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Evaluating midpregnancy Gas6 levels as predictive value for gestational diabetes and birth outcomes

Gebeliğin ortasında Gas6 düzeylerinin gebelik diyabeti ve doğum sonuçları için öngörü değeri olarak değerlendirilmesi

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Abstract

Objective: This study investigated the relationship between maternal serum growth arrest-specific 6 (Gas6) levels measured in the second trimester of pregnancy and the development of gestational diabetes mellitus (GDM); it also evaluated the possible links between this biomarker and maternal and neonatal outcomes.

Materials and Methods: A total of 173 pregnant women were included in this prospective study (89 diagnosed with GDM, 84 healthy controls). Gas6 levels were measured using the ELISA method from blood samples taken during routine screening in the second trimester. The relationships between Gas6 levels and body mass index (BMI), oral glucose tolerance test results, and neonatal data were statistically analysed.

Results: Gas6 levels were significantly higher in the GDM group ($p<0.001$). A strong positive correlation was found between Gas6 and maternal BMI ($r=0.774$), and a moderate positive correlation between Gas6 and oral glucose tolerance test 1-hour glucose level ($r=0.577$). Additionally, high Gas6 levels were found to be statistically significant in association with increased birth weight and intensive care requirements.

Conclusion: Increased Gas6 levels in the second trimester may be a potential biomarker for early prediction of GDM risk and perinatal complications.

Keywords: Gas6, gestational diabetes mellitus, second trimester, biomarker

Öz

Amaç: Bu çalışma, gebeliğin ikinci trimesterinde ölçülen maternal serum büyüme durdurma-spesifik 6 (Gas6) düzeyleri ile gebelik diyabeti gelişimi arasındaki ilişkiyi araştırmış; ayrıca bu biyobelirteç ile maternal ve neonatal sonuçlar arasındaki olası bağlantıları değerlendirmiştir.

Gereç ve Yöntemler: Bu prospektif çalışmaya toplam 173 hamile kadın dahil edildi [89'u gestasyonel diabetes mellitus (GDM) tanısı almış, 84'ü sağlıklı kontrol grubu]. Gas6 düzeyleri, ikinci trimesterde rutin tarama sırasında alınan kan örneklerinden ELISA yöntemi kullanılarak ölçüldü. Gas 6 düzeyleri ile vücut kitle indeksi, oral glukoz tolerans testi sonuçları ve yenidoğan verileri arasındaki ilişkiler istatistiksel olarak analiz edildi.

Bulgular: Gas6 düzeyleri gestasyonel diyabet grubunda anlamlı olarak daha yüksekti ($p<0,001$). Gas6 ile anne vücut kitle indeksi arasında güçlü bir pozitif korelasyon ($r=0,774$) ve Gas 6 ile oral glukoz tolerans testi 1 saatlik glukoz düzeyi arasında orta derecede pozitif bir korelasyon ($r=0,577$) bulundu. Ek olarak, yüksek Gas6 düzeylerinin doğum ağırlığının artması ve yoğun bakım gereksinimi ile istatistiksel olarak anlamlı bir şekilde ilişkili olduğu bulundu. Çalışmamızda GDM grubunda ortalama yaş 30,8±4,9 yıl iken, kontrol grubunda ise 31,3±5,4 yıldı.

Sonuç: İkinci trimesterde artan Gas6 düzeyleri, gestasyonel diyabet riski ve perinatal komplikasyonların erken tahmini için potansiyel bir biyomarker olabilir.

Anahtar Kelimeler: Gas6, gestasyonel diabetes mellitus, ikinci trimester, biyobelirteç

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Introduction

Gestational diabetes mellitus (GDM) is an important metabolic disorder characterised by hyperglycaemia that develops during pregnancy and usually disappears after delivery[1]. GDM can cause complications that threaten both maternal and foetal health, including pre-eclampsia, foetal macrosomia, increased caesarean section rates, neonatal hypoglycaemia, and neonatal intensive care unit (NICU) requirements[2]. GDM diagnosis is usually made using a 75-gram oral glucose tolerance test (OGTT) administered between the 24th and 28th weeks of pregnancy[3]. However, due to certain limitations regarding applicability of this test and patient compliance, we need to identify alternative biomarkers with high sensitivity and specificity that are easy to apply for the diagnosis of GDM.

