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Original Research

Serum Periostin Levels as a Predictor of Gestational Diabetes Mellitus

Emine Ahu Koc[1], Zehra Yılmaz[2], Samettin Celik[3], Sakine Merve Aydın[3], Mevlude Alpaslan Arar[4], Neset Gumusburun[5,*]

[1]Department of Obstetrics and Gynaecology, Perinatology Unit, Giresun University, 28200 Giresun, Turkiye
[2]Department of Obstetrics and Gynecology, Private Practice, 55200 Samsun, Turkiye
[3]Department of Obstetrics and Gynecology, Faculty of Medicine, Samsun University, Samsun Training and Research Hospital, 55090 Samsun, Turkiye
[4]Department of Nursing, Samsun Provincial Health Directorate, 55080 Samsun, Turkiye
[5]Department of Obstetrics and Gynecology, Istanbul Aydın University, 34295 Istanbul, Turkiye
*Correspondence: gumusburun@outlook.com (Neset Gumusburun)

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Abstract

Background: Gestational diabetes mellitus (GDM) is a common pregnancy complication associated with adverse maternal and neonatal outcomes. The identification of novel biomarkers for GDM remains an important clinical objective. The aim of this study was to investigate whether maternal serum periostin levels measured between 24 and 28 weeks of gestation could serve as a biomarker for the diagnosis of GDM and to evaluate their association with maternal and neonatal outcomes. **Methods:** This case-control study was conducted at Samsun Training and Research Hospital between January 2024 and February 2025. Serum periostin levels were measured by enzyme-linked immunosorbent assay (ELISA). **Results:** Serum periostin levels were significantly higher in the GDM group than in the control group (101.4 (53.6) vs. 34.6 (23.9) ng/mL, $p < 0.001$). Correlation analysis revealed that serum periostin levels were positively correlated with fasting glucose ($r = 0.453$, $p < 0.001$), 1-hour oral glucose tolerance test (OGTT) ($r = 0.525$, $p < 0.001$), 2-hour OGTT ($r = 0.481$, $p < 0.001$), maternal body mass index (BMI) ($r = 0.750$, $p < 0.001$), and fetal birth weight ($r = 0.351$, $p < 0.001$). Receiver operating characteristic (ROC) curve analysis demonstrated excellent diagnostic performance for serum periostin (area under the curve [AUC] = 0.932, 95% confidence interval [CI]: 0.899–0.966, $p < 0.001$). The multivariable model showed even higher diagnostic accuracy (AUC = 0.976, 95% CI: 0.957–0.994, $p < 0.001$). **Conclusions:** Maternal serum periostin levels are significantly associated with the presence of GDM and adverse perinatal outcomes. These findings suggest that periostin may represent a potentially useful biomarker associated with GDM; however, its role in screening or prediction requires further prospective validation.

Keywords: gestational diabetes mellitus; periostin; biomarker; pregnancy; second trimester

1. Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance that develops during pregnancy or is first recognized during pregnancy [1]. Its pathogenesis involves insulin resistance and beta cell dysfunction, which are further exacerbated by the proinflammatory and hormonal changes associated with pregnancy [2,3]. GDM affects approximately 14% of pregnancies worldwide; however, prevalence rates vary according to population characteristics and diagnostic criteria [4]. Factors such as advanced maternal age, obesity and ethnicity play a role in the increasing prevalence of GDM [5,6,7]. GDM is a major public health concern not only due to its increasing prevalence but also due to its association with maternal and foetal complications, including macrosomia, birth trauma, shoulder dystocia, and preeclampsia. Despite its increasing clinical importance, no universally accepted gold standard screening test for GDM exists [8,9]. Various organizations propose different screening strategies, leading to variations in clinical practice worldwide. The International Association of Diabetes and Pregnancy Study Groups (IADPSG) and the World Health Organisation (WHO) recommend a single-step approach involving a 75 g oral glucose tolerance test (OGTT), whereas the American College of Obstetricians and Gynecologists (ACOG) recommends a two-step protocol consisting of a 50 g glucose challenge test followed by a 100 g OGTT for diagnostic purposes [2,10,11]. These differences contribute to inconsistencies in diagnosis and reported prevalence rates, thereby complicating comparative research and public health policies. Therefore, there is a continuing need for a standardized screening strategy that balances sensitivity and specificity and can be applied consistently across diverse clinical settings [12,13,14].

Periostin is a matrix cell protein encoded by the POSTN gene, notable for its role in metabolic and inflammatory pathways [15]. It is expressed in tissues such as the heart, lungs, bone, blood vessels and skin, and is involved in extracellular matrix remodeling, wound healing, fibrosis, and inflammatory responses [16]. A recent study has shown that periostin contributes to obesity-related inflammation and insulin resistance via the PI3K/Akt and TGF-beta signalling pathways [17]. Experimental models have demonstrated that periostin expression increases in adipose and hepatic tissues under metabolic stress conditions [18].

