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Original Research Article

Accuracy of glycosylated fibronectin-based cut-off levels for predicting gestational diabetes mellitus

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is a common metabolic complication of pregnancy and is associated with adverse maternal and neonatal outcomes. Early identification of women at risk remains challenging, as routine screening is typically performed in mid-pregnancy. This study aimed to assess the accuracy of first-trimester maternal serum glycosylated fibronectin cut-off levels for predicting GDM.
Methods: A prospective cohort study was conducted at the Department of Obstetrics and Gynecology at Dhaka Medical College Hospital, Dhaka, Bangladesh, from December 2020 to November 2021. Ninety-five pregnant women with singleton pregnancies between 10 and 15 weeks of gestation were enrolled. Maternal serum glycosylated fibronectin was measured using ELISA. Participants were followed until delivery and GDM was diagnosed using WHO criteria at 24-28 weeks. Statistical analysis was performed using SPSS version 23.
Results: Most participants were aged 21–30 years (66.3%) and overweight (75.8%). Women who developed GDM had significantly higher mean glycosylated fibronectin levels than non-GDM women (226.7±73.3 vs. 114.2±57.9 µg/ml; $p<0.001$). Among women with glycosylated fibronectin ≥145.0 µg/ml, 83.3% developed GDM, whereas only 16.7% of GDM cases occurred below this threshold. Mean body mass index was also significantly higher among women with elevated glycosylated fibronectin levels ($p=0.01$).
Conclusions: Elevated first-trimester maternal serum glycosylated fibronectin is strongly associated with subsequent development of GDM and may serve as an effective early screening biomarker for identifying high-risk pregnancies.

Keywords: Early pregnancy biomarker, Gestational diabetes mellitus, Glycosylated fibronectin

INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the most common metabolic complications of pregnancy and is associated with significant short- and long-term adverse outcomes for both mother and child.[1] The global prevalence of hyperglycemia in pregnancy has been rising, particularly in low- and middle-income countries, due to increasing maternal age, obesity and lifestyle changes.[2,3] In Bangladesh, the burden of GDM is substantial, with reported prevalence varying across trimesters and populations.[4,5]

GDM is associated with increased risks of preeclampsia, cesarean delivery, macrosomia and neonatal metabolic complications, as well as long-term risks of type 2 diabetes mellitus and cardiovascular disease in both mother and offspring.[6,7] Early identification of women at risk is therefore critical to enable timely intervention and mitigate

adverse outcomes. Conventional screening strategies typically rely on oral glucose tolerance testing (OGTT) at 24-28 weeks of gestation; however, this approach fails to identify women who develop metabolic dysregulation earlier in pregnancy.[8]

Emerging evidence suggests that pathophysiological changes underlying GDM begin well before the conventional screening window, involving insulin resistance, inflammation, oxidative stress and altered placental function.[9,10] Consequently, considerable research interest has focused on identifying early pregnancy biomarkers capable of predicting GDM before clinical onset.[11] Several biochemical markers, including adiponectin, C-reactive protein, uric acid and liver enzymes, have been evaluated with varying predictive accuracy.[12,13]

Fibronectin is a high-molecular-weight glycoprotein involved in cell adhesion, extracellular matrix remodeling and placental development.[14] Glycosylated fibronectin, a post-translationally modified form of fibronectin, has been implicated in metabolic and vascular dysregulation during pregnancy.[15] Proteomic studies have demonstrated elevated circulating glycosylated fibronectin levels in women who later develop GDM, suggesting its potential role as an early biomarker.[16]

Räsänen et al. first reported the association between first-trimester glycosylated fibronectin and subsequent GDM development, proposing a specific cut-off value for risk stratification.[17] Subsequent studies, including cohort and multicenter investigations, have supported its predictive utility, highlighting its potential as a universal early screening tool.[18,19] Nevertheless, the diagnostic accuracy and optimal cut-off values of glycosylated fibronectin may vary across populations due to genetic, metabolic and environmental differences.

Despite the growing evidence from high-income settings, data on glycosylated fibronectin as an early predictor of GDM in South Asian populations remain limited. Given the high baseline risk of GDM and distinct anthropometric and metabolic profiles of South Asian women, population-specific validation of early biomarkers is essential.[5,20] This study aimed to evaluate the accuracy of first-trimester maternal serum glycosylated fibronectin levels and a predefined cut-off value for predicting the development of GDM among Bangladeshi women.