Growth arrest-specific 6 (Gas6) protein is a multifunctional glycoprotein synthesised in a vitamin K-dependent manner, and exhibits its biological effects primarily through the Axl, Mer, and Tyro3 receptor tyrosine kinases. At the cellular level, it plays key roles in proliferation, suppression of apoptosis, regulation of inflammatory processes, and cell survival[4]. The Gas6/TAM receptor axis is particularly important in the vascular system, where it plays a critical role in platelet activation, endothelial stability, and modulation of immune responses[5,6]. The biological effects of this molecule have made it a potential target not only in terms of basic cell biology, but also in the pathophysiology of many diseases.

Recent studies have shown that the Gas6 protein undergoes significant changes in diseases associated with insulin resistance, such as diabetes, obesity and metabolic syndrome[7,8]. It has been shown that dysfunction develops in endothelial cells via Axl in hyperglycaemic environments, suggesting vascular effects of the Gas6-Axl signalling pathway[9]. In addition, Gas6 levels were found to be associated with increased systemic inflammation. This condition was also linked to type 2 diabetes and its complications[10]. However, it is noteworthy that Gas6 levels may vary in individuals with type 2 diabetes depending on genetic differences, inflammatory processes, and vascular complications[10,11].

Considering the role of Gas6 in the pathophysiology of diabetes, it is thought that similar mechanisms may also be influential in the development of gestational diabetes. However, the number of studies evaluating Gas6 levels during pregnancy and establishing its relationship with GDM is quite limited. This deficiency indicates that the potential role of Gas6 in the diagnosis and prediction of GDM has not yet been sufficiently elucidated. The aim of this study is to evaluate the relationship between maternal serum Gas6 levels measured in the second trimester of pregnancy (between 15 and 20 weeks) and the development of GDM, and to elucidate the potential of this biomarker in predicting perinatal outcomes.

Materials and Methods

This study was designed as a prospective, observational study and was conducted at the Gynaecology and Obstetrics Clinic of University of Health Sciences Türkiye, Samsun Training and Research Hospital between November 2023 and May 2024. Prior to the study, approval was obtained from the Samsun University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (protocol no: SUKAEK-2023/20/1, date: 01.11.2023). All participants were provided with detailed information about the study and their written consent was obtained. The study was conducted in accordance with the ethical principles of the Helsinki Declaration. Pregnant women who applied for the triple screening test between the 15th and 20th weeks of pregnancy and underwent the OGTT between the 24th and 28th weeks were included in the study. Subsequently, the births of these pregnant women took place at the same hospital. As a result, two groups were formed: those diagnosed with GDM (patients) and healthy pregnant women (controls).

The study included healthy pregnant women aged 18-45 years with a single pregnancy, diagnosed with GDM or without systemic disease, while those with multiple pregnancies, foetal structural anomalies, pre-pregnancy hypertension, renal failure, pre-gestational diabetes and chronic disease, and those under 18 or over 45 years of age were excluded.

Gas6 levels were measured from blood samples taken from pregnant women included in the study during the triple screening test between the 15th and 20th weeks of pregnancy. Subsequently, a standard 75-gram (g) OGTT was administered between the 24th and 28th weeks, and the glucose values at 0, 1, and 2 hours were recorded. Additionally, maternal body mass index (BMI), gestational age, gravida, parity, mode of delivery, newborn birth weight, Apgar scores (at 1 and 5 minutes), the need for neonatal intubation, the presence of meconium, and admission to the NICU were monitored postpartum and evaluated as part of the analysis.

GDM diagnosis was made based on the results of a 75 g OGTT performed between the 24th and 28th weeks of pregnancy. During the test, fasting, 1-hour, and 2-hour serum glucose levels were evaluated using the following threshold values: ≥92 mg/dL, ≥180 mg/dL, and ≥153 mg/dL, respectively. If any of these threshold values were exceeded, a diagnosis of GDM was made in accordance with the recommendations of the International Association of Diabetes and Pregnancy Study Groups[12].