Furthermore, periostin has been reported to disrupt insulin signalling by promoting proinflammatory cytokine release and inducing matrix stiffening [19,20].

Insulin sensitivity decreases physiologically during pregnancy, making the potential effects of periostin particularly relevant in this context. Recent clinical studies have demonstrated a significant association between serum periostin levels and GDM [21,22]. Due to its role in insulin resistance and inflammation, periostin is being evaluated as a potential biomarker for the early detection and risk classification of GDM. In this study, we investigated the association between serum periostin levels and GDM, evaluated their diagnostic performance, and examined their relationship with GDM-related complications.

2. Materials and Methods

2.1 Study Design

This observational case-control study was performed at the Department of Obstetrics and Gynecology, Samsun Training and Research Hospital, between January 2024 and February 2025. Ethical approval was obtained from the Samsun University Clinical Research Ethics Committee (Approval No.: SÜKAEK2023 20/20; November 1, 2023), and written informed consent was obtained from all participants before enrollment. All study procedures were performed in accordance with the ethical principles of the Declaration of Helsinki. The primary objective was to investigate the association between second-trimester maternal serum periostin concentrations and the presence of GDM.

2.2 Participants

Eligible participants were women aged 18–45 years with singleton pregnancies who underwent routine screening with a 75 g OGTT between 24 + 0 and 28 + 6 weeks of gestation. Participants were classified into either the GDM group or the healthy control group according to their OGTT results. GDM was diagnosed according to the IADPSG recommendations [23]. Following an overnight fast of at least 8 hours, a fasting venous blood sample was collected. Participants then ingested a 75 g glucose solution within 5 minutes, and additional venous blood samples were collected at 1 and 2 hours after glucose administration. GDM was diagnosed when one or more of the following plasma glucose thresholds were met or exceeded: fasting glucose ≥92 mg/dL, 1-hour glucose ≥180 mg/dL, or 2-hour glucose ≥153 mg/dL. Gestational age was determined primarily from the first day of the last menstrual period and was confirmed by first-trimester ultrasonography when menstrual dating was unavailable or considered unreliable.

Women were excluded if they had preexisting diabetes mellitus, chronic hypertension, autoimmune or inflammatory disorders, renal, hepatic, or cardiovascular disease, multiple gestation, fetal structural anomalies detected by ultrasonography, smoking or substance use during pregnancy, treatment with medications known to affect glucose metabolism, or any systemic condition considered capable of altering maternal or fetal metabolic status.

A total of 190 pregnant women were initially assessed for eligibility. Of these, 15 women were excluded: 3 due to preexisting diabetes mellitus, 2 due to chronic hypertension, 2 due to autoimmune or inflammatory disorders, 1 due to renal, hepatic, or cardiovascular disease, 2 due to multiple gestation, 1 due to fetal structural anomalies, 3 due to smoking or substance use during pregnancy, and 1 due to the use of medications known to affect glucose metabolism. No participants were excluded because of other systemic conditions considered capable of altering maternal or fetal metabolic status. Finally, 175 women were included in the study, comprising 86 women with GDM and 89 healthy controls.

2.3 Data Collection

Maternal demographic characteristics, obstetric history, biochemical measurements, and neonatal outcomes were prospectively recorded for all participants. Collected variables included maternal age, gravidity, parity, prepregnancy body mass index (BMI), gestational age at delivery, mode of delivery (vaginal birth or cesarean section), neonatal birth weight, fasting and post-load glucose concentrations measured during the 75 g OGTT (0-, 1-, and 2-hour values), insulin therapy during pregnancy, serum periostin concentration, 1- and 5-minute Apgar scores, the occurrence of meconium-stained amniotic fluid (MSAF), neonatal intensive care unit (NICU) admission, and the requirement for neonatal intubation.

2.4 Sample Collection and Laboratory Analysis

Additionally, a 5 mL maternal venous blood sample was collected during the OGTT. Blood samples were collected into serum separator tubes, allowed to stand at room temperature for 30 minutes, and centrifuged at 3000 rpm for 10 minutes. The serum was aliquoted and stored at –80 °C until analysis. Serum periostin levels were measured using a commercial Human Periostin enzyme-linked immunosorbent assay (ELISA) kit (BT Lab, Cat. No. E3226Hu, Shanghai, China) according to the manufacturer's instructions. The intra-assay and inter-assay coefficients of variation reported by the manufacturer were within acceptable limits, supporting the reliability and reproducibility of the measurements. All measurements were performed using a standardized ELISA protocol, minimizing operator-dependent variability.

