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Evaluation of Serum Fibroblast Growth Factor 21 Levels in Gestational Diabetes Mellitus Patients

Gestasyonel Diabetes Mellituslu Gebelerde Serum Fibroblast Growth Factor 21 Düzeylerinin Değerlendirilmesi

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Abstract

Objective: This study aimed to compare the clinical characteristics of pregnant women diagnosed with gestational diabetes mellitus (GDM) based on a 75-g oral glucose tolerance test (OGTT) with those of pregnant women who had normal test results and to evaluate the potential role of serum fibroblast growth factor-21 (FGF-21) levels in the diagnosis of GDM.

Method: This prospective, controlled cohort study. A total of thirty-six pregnant women diagnosed with GDM based on a 75-g OGTT and thirty-six pregnant women with normal test results who presented to the Department of Obstetrics and Gynecology at University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital between 01/12/2021 and 01/04/2022 were included in the study. The participants' age and obstetric outcomes

Neonatal characteristics, and laboratory results, including FGF-21 levels, were recorded.

Results: When the general characteristics of the participants in our study were evaluated, no statistically significant differences were found between the groups with and without gestational diabetes in terms of age, gravidity, parity, weight, birth weight, birth length, gestational week, hemoglobin, platelet count, and alanine transaminase and aspartate transaminase levels, indicating that the two groups were similar ($p<0.05$). However, when evaluated in terms of FGF-21 levels, a statistically significant difference was found between the group diagnosed with gestational diabetes and the group without it ($p<0.001$), with the group diagnosed with gestational diabetes had higher mean FGF-21 levels. No statistically significant relationship was found between FGF-21 levels and diet, medication use, or intensive care unit admissions ($p>0.005$). However, a statistically significant difference was found between FGF-21

Öz

Amaç: Bu çalışmada 75 gr oral glikoz tolerans testi (OGTT) yapılarak gestasyonel diabetes mellitus (GDM) tanısı almış gebelerle ve test sonucu normal sınırlarda olan gebelerin klinik özelliklerinin karşılaştırılması, ve serum fibroblast growth factor-21 (FGF-21) düzeyinin GDM tanısında kullanılmasının yerinin değerlendirilmesi amaçlanmıştır.

Yöntem: Bu çalışma prospektif, kontrollü kohort çalışması olarak planlanmıştır. 01/12/2021 ve 01/04/2022 tarihleri arasında Sağlık Bilimleri Üniversitesi, Prof. Dr. Cemil Taşcıoğlu Şehir Hastanesi, Kadın Hastalıkları ve Doğum Kliniği'ne başvuran, 75 gr OGTT sonucuna göre GDM tanısı almış otuz altı gebe ve test sonucu normal sınırlarda olan otuz altı gebe çalışmaya dahil edilmiştir. Olguların yaşı, obstetrik sonuçları, yenidoğan özellikleri ve FGF-21'de dahil olmak üzere laboratuvar sonuçları kaydedilmiştir.

Bulgular: Çalışmamıza katılan kişilerin genel özellikleri gestasyonel diyabet olanlar ve olmayanlar açısından değerlendirildiğinde yaş, gravida, parite, kilo, doğum kilosu, doğum boyu, doğum haftası, hemoglobin, platelet, alanin transaminaz, aspartat transaminaz açısından istatistiksel olarak anlamlı bir fark saptanmadı ve iki grubun benzer özellik gösterdiği gözlendi ($p<0,05$). FGF-21 değerleri açısından değerlendirildiğinde ise gestasyonel diyabet tanısı alan grupla almayan grup arasında istatistiksel olarak anlamlı bir fark olduğu saptandı ($p<0,001$) ve gestasyonel diyabet olan grubun FGF-21 ortalama değerinin daha yüksek olduğu görüldü. Katılımcıların FGF-21 değerleri ile diyet, ilaç, yoğun bakım yatışı durumları incelendiğinde istatistiksel olarak anlamlı bir ilişki saptanmadı ($p>0,005$). FGF-21 değeri ile AFI artışı arasında ise istatistiksel olarak anlamlı bir fark saptandı. ($p=0,003$). Amniyon sıvısı indeksi (AFI) artışı olan kişilerde FGF-21 ortalama değerinin AFI normal olan gruba göre daha yüksek olduğu gözlendi.

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Abstract

levels and amniotic fluid index (AFI) increase (p=0.003). It was observed that participants with increased AFI had higher mean FGF-21 levels than those with normal AFI.

Conclusion: In this study, serum FGF-21 levels were higher in pregnant women with GDM than in those without GDM.

Keywords: FGF-2l, Gestational diabetes mellitus, OGTT, pregnancy

Öz

Sonuç: Bu çalışmada GDM'li gebelerde serum FGF-21 düzeyi GDM olmayanlara göre daha yüksek bulundu.

Anahtar kelimeler: FGF-2l, gebelik, gestasyonel diabetes mellitus, OGTT

Introduction

Gestational diabetes mellitus (GDM) is a carbohydrate intolerance condition that begins or is diagnosed during pregnancy. Diabetes mellitus (DM) is not present before pregnancy but is diagnosed in the second or third trimester of pregnancy (1). The prevalence of GDM varies in direct proportion to the prevalence of type 2 diabetes. It is thought that 6-7% of pregnancies are complicated by DM, and approximately 90% of these are GDM (2).

Maternal tissues that provide adequate nutrition to the fetus throughout pregnancy become insensitive to insulin due to metabolic changes (3). One of these changes is that insulin-mediated glucose excretion decreases by 40-60% and an increase in insulin secretion of approximately 200-250% is required to maintain normal blood sugar levels (4). GDM occurs when a pregnant woman cannot produce enough insulin to compensate for this insulin resistance (4,5). Women diagnosed with GDM are at high risk for cesarean delivery and the development of preeclampsia. Additionally, women diagnosed with GDM have an increased risk of developing diabetes (usually type 2 DM) later in life (5,6).