Blood Sampling and Analysis Method

In the second trimester, additional serum samples taken during the triple screening test were collected in yellow-capped tubes in the biochemistry laboratory and then centrifuged at 4000 × g for 10 minutes to separate the serum fraction. The serum samples obtained were stored at -80 °C until the day of analysis. Gas6 levels were measured using a double antibody sandwich method with a human Gas6 ELISA kit, branded BT Lab Bioassay Technology Laboratory (Cat No. E3257Hu, Shanghai, China). Measurements were performed at 450 nm wavelength using a TECAN brand microtiter reader. The sensitivity limit of the test was 0.13 ng/mL, and the dynamic range was 0.3-90 ng/mL. Values were recorded in ng/mL. Samples exceeding

the measurement range were reanalysed after dilution when necessary.

Statistical Analysis

Statistical analyses were performed using SPSS 25.0 software. The distribution of numerical variables was evaluated using the Kolmogorov-Smirnov test, and appropriate tests were selected in accordance with the normality assumption. Parameters showing a normal distribution were expressed as mean ± standard deviation; those not normally distributed were expressed as median (minimum-maximum). For intergroup comparisons, the independent samples t-test was used for normally distributed data, the Mann-Whitney U test for non-normally distributed data, and the chi-square test for categorical data. The relationship between Gas6 levels and maternal BMI, OGTT results, birth weight, and other parameters was evaluated using Spearman's correlation analysis. The diagnostic accuracy of Gas6 levels in GDM diagnosis was analysed using the receiver operating characteristic (ROC) curve. The area under the curve (AUC), cut-off value, sensitivity, specificity, and positive and negative predictive values were calculated. A significance level of $p<0.05$ was accepted for all statistical tests. A post-hoc power analysis (G*Power 3.1.9.7) for a two-tailed independentsamples t-test based on the observed GAS6 means and standard deviations yielded a pooled standard deviation of 18.61 and an effect size of Cohen's d=1.89. At $\alpha=0.05$, the achieved power ($1-\beta$) was >0.999, indicating a highly powered study.

Results

A total of 198 pregnant women were initially assessed for eligibility in the study, and 25 were excluded based on predefined criteria (Figure 1). The inclusion and exclusion process of the study population is summarised in Figure 1. Ultimately, a total of 173 pregnant women were evaluated in this study; 89 of them were diagnosed with GDM, and 84 formed the healthy control group. Data on the demographic, clinical, and laboratory characteristics of the participants are presented in Table 1. No significant differences were found between the groups in terms of maternal age (p=0.521), gestational age (p=0.658), gravida (p=0.412), and parity (p=0.119).

The maternal BMI was significantly higher in the GDM group (GDM: 31.9±6.1; control: 25.4±5.6; p<0.001). Neonatal birth weight was measured as 3903.9±395.7 grams in the GDM group and 3518.8±416.6 grams in the control group. The difference between the two groups was found to be statistically significant (p<0.001).

Fasting blood glucose levels were 102.2±21.9 mg/dL in the GDM group and 86.1±5.6 mg/dL in the control group (p<0.001). The 1-hour glucose value in the OGTT was 204.3±36.6 mg/dL in the GDM group and 157.2±22.4 mg/dL in the control group (p<0.001). The 2-hour glucose value in the OGTT was 164.1±49.8 mg/dL in the GDM group and 129.0±16.3 mg/dL in the control group; significant differences were found in both parameters (p<0.001).

The Apgar scores of newborns in the GDM group were also lower than those in the control group. The 1-minute Apgar score was 8.3±1.0 in the GDM group and 8.7±0.7 in the control group (p<0.001); the 5-minute Apgar score was 9.2±1.1 and 9.7±0.8, respectively (p<0.001).

Maternal serum Gas6 levels were significantly higher in the GDM group (GDM: 53.0±21.6 ng/mL; control: 17.8±14.8 ng/mL; p<0.001).