2.5 Statistical Analysis

Prior to the study initiation, a sample size analysis was performed using G*Power version 3.1.9.7 (Heinrich Heine University Düsseldorf, Düsseldorf, Germany). The analysis was based on an effect size of Cohen's d = 0.5, a two-tailed significance level of 5% ($\alpha = 0.05$) and a statistical power of 90% ($1-\beta = 0.90$). The analysis determined

that at least 85 participants were required in each group. Due to the limited availability of prior data on periostin in GDM populations, a conventional medium effect size was assumed. Statistical analyses were conducted using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as the median (interquartile range [IQR]), whereas categorical variables were presented as frequency (n, %). The normality of the continuous variables was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Categorical variables were compared using the chi-squared test or Fisher's exact test, as appropriate, whereas continuous variables were compared using the Mann–Whitney U test. The relationship between serum periostin levels and continuous variables was assessed using Spearman's correlation analysis. Univariate and multivariate logistic regression analyses were performed to identify factors independently associated with GDM. Variables included in the multivariable model, such as maternal age, maternal BMI, gravidity, parity, and serum periostin level, were selected based on their established clinical relevance and/or statistical significance in the univariate analysis to control for potential confounding effects. The diagnostic performance of serum periostin levels and the multivariate logistic regression model was assessed using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC), 95% confidence interval (CI), optimal cutoff value determined using the Youden index, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. A two-tailed *p*-value of <0.05 was considered statistically significant. All ROC analyses, including cutoff determination, sensitivity, specificity, PPV, and NPV calculations, were performed on the same study population. No internal or external validation (e.g., cross-validation or bootstrapping) was applied.

3. Results

A total of 175 pregnant women were included in the study, comprising 86 women diagnosed with GDM and 89 women with normal glucose tolerance. Baseline maternal characteristics, perinatal outcomes, and biochemical parameters of the study population are summarized in Table 1. No statistically significant differences were observed between the groups in terms of maternal age and gestational age at delivery ($p = 0.544$ and $p = 0.989$, respectively). However, women in the GDM group exhibited significantly higher BMI, gravidity, and parity compared with the control group (all $p \leq 0.001$). Fetal birth weight was significantly greater in the GDM group ($p < 0.001$). Similarly, all glucose measurements obtained during the OGTT (fasting, 1-hour, and 2-hour values) were significantly elevated in patients with GDM (all $p < 0.001$). Regarding neonatal outcomes, the 5-minute Apgar score was slightly but significantly lower in the GDM group ($p = 0.037$), whereas no significant difference was observed for the 1-minute Apgar score ($p = 0.100$). Serum periostin levels were significantly higher in the GDM group than in the control group (101.4 (53.6) vs. 34.6 (23.9) ng/mL, $p < 0.001$), indicating a strong association between periostin and gestational glucose dysregulation. Regarding obstetric outcomes, the cesarean section rate was significantly higher in the GDM group than in the control group (50.0% vs. 15.7%, $p < 0.001$). Additionally, NICU admission was more frequent among infants born to mothers with GDM (20.9% vs. 7.9%, $p = 0.024$). No statistically significant differences were detected between the groups regarding the rates of MSAF ($p = 0.108$) or neonatal intubation ($p = 0.188$).

In Table 2, serum periostin levels were evaluated according to obstetric and neonatal outcomes. Women who underwent cesarean delivery exhibited significantly higher serum periostin levels compared with those who delivered vaginally (85.2 (71.3) ng/mL vs. 49.4 (61.5) ng/mL, $p < 0.001$). Similarly, cases with MSAF demonstrated markedly increased periostin levels compared with those without meconium staining (143.4 (56.5) ng/mL vs. 56.0 (61.4) ng/mL, $p < 0.001$). Serum periostin levels were also significantly elevated in neonates requiring intubation compared with those who did not require intubation (140.6 (56.9) ng/mL vs. 56.0 (62.0) ng/mL, $p < 0.001$). Furthermore, periostin levels were significantly higher in cases requiring NICU admission than those without NICU admission (135.3 (54.0) ng/mL vs. 50.5 (53.6) ng/mL, $p < 0.001$).

Spearman correlation analysis demonstrated that serum periostin levels were positively correlated with fasting blood glucose, 1-hour and 2-hour OGTT glucose levels, maternal BMI, and fetal birth weight, with all correlations reaching statistical significance ($p < 0.001$). The strongest correlation was observed between serum periostin levels and maternal BMI (r = 0.750), followed by correlations with 1-hour OGTT glucose (r = 0.525), 2-hour OGTT glucose (r = 0.481), fasting blood glucose (r = 0.453), and fetal birth weight (r = 0.351), as summarized in Table 3.

In the univariate logistic regression analysis, maternal BMI (odds ratio [OR] = 1.121, 95% CI: 1.061–1.185, $p < 0.001$), gravidity (OR = 1.355, 95% CI: 1.102–1.665, $p = 0.004$), parity (OR = 1.727, 95% CI: 1.298–2.324, $p < 0.001$), and serum periostin levels (OR = 1.069, 95% CI: 1.049–1.088, $p < 0.001$) were all significantly associated with the presence of GDM. In contrast, maternal age was not identified as a significant predictor (OR = 1.015, 95% CI: 0.960–1.073, $p = 0.605$).