METHODS

This prospective cohort study was conducted in the Department of Obstetrics and Gynecology, Dhaka Medical College Hospital, Dhaka, Bangladesh, over one year from December 2020 to November 2021. The study population comprised 95 pregnant women with viable singleton pregnancies attending the antenatal clinic between 10 and 15 weeks of gestation.

Inclusion criteria

Singleton pregnancy between 10-15 weeks of gestation, maternal age between 18 and 35 years, no prior history of diabetes mellitus or gestational diabetes, willingness to provide informed written consent were included.

Exclusion criteria

Patients with pre-existing diabetes mellitus or GDM diagnosed at booking, family history of diabetes mellitus, BMI >35 kg/m², use of medications affecting glucose or thyroid metabolism, presence of chronic systemic diseases, fetal anomalies, and maternal age <18 or >35 years were excluded.

Data collection procedure

Data were collected using a pre-designed semi-structured questionnaire and checklist. Eligible participants were recruited through purposive convenience sampling after ethical approval. Following informed consent, socio-demographic data, medical and obstetric history were recorded. Anthropometric measurements, including height, weight and blood pressure, were obtained using standardized procedures. Gestational age was confirmed by early ultrasonography.

At 10-15 weeks of gestation, fasting blood glucose and 2-hour post-75 g oral glucose levels were measured. Additionally, 3 ml of maternal venous blood was collected for glycosylated fibronectin estimation. Serum samples were separated by centrifugation and stored at -20°C to -80°C until analysis. Glycosylated fibronectin concentration was measured using enzyme-linked immunosorbent assay (ELISA) with commercially available kits, following manufacturer instructions, using the Siemens Access Immunoassay Analyzer (SMT-680 version).

Participants were followed throughout pregnancy, with oral glucose tolerance tests performed at 24-28 weeks and repeated at 34-36 weeks if results were normal. Diagnosis of GDM was based on the WHO criteria. Women diagnosed with GDM received closer follow-up according to institutional protocols.

Ethical considerations

Ethical approval was obtained from the Ethical Review Committee of Dhaka Medical College Hospital. Written informed consent was secured from all participants. Confidentiality of participant data was strictly maintained.

Statistical analysis

Data were analyzed using SPSS version 23. Descriptive statistics were expressed as mean ± standard deviation or frequency and percentage. Chi-square tests, Student's t-test and ANOVA were applied as appropriate. A

glycosylated fibronectin cut-off ≥145.0 µg/ml was considered positive. A p-value <0.05 was regarded as statistically significant.

RESULTS

Table 1 presents the baseline socio-demographic and obstetric characteristics of the 95 participants. The majority of women were aged between 21 and 30 years (66.3%), followed by those aged ≤20 years (23.2%). Most participants were overweight (75.8%), while 23.2% had normal BMI. Nearly half of the women had secondary or higher education (47.4%) and the majority were housewives (88.4%). Regarding socioeconomic status, most belonged to the middle-income group (60.0%). In terms of parity, primiparous women constituted the largest group (43.2%), followed by multiparous (30.5%) and nulliparous women (26.3%).

Table 1: Demographic characteristics of the study patients.

Variables		Number of patients	Percentage
Age (years)	≤20	22	23.2
	21-30	63	66.3
	>30	10	10.5
BMI	Underweight (<18.5 kg/m^2)	1	1.1
	Normal (18.5-24.9 kg/m^2)	22	23.2
	Overweight (≥25 kg/m^2)	72	75.8
Educational status	Illiterate	1	1.1
	Only can sign her name	7	7.4
	Primary	42	44.2
	Secondary and above	45	47.4
Occupational status	Housewife	84	88.4
	Working	11	11.6
Socio economic status	Lower	20	21.1
	Middle	57	60.0
	Upper	18	18.9
Parity	Nulliparous	25	26.3
	Primiparous	41	43.2
	Multiparous	29	30.5

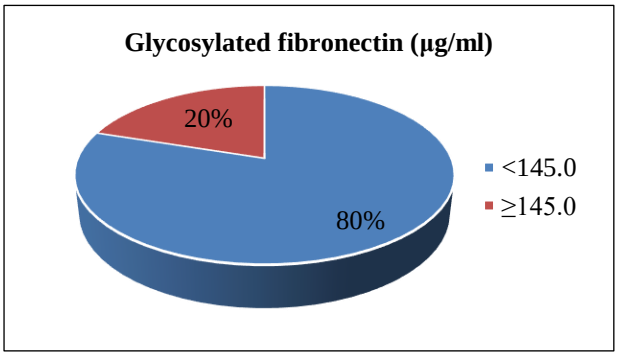

Figure 1: Distribution of glycosylated fibronectin level in the study population.