According to the results of correlation analysis, a strong positive correlation was found between serum Gas6 levels and maternal BMI (r=0.774; p<0.001). There was a moderate correlation between OGTT 1-hour glucose value and maternal BMI (r=0.577; p<0.001), OGTT 2-hour glucose value (r=0.451; p=0.001), fasting blood sugar (r=0.414; p<0.001) and birth weight (r=0.398; p<0.001). In addition, obstetric and neonatal outcomes were compared between the groups, and these results are summarised in Table 2.

The results of the ROC analysis performed to evaluate diagnostic performance are summarized in Figure 1 and Table 3. Gas6 levels were found to be highly predictive of GDM diagnosis, with an AUC value of 0.94 (95% confidence interval: 0.90-

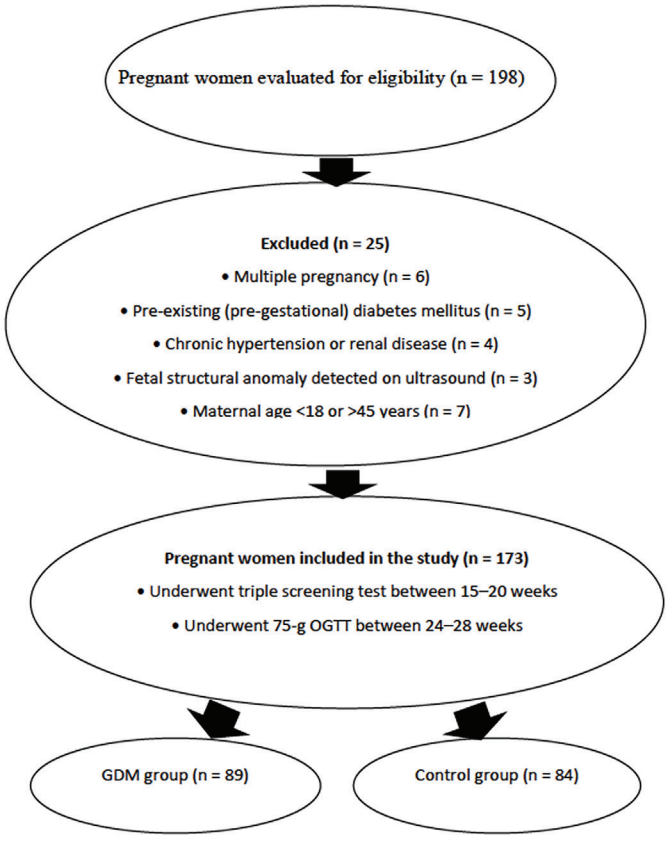

Figure 1. Flowchart of study population selection

GDM: Gestational diabetes mellitus

Table 1. Demographic, laboratory, and clinical data of patients

	Presence of gestational diabetes				p-valueβ
	Yes (n=89)		No (n=84)		
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
Maternal age (years)	30.8±4.9	31.0 (20-43)	31.3±5.4	31.0 (20-43)	0.521
Neonatal birth weight (g)	3903.9±395.7	3890.0 (3000-5100)	3518.8±416.6	3450.0 (2700-4500)	**<0.001**
Maternal BMI	31.9±6.1	30.0 (21-44)	25.4±5.6	24.0 (19-42)	**<0.001**
Gestational age (weeks)	37.8±1.5	38.0 (35-40)	37.9±1.4	38.0 (35-40)	0.658
Gravida	2.5±1.4	2.0 (1-6)	2.3±1.4	2.0 (1-7)	0.412
Parity	1.2±1.0	1.0 (0-4)	0.9±1.1	1.0 (0-4)	0.119
Fasting blood glucose (mg/dL)	102.2±21.9	98.0 (74.3-176.1)	86.1±5.6	89.8 (72.9-91.0)	**<0.001**
OGTT 1 (1-hour glucose tolerance Test) (mg/dL)	204.3±36.6	199.1 (126.4-339.4)	157.2±22.4	165.4 (101.6-179.0)	**<0.001**
OGTT 2 (2-hour glucose tolerance test) (mg/dL)	164.1±49.8	156.6 (84.1-378.8)	129.0±16.3	132.2 (58.7-155.2)	**<0.001**
Apgar score (1st minute)	8.3±1.0	9.0 (5-9)	8.7±0.7	9.0 (6-9)	**<0.001**
Apgar score (5th minute)	9.2±1.1	10.0 (7-10)	9.7±0.8	10.0 (7-10)	**<0.001**
Gas 6 level (ng/mL)	53.0±21.6	43.5 (25.5-98.0)	17.8±14.8	14.9 (0.2-82.0)	**<0.001**

