and consent to participate**

26 The study was conducted after ethical approval was obtained from the Institute for Advanced  
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1 the study. All participants signed (written or thumb-printed) informed consent form, after, they  
2 received a face to face explanation about the objectives of the study. The collected information  
3 during the course of the research was treated with the utmost confidentiality.

#### 4 **Availability of data and materials**

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

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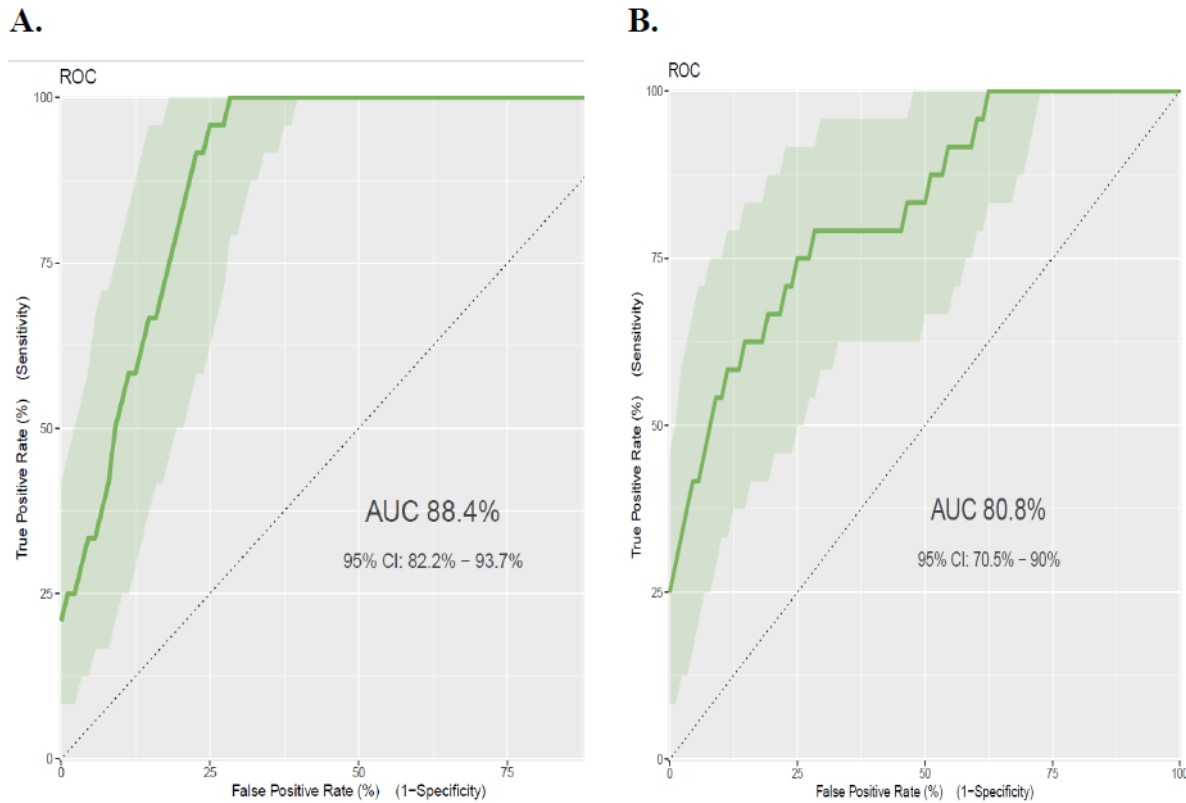
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### 33 **List of figures**

34 27 **Figure 1.** ROC curve for prediction of postpartum glucose intolerance using different models

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38 31 **Figure 3.** ROC curve for the combined predictors of FPG at diagnosis, MUAC and antenatal  
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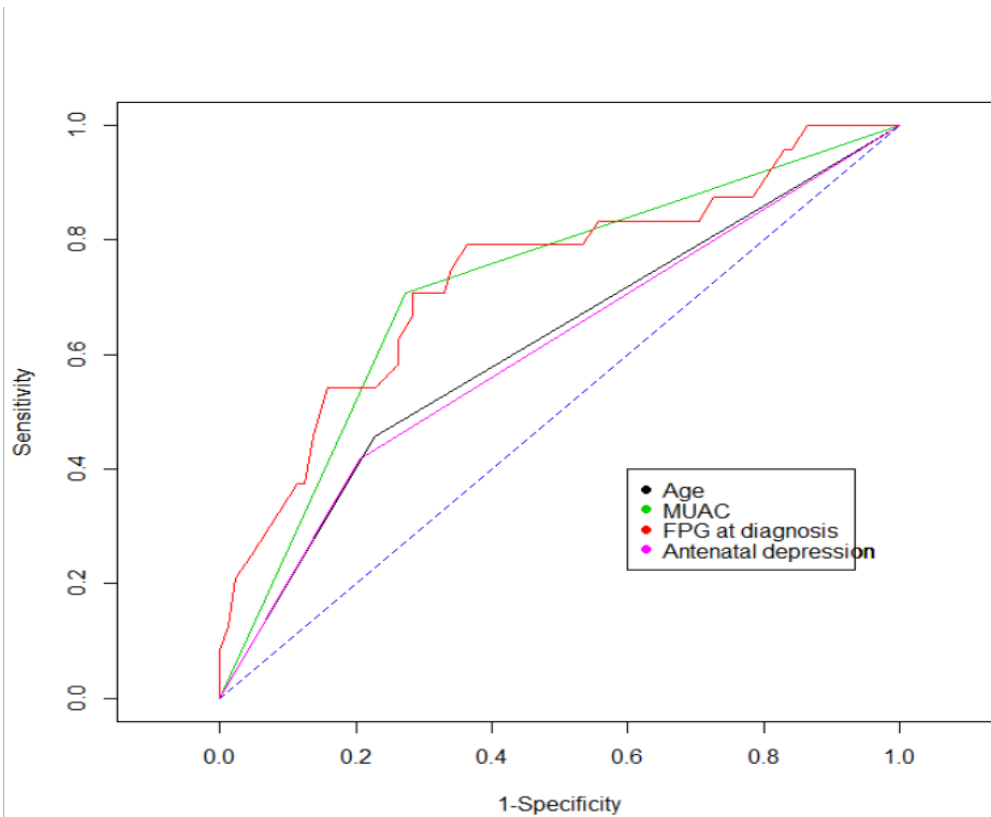