Figure 1 illustrates the overall distribution pattern of maternal serum glycosylated fibronectin concentrations measured between 10 and 15 weeks of gestation. The values show a wide range, indicating inter-individual variability within the study population.

Table 2 describes the mean serum glycosylated fibronectin levels according to age, parity and BMI categories. Mean glycosylated fibronectin levels increased with advancing age, with the highest mean observed among women aged >30 years (165.2±101.6 µg/ml), though the difference was not statistically significant (p=0.219). No significant variation was observed across parity groups (p=0.888). Similarly, mean glycosylated fibronectin levels did not differ significantly across BMI categories (p=0.739).

Table 3 compares maternal characteristics between women with glycosylated fibronectin levels <145.0 µg/ml and ≥145.0 µg/ml. Most participants (80.0%) had levels below 145.0 µg/ml. Age, parity and BMI category distributions were comparable between the two groups, with no statistically significant differences observed. However, the mean BMI was significantly higher among women with glycosylated fibronectin ≥145.0 µg/ml compared to those with lower levels (27.14±1.40 vs. 25.74±1.95 kg/m²; p=0.01).

Figure 2 depicts the proportion of women who developed GDM during follow-up compared with those who did not. A minority of participants were diagnosed with GDM during pregnancy.

Table 4 compares glycosylated fibronectin levels between women who developed GDM and those who did not. Among women with glycosylated fibronectin ≥145.0 µg/ml, 83.3% developed GDM, whereas only 16.7% of

GDM cases were observed among those with lower levels. Mean glycosylated fibronectin concentration was significantly higher in the GDM group compared to the non-GDM group (226.7 ± 73.3 vs. 114.2 ± 57.9 µg/ml; p<0.001).

Table 2: Mean variation of glycosylated fibronectin among the study population.

Variables		Number	Glycosylated fibronectin (µg/ml) Mean±SD	P value
Age (years)	≤20	22	122.7±68.9	0.219
	21-30	63	124.6±64.6	
	>30	10	165.2±101.6	
Parity	Nulliparous	25	124.5±73.1	0.888
	Primiparous	41	127.2±65.3	
	Multiparous	29	133.6±77.2	
BMI	Underweight (<18.5 kg/m^2)	1	76.0±0.0	0.739
	Normal (18.5-24.9 kg/m^2)	22	132.1±71.7	
	Overweight (≥25 kg/m^2)	72	128.0±70.8	

Table 3: Relationship of maternal factors with glycosylated fibronectin (µg/ml) level between <145.0 and ≥145.0 µg/ml.

Variables		Glycosylated fibronectin (µg/ml)				P value
		<145.0 (n=76)		≥145.0 (n=19)		
		Number	Percent	Number	Percent	
Age (years)	≤20	18	23.68	4	21.05	0.7
	21-30	51	67.11	12	63.16	
	>30	7	9.21	3	15.79	
Parity	Nulliparous	21	27.63	4	21.05	0.83
	Primiparous	32	42.11	9	47.37	
	Multiparous	23	30.26	6	31.58	
BMI	Underweight (<18.5 kg/m^2)	1	1.32	0	0	0.84
	Normal (18.5-24.9 kg/m^2)	18	23.68	4	21.05	
	Overweight (≥25 kg/m^2)	57	75	15	78.95	
	Mean BMI (kg/m^2)	25.74±1.95		27.14±14		0.01

Table 4: Comparison of glycosylated fibronectin among GDM and Non GDM women.

GDM	Number	Glycosylated fibronectin (µg/ml)		Mean±SD	P value
		<145.0 (n=76)	≥145.0 (n=19)		
GDM	12	02 (16.7)	10 (83.3)	226.7±73.3	<0.001
Non GDM	83	74 (89.2)	09 (10.8)	114.2±57.9	

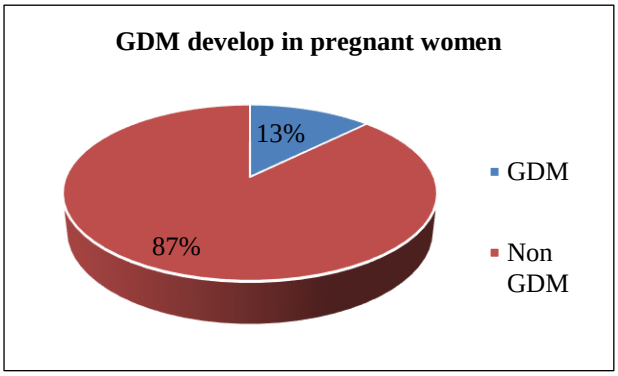

Figure 2: Distribution of GDM in the study population.