* t-test, β: Mann-Whitney U test, BMI: Body mass index, OGTT: Oral Glucose tolerance test, Gas6: Growth arrest–specific 6 protein, SD: Standard deviation, min: Minimum, max: Maximum

Table 2. Distribution between groups according to obstetric and neonatal outcomes and associated Gas6 levels

	Presence of gestational diabetes				p-value*
	Yes (n=89)		No (n=84)		
	n	%	n	%	
Mode of delivery					
Normal delivery	40	44.9	70	83.3	**<0.001**
Cesarean section	49	55.1	14	16.7	
Presence of meconium					
Yes	11	12.4	5	6	0.234
No	78	87.6	79	94	
Neonatal intubation status					
Yes	16	18	9	10.7	0.254
No	73	82	75	89.3	
Admission to neonatal intensive care unit					
Yes	29	32.6	10	11.9	**0.002**
No	60	67.4	74	88.1	

*: Chi-square test, NICU: Neonatal intensive care unit, GAS6: Growth arrest–specific 6 protein

0.98; p<0.001). The optimal cut-off value was determined to be 30.0 ng/mL, with a sensitivity of 94.4%, specificity of 85.7%, positive predictive value of 87.6%, and negative predictive value of 85.7% at this point.

Discussion

This study revealed that maternal serum Gas6 levels measured in the second trimester are strongly associated with GDM. Our findings show that Gas6 levels are significantly increased in individuals diagnosed with GDM, and also correlate with maternal BMI, OGTT results, birth weight, and neonatal outcomes.

Gas6 is a vitamin K-dependent glycoprotein that interacts with Tyro3, Axl, Mer receptors and plays a role in cell proliferation, suppression of apoptosis, modulation of inflammation, and regulation of thrombosis[13]. Zhai et al.[14] linked the Axl-Gas6 axis to metabolic disorders, reporting that plasma levels increase in conditions such as type 2 diabetes, obesity, and hypertension. Insulin resistance, inflammation and vascular dysfunction are known to play a prominent role in the pathophysiology of gestational diabetes[15]. In this context, Gas6's effects of both activating the immune response and regulating the cellular stress response through anti-apoptotic mechanisms make its association with GDM plausible. In line with these findings, the data obtained in our study also suggest that Gas6 levels may be associated with metabolic and inflammatory processes related to gestational diabetes and provide a meaningful parallel with the existing literature.

In a previous study, Varsamis et al.[15] showed that Gas6 levels were significantly higher in patients with type 2 diabetes compared to the control group, and that this increase was associated with BMI and glycemic control. Similarly, in a study conducted by Lee et al.[9], it was reported that Axl receptor expression increased in a hyperglycaemic environment and was associated with endothelial dysfunction and impaired insulin signalling. In our study, the positive correlation between Gas6 levels and both BMI and OGTT 1- and 2-hour glucose levels supports the notion that this biomarker reflects glucose intolerance[16].