When these variables were entered into a multivariate logistic regression model, only maternal BMI (adjusted OR = 0.556, 95% CI: 0.435–0.711, $p < 0.001$) and serum periostin levels (adjusted OR = 1.204, 95% CI: 1.126–1.286, $p < 0.001$) remained independently associated with GDM. Maternal age ($p = 0.836$), gravidity ($p = 0.477$), and parity ($p = 0.168$) were no longer statistically significant after adjustment.

Overall, the logistic regression model was statistically significant (Omnibus test, $p < 0.001$) and demonstrated a

Table 1. Maternal characteristics, perinatal and neonatal outcomes, and serum periostin levels in pregnant women with and without GDM.

		Pregnant women with GDM (n = 86)	Pregnant women without GDM (n = 89)	*p*-value
		Median (IQR)	Median (IQR)	
Maternal age (years)		31.0 (7.0)	31.0 (7.0)	0.544*
Birth weight (g)		3890.0 (500.0)	3490.0 (600.0)	**<0.001***
Maternal BMI (kg/m^2)		30.0 (7.0)	24.0 (7.5)	**<0.001***
Gestational age at birth (weeks)		38.0 (2.0)	38.0 (2.0)	0.989*
Gravidity		3.0 (2.0)	2.0 (2.0)	**0.001***
Parity		2.0 (1.0)	1.0 (2.0)	**<0.001***
Fasting blood glucose (mg/dL)		100.2 (16.40)	90.0 (7.5)	**<0.001***
OGTT 1-hour (mg/dL)		202.0 (34.6)	164.8 (35.9)	**<0.001***
OGTT 2-hour (mg/dL)		163.0 (40.0)	140.0 (37.0)	**<0.001***
APGAR Score (1 min)		9.0 (1.0)	9.0 (0.0)	0.100*
APGAR Score (5 min)		10.0 (1.0)	10.0 (0.5)	**0.037***
Serum Periostin level (ng/mL)		101.4 (53.6)	34.6 (23.9)	**<0.001***
		n (%)	n (%)	
Mode of Delivery	Cesarean section	43 (50.0)	14 (15.7)	**<0.001****
	Vaginal delivery	43 (50.0)	75 (84.3)	
Insulin treatment		9 (10.5)	0 (0.0)	**<0.001****
Meconium staining		12 (14.0)	5 (5.6)	0.108**
Neonatal intubation status		12 (14.0)	6 (6.7)	0.188**
NICU admission		18 (20.9)	7 (7.9)	**0.024****

* Mann-Whitney U test; ** Chi-square test. Data are presented as median (IQR) for continuous variables and number (n) (percentage, %) for categorical variables. Comparisons between groups were performed using the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables. A p-value < 0.05 was considered statistically significant. Bold values show $p < 0.05$. Abbreviations: BMI, body mass index; OGTT, oral glucose tolerance test; GDM, gestational diabetes mellitus; IQR, interquartile range; NICU, neonatal intensive care unit.

Table 2. Comparison of serum periostin levels according to mode of delivery and neonatal outcomes.

		Serum periostin levels (ng/mL)	*p*-value
		Median (IQR)	
Mode of delivery	Cesarean section	85.2 (71.3)	**<0.001**
	Vaginal delivery	49.4 (61.5)	
Meconium staining	Yes	143.4 (56.5)	**<0.001**
	No	56.0 (61.4)	
Insulin treatment	Yes	149.9 (11.0)	**<0.001**
	No	59.9 (63.8)	
Intubation status of newborn	Yes	140.6 (56.9)	**<0.001**
	No	56.0 (62.0)	
NICU admission	Yes	135.3 (54.0)	**<0.001**
	No	50.5 (53.6)	

Data are presented as median (IQR). Comparisons between two groups were performed using the Mann–Whitney U test. Bold p-values indicate statistical significance ($p < 0.05$).

good fit to the observed data (Hosmer–Lemeshow test, $p = 0.846$). The model also showed a high explanatory capacity, with a Nagelkerke R^2 value of 0.845. Detailed results of the univariate and multivariate logistic regression analyses are presented in Table 4.