DISCUSSION

The present prospective cohort study demonstrates that elevated first-trimester maternal serum glycosylated fibronectin is strongly associated with the subsequent development of gestational diabetes mellitus (GDM). Women with glycosylated fibronectin levels ≥145.0 µg/ml showed a markedly higher incidence of GDM compared to those below this threshold, with significantly higher mean concentrations observed among GDM cases. These findings support the potential clinical utility of glycosylated fibronectin as an early predictive biomarker for GDM.

Early metabolic alterations precede the clinical diagnosis of GDM, reflecting progressive insulin resistance,

placental dysfunction and inflammatory activation beginning in early gestation. Plows et al described the complex pathophysiology of GDM as a convergence of impaired β-cell adaptation and exaggerated insulin resistance mediated by placental hormones and inflammatory pathways.[9] The observed elevation of glycosylated fibronectin in early pregnancy may reflect these early pathophysiological changes, particularly altered extracellular matrix remodeling and endothelial dysfunction.

Räsänen et al were among the first to report that glycosylated fibronectin measured in the first trimester could predict GDM with high accuracy, proposing a similar cut-off value to that used in the present study.[16] Subsequent validation by Alanen et al reinforced its predictive value in a large population-based cohort, demonstrating significantly higher glycosylated fibronectin levels in women who later developed GDM.[17] The current findings are consistent with these studies and extend their applicability to a South Asian population, which has distinct metabolic risk profiles.

The strong association between glycosylated fibronectin ≥145.0 µg/ml and GDM observed in this study aligns with proteomic evidence indicating dysregulated fibronectin glycosylation in pregnancies complicated by metabolic disorders. Nagalla et al highlighted glycosylated fibronectin as a promising serum biomarker reflecting early placental maladaptation and systemic insulin resistance.[19] Similarly, Zhao et al identified fibronectin-related peptides among early pregnancy biomarkers predictive of GDM using quantitative proteomics.[21]

Unlike several conventional clinical risk factors, glycosylated fibronectin demonstrated predictive value independent of maternal age, parity and BMI categories in this cohort. Although the mean BMI was significantly higher in women with elevated glycosylated fibronectin levels, categorical BMI distribution did not differ significantly between groups. This suggests that glycosylated fibronectin may capture metabolic risk beyond anthropometric measures alone. Shah et al previously demonstrated that BMI-based risk stratification for GDM varies considerably across populations, underscoring the need for biomarker-based approaches.[22]

Current screening strategies relying on OGTT at 24-28 weeks may delay diagnosis and miss opportunities for early intervention. Huhn et al emphasized the clinical value of early pregnancy biomarkers in enabling preventive strategies before irreversible metabolic derangements occur.[18] Early identification of high-risk women could facilitate targeted lifestyle modification, closer monitoring and timely pharmacological intervention, potentially reducing maternal and neonatal complications.

The findings of this study are particularly relevant in the context of Bangladesh, where GDM prevalence is increasing and healthcare resources are constrained. Jesmin et al reported significant underdiagnosis of GDM due to limited screening coverage.[5] A reliable first-trimester biomarker such as glycosylated fibronectin could improve risk stratification and optimize resource allocation by identifying women who would benefit most from intensified surveillance.

Overall, the present findings corroborate growing evidence that glycosylated fibronectin is a biologically plausible and clinically meaningful early marker for GDM. Integration of this biomarker into antenatal screening protocols may enhance early risk prediction, particularly in high-risk populations.

This study has few limitations. This study was conducted at a single tertiary center with a modest sample size.

CONCLUSION

First-trimester maternal serum glycosylated fibronectin demonstrates strong predictive value for the development of gestational diabetes mellitus. A cut-off level of ≥145.0 µg/ml was significantly associated with GDM occurrence, highlighting its potential role as an early screening biomarker. Incorporation of glycosylated fibronectin into antenatal assessment may enable earlier risk stratification and timely preventive interventions, particularly in high-risk populations.

Recommendations

Multicenter studies with larger, diverse populations are recommended to validate optimal cut-off values and assess cost-effectiveness before routine clinical implementation.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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