One of the notable findings in our study is that Gas6 levels are associated with neonatal birth weight, Apgar scores, and NICU admission rates. In pregnancies with gestational diabetes, macrosomia, respiratory distress at birth, and high NICU admission rates are known to occur[17,18]. In the literature, it has been reported that placental growth factors and maternal metabolism play a decisive role in foetal macrosomia[19,20]. In particular, insulin-like growth factors and hormones such as placental lactogen regulate placental development and foetal growth; changes in these factors increase the risk of macrosomia. Kabaran[21] also showed that maternal nutrition, obesity, and diabetes contribute to the development of foetal macrosomia by affecting placental growth factors. Considering the effects of Gas6 on placental immunity and functions, this biomarker may be considered clinically significant not only for maternal but also for foetal outcomes. Indeed, in our study, the positive correlation found between maternal BMI and fetal birth weight in the GDM group with high Gas6 levels, indicates that Gas6 may be associated with both maternal weight gain and fetal growth processes. However, this relationship may not be causal, as increases in Gas6 levels may reflect maternal weight gain or metabolic changes associated with GDM, or they may arise secondarily to developing fetal macrosomia. Further mechanistic studies are needed to clarify this distinction. Additionally, the relationship observed in our study between high Gas6 levels and caesarean delivery may be relevant to clinical intervention decisions aimed at preventing obstetric complications that may develop due to GDM.

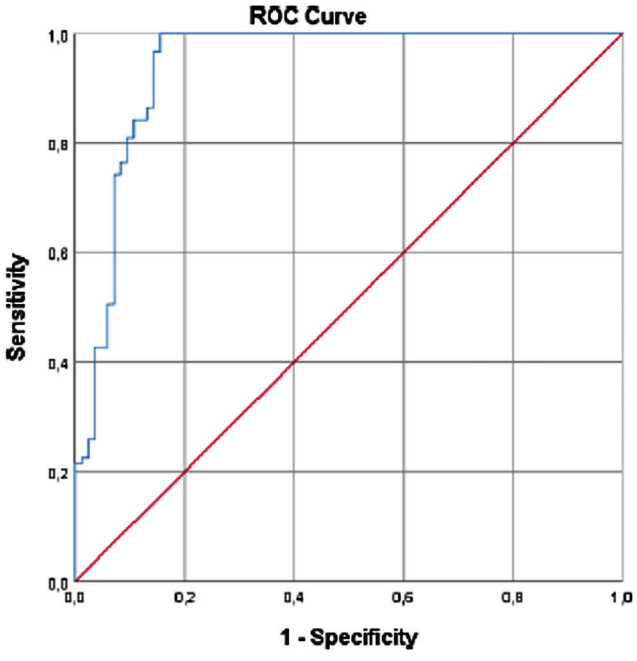

Figure 2. ROC curve for the diagnosis of gestational diabetes mellitus based on serum Gas6 levels

GAS6: Growth arrest–specific 6 protein, ROC: Receiver operating characteristic

Similar results have been obtained in other studies on the potential use of Gas6 as a biomarker. For example, in an animal model by Schott et al.[22], Gas6 deficiency was reported to improve glucose tolerance, whereas overexpression caused insulin resistance. This situation shows that Gas6 levels increase in parallel with metabolic stress and play an active role in pathophysiological processes. Our findings confirmed the literature that high Gas6 levels are associated with glucose intolerance.

However, there are conflicting findings in the literature regarding the relationship between Gas6 levels and insulin resistance, and glucose metabolism. Some studies have reported that low Gas6 levels are more common in individuals with type 2 diabetes, showing a positive correlation with insulin sensitivity and a negative correlation with inflammation[7,23,24]. However, it was also noted that certain genetic variants and Gas6 levels in obese individuals may be positively associated with insulin resistance[23,25,26]. In our study, the significantly higher serum Gas6 levels measured in the second trimester in individuals diagnosed with GDM, and those with obesity, support the existing literature reporting a positive association between Gas6 and insulin resistance and metabolic dysfunction. The conflicting findings in this area are likely due to clinical heterogeneity among patient populations, differences in the sensitivity of the ELISA kits used, timing of biomarker measurements, and genetic variations.