ROC curve analysis demonstrated that serum periostin levels exhibited excellent discriminative ability for identifying GDM, with an AUC of 0.932 (95% CI: 0.899–0.966, $p < 0.001$). At the optimal cutoff value of 43.6 ng/mL, determined using the Youden index, serum periostin yielded a sensitivity of 97.7% and a specificity of 74.2%. The corresponding PPV and NPV were 84.2% and 91.0%, respectively. The diagnostic performance of the multivariate logistic regression model was higher, with an AUC of 0.976

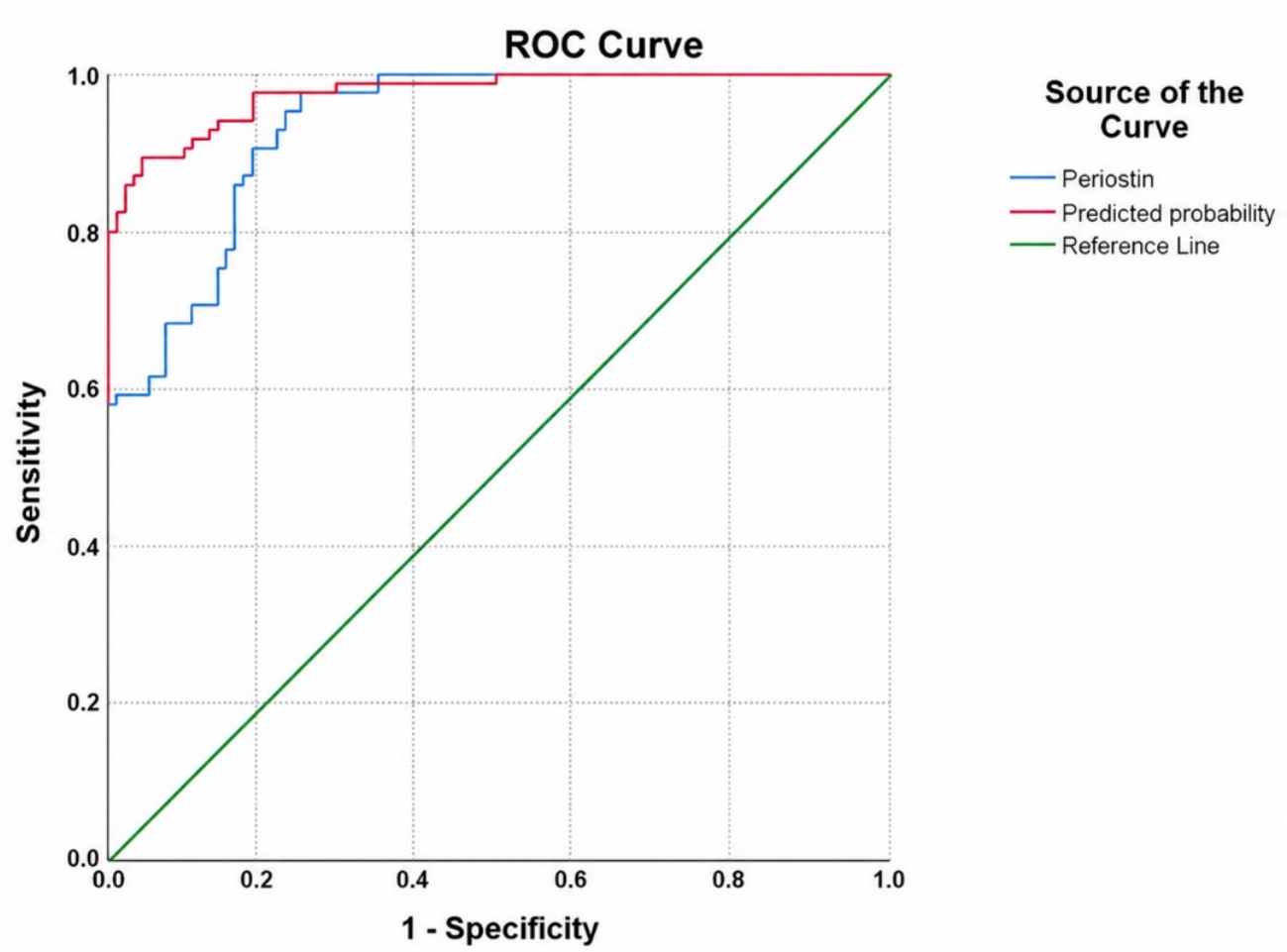

Fig. 1. ROC curves for serum periostin level and the multivariable logistic regression model in predicting GDM.

Table 3. Correlations between serum periostin levels and maternal blood glucose levels, maternal BMI, and fetal birth weight.

		Serum periostin level (ng/mL)
Fasting blood glucose	r	0.453
	p	**<0.001**
OGTT 1-hour	r	0.525
	p	**<0.001**
OGTT 2-hour	r	0.481
	p	**<0.001**
Birth weight	r	0.351
	p	**<0.001**
Maternal BMI	r	0.750
	p	**<0.001**

Data are presented as Spearman's correlation coefficient (r) and corresponding *p*-values. Bold values show $p < 0.05$.