**Figure 1.** ROC curve for prediction of postpartum glucose intolerance using different models:

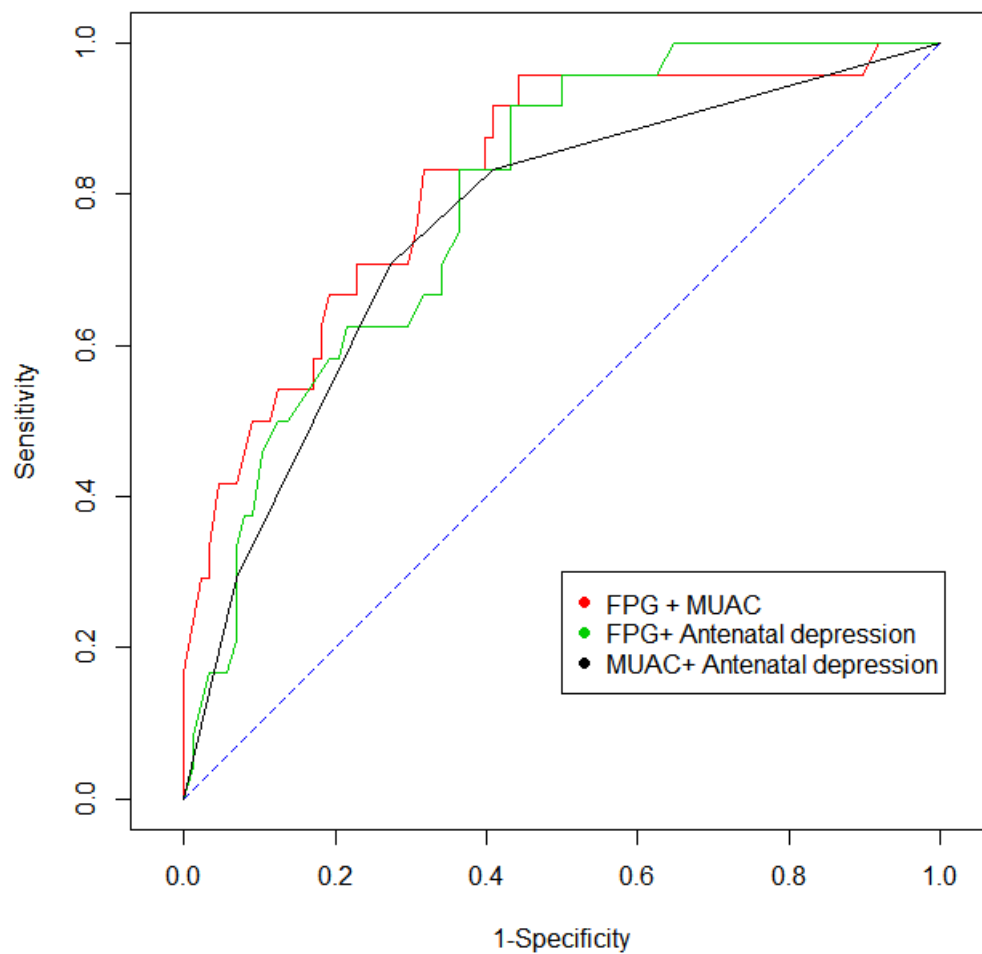
**A.** Linear predictor model for estimated risk of postpartum glucose intolerance =  $1/(1+\exp(-11.87007 + 1.48 * \text{age} (\geq 35 \text{ years}) + 1.716 * \text{overweight and/or obesity (MUAC} \geq 28\text{CM)} + 0.081 * \text{FPG at diagnosis} + 1.637 * \text{antenatal depression (yes)})$

**B.** Simplified risk score predictor model for estimated risk of postpartum glucose intolerance =  $(\text{age} \geq 35 \text{ years} * 4) + (\text{overweight and/or obesity (MUAC} \geq 28\text{CM)} * 4) + (\text{FPG at diagnosis} * 1) + (\text{antenatal depression} * 5)$





**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.



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

Section/Topic	Item #	Recommendation	Reported on page #
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			

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
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	12-14
<b>Limitations</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).