The AUC value of 0.94 obtained in our study demonstrates that Gas6 has a very high predictive power in the diagnosis of GDM. The sensitivity and specificity rates of 94.4% and 85.7%, respectively, obtained with a cut-off value of 30.0 ng/

Table 3. Cut-off values for Growth arrest–specific 6 protein protein in the diagnosis of gestational diabetes mellitus

Cut-off value	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
25.0	100.0	84.5	87.3	84.5
30.0	94.4	85.7	87.6	85.7

mL are clinically significant. While this level of performance may not replace the current OGTT test, it has the potential to serve as a non-invasive and rapid alternative for preliminary screening. Clinically, integrating Gas6 levels into routine screening programmes could enable earlier diagnosis and timely intervention, particularly in high-risk pregnancies. Early diagnosis of GDM will significantly contribute to the prevention of maternal and neonatal complications through dietary adjustments, exercise programmes, and pharmacological treatment, if necessary.

Gas6 has been considered a biomarker of interest not only in metabolic processes but also in obstetric pathologies in recent years. Dai et al.[27] showed that low Gas6 expression in decidual stromal cells in individuals with recurrent pregnancy loss is associated with a decrease in M2 macrophages responsible for immune tolerance. This situation suggests that immune imbalance in early pregnancy loss may be related to Gas6 deficiency. Another notable role of Gas6 is its relationship with preeclampsia. Studies conducted in this context have reported that excessive activation of the Gas6/Axl pathway is associated with symptoms such as trophoblast invasion disorder, oxidative stress, proteinuria, and hypertension, while Axl inhibitors have been shown to reduce these effects[28-31]. In addition, Sang et al.[32] found a correlation between increased Gas6 expression in preeclamptic placentas and blood pressure. In parallel with these findings, it was observed that Axl inhibitors alleviated preeclampsia-like symptoms in experimental models, bringing the potential of this pathway for treatment to the fore. Finally, it was found that Gas6 levels were elevated in intrauterine growth restriction (IUGR) cases and that this may be related to placental inflammation[33]. When evaluated in light of these data, Gas6 is a multifaceted biomarker that may play a role in the diagnosis and treatment not only of gestational diabetes but also of obstetric complications such as preeclampsia, early pregnancy loss, and IUGR, and thus appears to warrant further investigation.

The most important strengths of this study are its prospective design, the correlation of serum samples taken in the second trimester with birth outcomes, and the analysis of a large sample size. In addition, the objective evaluation of Gas6 levels using ROC analysis enabled the diagnostic power of the biomarker to be demonstrated. However, the fact that the study was conducted at a single centre may limit its general validity.

Study Limitations

Furthermore, preanalytical variables and the follow-up period not covering the early stages of pregnancy are among the potential limitations. In addition, this study evaluated only serum Gas6 levels without including mechanistic biomarkers such as oxidative stress, or inflammatory markers, which may limit the understanding of the underlying pathophysiology. Furthermore, the lack of immunohistochemical comparison of placental Gas6 expression is another limitation that could have provided insight into tissue-level mechanisms. Future studies incorporating both systemic and placental analyses may better clarify the mechanistic role of Gas6 in the development of GDM. Validating the findings in the early stages of pregnancy using multicentre designs and long-term follow-ups in the postpartum period will help clarify the diagnostic and prognostic value of Gas6.

Conclusion

This study showed that maternal Gas6 levels measured in the second trimester were significantly associated with gestational diabetes and related adverse perinatal outcomes. The correlation of Gas6 with BMI and OGTT results in particular supports the possibility that this biomarker may be an early indicator of metabolic dysfunction. In clinical practice, Gas6 measurement can be considered as an auxiliary tool in GDM risk classification. Using this measurement can potentially lead to improved outcomes for foeto-maternal health. However, further multicentre and longitudinal studies are needed to establish the prognostic and diagnostic value of Gas6 on a more solid foundation. Gas6 is a strong candidate biomarker for GDM, offering the opportunity for early intervention.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Samsun University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (protocol no: SUKAEK-2023/20/1, date: 01.11.2023).

Informed Consent: All participants were provided with detailed information about the study and their written consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.C.Ü., S.S.Ü., K.Ş., Concept: N.G., S.Ç., Design: N.G., S.Ç., Data Collection or Processing: Y.C.Ü., S.S.Ü., K.Ş., Analysis or Interpretation: Y.C.Ü., S.S.Ü., K.Ş., Literature Search: N.G., Writing: N.G., S.Ç.

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