(95% CI: 0.957–0.994, $p < 0.001$). Using a probability threshold of 0.48 for the model, sensitivity was calculated as 89.5%, specificity as 95.5%, PPV as 95.0%, and NPV as 90.0%. The detailed ROC analysis is presented in Table 5, and the corresponding ROC curves are shown in Fig. 1.

4. Discussion

This study demonstrated that serum periostin levels were significantly higher in pregnant women with GDM than in those with normal glucose tolerance and were positively correlated with maternal glycemic parameters and perinatal outcomes. Correlation analysis revealed significant positive associations between serum periostin levels and fasting glucose, 1-hour OGTT glucose, 2-hour OGTT glucose, maternal BMI, and fetal birth weight, further supporting the association with metabolic and perinatal parameters. Our findings suggest that periostin may play a role in the metabolic alterations observed in GDM and may have potential as a diagnostic biomarker. Importantly, serum periostin remained an independent predictor of GDM even after adjustment for maternal BMI and other clinical variables, supporting its potential clinical relevance. However, it should be emphasized that periostin levels were measured concurrently with the OGTT in our study. Therefore, the present study design does not allow evaluation of its predictive or screening value for the future development of GDM.

Periostin is a 90 kDa glycoprotein that plays an active role in extracellular matrix remodeling, fibrosis, and

Table 4. Univariable and multivariable logistic regression analyses identifying independent predictors of GDM.

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-value	Adjusted OR	95% CI	*p*-value
Maternal age (years)	1.015	0.960–1.073	0.605	1.013	0.900–1.139	0.836
Maternal BMI (kg/m^2)	1.121	1.061–1.185	**<0.001**	0.556	0.435–0.711	**<0.001**
Gravidity	1.355	1.102–1.665	0.004	0.688	0.245–1.932	0.477
Parity	1.727	1.298–2.324	**<0.001**	2.961	0.632–13.868	0.168
Serum periostin level (ng/mL)	1.069	1.049–1.088	**<0.001**	1.204	1.126–1.286	**<0.001**

Univariate and multivariate logistic regression analyses were performed to identify factors independently associated with GDM. Variables included in the multivariate model were maternal age, maternal BMI, gravidity, parity, and serum periostin level. The enter method was used for variable entry. Model fit was assessed using the Hosmer–Lemeshow goodness-of-fit test ($p = 0.846$), and the model was statistically significant according to the Omnibus test ($p < 0.001$), with a Nagelkerke R^2 of 0.845. Bold *p*-values indicate statistical significance ($p < 0.05$). OR, odds ratio; CI, confidence interval.

Table 5. Diagnostic performance of serum periostin levels and the multivariable logistic regression model for predicting GDM.

Marker	n (GDM/Control)	AUC (95% CI)	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	*p*-value
Serum periostin level (ng/mL)	86/89	0.932 (0.899–0.966)	43.6	97.7	74.2	84.2	91.0	**<0.001**
Multivariable model (predicted probability)	86/89	0.976 (0.957–0.994)	0.48	89.5	95.5	95.0	90.0	**<0.001**

Diagnostic performance of serum periostin level and the multivariable logistic regression model for predicting GDM. Bold *p*-values indicate statistical significance ($p < 0.05$). PPV, positive predictive value; NPV, negative predictive value; ROC, receiver operating characteristic; AUC, area under the curve.

inflammation. A recent study has shown that periostin is associated with metabolic disorders such as insulin resistance, obesity, and type 2 diabetes [15]. Given that insulin resistance and low-grade inflammation also play a central role in the GDM pathophysiology, Abbad et al. [24] suggested that periostin may act as an effective mediator in this process. In our study, the increased serum periostin levels observed in the GDM group support the possibility that this biomolecule may contribute to the pathogenesis of GDM. Furthermore, similar findings have been reported in the literature. Ji et al. [21] demonstrated that serum periostin levels were elevated in pregnant women with GDM and that this increase was correlated with inflammatory markers, such as C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α). In another experimental and clinical study, Feng et al. [25] demonstrated that increased expression of toll-like receptors (TLRs) and nuclear factor kappaB (NF-κB)-mediated inflammation in GDM contribute to insulin resistance. The same study further indicated that activation of the NF-κB pathway disrupts insulin signalling, leading to the production of proinflammatory cytokines such as TNF-α and interleukin-6 (IL-6). Therefore, the increase in periostin levels observed in our study and its relationship with glycemic parameters are consistent with the inflammatory mechanisms described in the literature. However, further mechanistic studies are required to directly demonstrate this process.

Accumulating evidence suggests that periostin plays a significant role in metabolic disorders, particularly obesity and type 2 diabetes. Experimental studies by Lu et al. [18] demonstrated that obese mice exhibit increased periostin expression in hepatic tissue, which is associated with enhanced triglyceride accumulation. Moreover, periostin was shown to impair fatty acid oxidation through downregulation of peroxisome proliferator-activated receptor alpha (PPAR-α), thereby contributing to disrupted lipid metabolism [26]. Consistent with these findings, Luo et al. [15] reported that circulating periostin levels were positively correlated with both glycemic parameters and lipid profiles in individuals with obesity and type 2 diabetes. Taken together, these observations provide a biological context for our findings, in which elevated serum periostin levels in pregnant women with GDM, together with higher BMI values, may reflect underlying metabolic dysregulation associated with obesity-related lipid disturbances. Importantly, even after adjustment for maternal BMI in the multivariable analysis, periostin remained independently associated with GDM, suggesting that its role may not be solely explained by obesity-related mechanisms but may also involve additional metabolic pathways. Another notable finding of our study is that, although BMI showed a positive association in the univariate analysis, it exhibited a negative coefficient in the multivariable model. This finding may be explained by a ‘suppression effect’, in which

a change in the direction of a coefficient occurs in multivariable logistic regression due to the strong correlation observed between BMI and serum periostin levels, or by the presence of multicollinearity. Consequently, the coefficient for BMI in the multivariate model should not be interpreted as indicating an independent biological protective effect but should be evaluated within the context of the interrelationships between the variables.

Growing evidence emphasizes the central role of inflammation in the pathophysiology of GDM, with several studies reporting elevated levels of inflammatory biomarkers in affected patients [27,28,29,30]. In this context, Ipekci et al. [31] demonstrated that serum neopterin levels were significantly increased in pregnant women with GDM and preeclampsia, suggesting a link with obesity-related chronic inflammatory processes. As neopterin reflects activation of the cellular immune response, its elevation in GDM supports the hypothesis that periostin, a matrix-associated protein involved in inflammatory pathways, may also contribute to the underlying pathophysiological processes. Consistent with this concept, our findings revealed significantly higher serum periostin levels in the GDM group than in the control group, suggesting that periostin may reflect underlying inflammatory processes. Furthermore, multivariable analysis confirmed that both serum periostin levels and maternal BMI were independently associated with GDM, even after adjustment for potential confounders. Nevertheless, findings in the literature are inconsistent. Melekoğlu et al. [32] reported increased serum periostin levels in preeclamptic pregnancies, whereas no significant elevation was observed in women with GDM. This discrepancy may suggest that periostin is more prominently involved in conditions characterized by endothelial dysfunction and vascular inflammation. In contrast, its role in GDM may be more heterogeneous and influenced by differences among study populations. Overall, these findings suggest that periostin may reflect distinct pathophysiological pathways across different pregnancy-related complications.

Our study found that serum periostin levels were higher in cases of GDM requiring insulin treatment, supporting the association between this molecule and insulin resistance and increased insulin requirements. Previous research has shown that periostin levels may correlate not only with metabolic parameters but also with the severity of treatment requirements. For example, Farhan et al. [33] reported that periostin levels in obese and type 2 diabetic individuals were significantly associated with insulin usage status. Similarly, circulating periostin levels have been shown to be positively associated with fasting insulin and insulin resistance, particularly in overweight and obese individuals [34]. As such, it is suggested that periostin may be a potential biomarker for both the diagnosis of GDM as well as for predicting the need for insulin therapy.

One of the notable findings of the present study was the relationship between elevated maternal serum periostin concentrations and adverse perinatal outcomes. GDM is well recognized to increase the risk of several neonatal complications, including MSAF, respiratory morbidity, and NICU admission [35]. Consistent with these observations, pregnancies complicated by GDM in our cohort demonstrated a higher frequency of MSAF, and serum periostin concentrations were also significantly higher in these cases. Previous studies have suggested that MSAF is closely linked to intra-amniotic inflammation and activation of both maternal and fetal immune responses [36,37]. Within this biological framework, elevated periostin levels may represent an indicator of the inflammatory and tissue-remodeling processes accompanying the intrauterine environment in GDM rather than a simple metabolic alteration. In addition, periostin may be involved in placental remodeling. Experimental and histopathological studies have demonstrated that pregnancies affected by GDM frequently exhibit placental fibrosis and extracellular matrix remodeling, which may impair maternal-fetal exchange and contribute to unfavorable neonatal outcomes [38]. Consistent with this concept, neonatal intubation and NICU admission occurred more frequently in the GDM group, whereas 5-minute Apgar scores tended to be lower in this group. Although several of these differences did not reach statistical significance, the overall pattern was consistent with higher periostin levels observed in pregnancies with less favorable neonatal outcomes. Nevertheless, these findings should be interpreted cautiously. Serum periostin levels were higher in pregnancies complicated by NICU admission, MSAF, and neonatal intubation; however, GDM itself is an established determinant of these adverse outcomes. Consequently, the observed associations may largely reflect the underlying effects of GDM rather than an independent contribution of periostin, and no causal relationship can be inferred from the present data.

Recent studies have demonstrated that periostin may be an important biomarker not only in metabolic processes but also in obstetric pathologies [39,40]. In particular, it has been reported that placental periostin expression is significantly increased in placenta accreta spectrum (PAS) disorders. It has been suggested that this increase accelerates angiogenesis by activating the Notch signalling pathway, thereby contributing to the pathological vascular formation observed in PAS and supporting trophoblast proliferation and migration. Interestingly, the fact that these effects can be reversed by inhibiting the Notch pathway suggests that periostin plays an active role in placental invasion defects [39]. In addition, studies on early pregnancy loss have shown that changes in periostin levels are closely related to embryo implantation and pregnancy continuation. Furthermore, serum periostin levels increase over time in pregnancies that result in miscarriage, whereas these levels tend to decrease in ongoing healthy pregnancies [40]. This sit-

uation suggests that periostin may also be directly associated with the embryonic implantation and early placentation stages. Taken together, these findings suggest that periostin may have potential not only as a biomarker for pregnancy outcomes, but also as a diagnostic biomarker for GDM and may contribute to its pathogenesis.

Based on our findings, periostin appears to be a potentially useful biomarker associated with GDM. However, since periostin levels were measured concurrently with the OGTT in this study, its predictive or screening utility cannot be established. Therefore, periostin should not be considered a replacement for the OGTT at this stage, and further prospective longitudinal studies are required to evaluate its potential role in screening or early prediction. Furthermore, the fact that periostin can be measured using a routine venous blood sample increases its clinical applicability. Furthermore, the association between serum periostin levels and adverse perinatal outcomes, in addition to its diagnostic potential, suggests that this molecule may also have prognostic utility.

This study has several limitations that should be acknowledged. First, its single-center design and relatively modest sample size may limit the generalizability of the findings. In addition, serum periostin concentrations were measured only once, concurrently with the 24- to 28-week OGTT; therefore, temporal changes in periostin levels during pregnancy and its predictive or screening performance before routine GDM testing could not be assessed. Another limitation is the absence of adjusted analyses evaluating the independent association between serum periostin levels and perinatal outcomes. Consequently, the observed associations may have been influenced by confounding factors, particularly the presence of GDM. Furthermore, inflammatory biomarkers such as CRP, IL-6, and TNF-α were not evaluated, precluding direct assessment of the relationship between periostin levels and systemic inflammatory activity. Subgroup analyses were also limited by the relatively small number of participants in certain categories, and these findings should therefore be interpreted with caution. Similarly, several clinically relevant obstetric outcomes, including hypertensive disorders of pregnancy, shoulder dystocia, and categorical fetal macrosomia, were not assessed, limiting a more comprehensive evaluation of GDM-related maternal and neonatal complications. Moreover, effect size estimates, such as Cohen's *d*, were not calculated, which may reduce the interpretability of the magnitude of the observed differences. Finally, given the observational nature of the study and the lack of internal or external validation of the ROC analyses (e.g., cross-validation or bootstrapping), the reported cutoff values and diagnostic performance metrics should be interpreted with caution. No causal relationship between periostin and GDM can be inferred from these findings. Despite these limitations, the prospective case-control design represents a major strength by providing novel evidence regarding the association between maternal serum periostin levels, GDM, and adverse perinatal outcomes. Future multicenter studies with larger cohorts, longitudinal periostin measurements throughout pregnancy, comprehensive inflammatory profiling, and external validation of the diagnostic models are warranted to confirm and extend these findings.

5. Conclusions

Serum periostin levels were significantly elevated in pregnant women with GDM and were correlated with key metabolic parameters and neonatal outcomes. These findings suggest that periostin could be considered a potential biomarker for identifying women at risk for GDM and related complications. Furthermore, the association between periostin levels and perinatal outcomes suggests that this molecule may have potential utility not only as a diagnostic marker but also as a prognostic biomarker. The high diagnostic accuracy demonstrated by ROC analysis is encouraging; however, further prospective validation is required before clinical implementation. Multicentre, large-scale, prospective studies are needed to validate these findings, determine the clinical utility of periostin measurement, and further elucidate its role in the pathophysiology of gestational metabolic disorders.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

EAK and NG conceived and designed the study. ZY, SC, and SMA collected the data. SC, MA and ZY performed data analysis and interpretation. NG drafted the manuscript. EAK, ZY, SC, SMA and MA critically revised the manuscript for important intellectual content. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki. The research protocol was approved by the Samsun University Clinical Research Ethics Committee (Ethics Approval Number: SUKAEK-2023 20/20), and all participants provided signed informed consent forms.

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Conflicts of Interest

The authors declare no conflicts of interest. Zehra Yılmaz is affiliated with a private practice. This affiliation did not influence the design, conduct, analysis, interpretation, or reporting of the study. The author declares that there are no financial, commercial, or other relationships that could be perceived as a potential conflict of interest in relation to this work.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG53151.

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