GDM has negative effects on the fetus. Babies of women with GDM have an increased risk of birth trauma, shoulder dystocia, macrosomia, intrauterine growth restriction, fetal/neonatal hypertrophic cardiomyopathy, neonatal respiratory problems and metabolic complications, polyhydramnios, increased neonatal mortality and morbidity, risk of preterm birth, and respiratory distress syndrome (7-9).

The fibroblast growth factor (FGF-21) family comprises approximately 22 members. Their functions are generally related to angiogenesis, transformation, and mitosis. FGF-19, FGF-21, and FGF-23 have been proven to be endocrine factors (10). FGF-21 acts as an endocrine hormone. FGF-21 is produced by the liver, skeletal muscle, adipose tissue, pancreas, and placenta. It is an energy metabolism regulator that affects glucose and lipid metabolism (11). FGF-21 regulates glucose by increasing glucose uptake by adipocytes via glucose transporter-1 and decreasing blood glucose levels. This condition is independent of insulin (12). There is no interaction between FGF-21 and insulin during glucose reuptake. It has also been observed in animal experiments that FGF-21 inhibits glucagon release and lowers blood glucose levels (13). It has been observed that FGF-21 levels increase in insulin-resistant conditions such as Type 2 DM and obesity in humans (14). Some studies have shown that FGF-21 level has an independent diagnostic value for Type 2 DM (15,16).

Although the pathophysiology of GDM development remains unclear, the pathophysiology of GDM and Type 2 DM is believed to be similar. Insulin resistance and insulin insufficiency are caused by impaired pancreatic beta-cell function (1,8). For these reasons, whether a relationship similar to that between Type 2 DM and FGF-21 exists between GDM and FGF-21 is a subject for research. The aim of our study was to examine demographic characteristics by investigating the relationship between GDM and FGF-21.

Materials and Methods

This prospective, controlled cohort study was planned. In the power analysis, it was concluded that 22-25 patients were sufficient for the control and study groups. The study was terminated when 72 patients were reached within the target time. Of the patients who presented to the University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital Obstetrics and Gynecology Clinic between December 1, 2021, and April 1, 2022, the demographic, clinical, and laboratory values of thirty-six pregnant women who were diagnosed with GDM according to the 75-g OGTT result and thirty-six pregnant women whose test results were within normal limits were evaluated prospectively. Five patients were not included in the study because they had additional diseases. Three patients were excluded from the study because they were older than 40 years. GDM diagnosis was made in a single step as recommended by The International Association of the Diabetes and Pregnancy

Study Groups (17). Our study was conducted with the approval of Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital (02.07.2021/43991-62/21).The study group consisted of pregnant women between 28 and 40 gestational weeks who were diagnosed with GDM and had no comorbidities. The control group consisted of healthy pregnant women who were not diagnosed with GDM and had no additional diseases. Because the patients were admitted to the hospital at 28-40 weeks of gestation after diagnosis, blood samples were collected at these weeks. Informed consent forms were obtained from all pregnant women included in the study. The patients were between the ages of 18 and 40 years and had singleton pregnancies. Pregnant women with genetic diseases, endocrine disorders, liver diseases, kidney failure, a history of diabetes, cardiovascular disease, or hypertension were not included in the study.

A total of 72 pregnant women met all criteria and were included in the study. Thirty-six people constituted the study group and thirty-six people constituted the control group. A 75-g OGTT was performed between 24 and 28 gestational weeks. According to the test results, patients were included in the study and control groups. Demographic data included age, gravidity, parity, fetal USG results, birth week, newborn weight, and need for intensive care were noted. Laboratory parameters and serum FGF-21 levels were noted.

Venous blood samples were placed in gel biochemistry tubes and centrifuged at 2000 rpm for 20 min. The serum samples were placed in an Eppendorf tube and frozen at 40 °C until analysis. When the analyses were to be performed, the samples were brought to room temperature. The collected serum samples were studied in a private laboratory using Microplate Reader RT 2100C and MicroplateWasher RT 2600C devices with human laminin enzyme kits. Serum FGF-21 concentrations were measured in pg/mL, and the reference range was determined as 1.6-100.

This study was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, approved the study (02.07.2021/43991-62/21).

Statistical Analysis

In our study, version 21.0 of the SPSS (Statistical Package for the Social Sciences, Chicago, IL, USA) software was used for the statistical analysis of the data. In descriptive statistics, the mean, standard deviation, median, minimum, and maximum values were calculated for the variables.

As initial analyses, Kolmogorov-Smirnov and Shapiro-Wilk tests were used to evaluate the normal distribution. For comparisons between two groups, the Mann-Whitney U test was used for nonparametric data, and the t-test for independent groups was used for parametric data.

Spearman correlation analysis was used in the correlation analysis. In terms of correlation strength, r=0.00-0.24 was considered weak; r=0.25-0-49 was considered moderate; r=0.50-0.74 was considered strong; and r=0.75-1.00 was considered very strong.

The results were evaluated within the 95% confidence interval and $p<0.05$ was defined as statistically significant.

Results

Seventy-two pregnant women participated in the study. Gestational diabetes was diagnosed with OGTT in thirty-six of these pregnant women. The OGTT results of thirty-six pregnant women were normal, and they constituted the control group. When the general characteristics of the patients participating in our study were evaluated in terms of those with and without gestational diabetes, no statistically significant difference was detected in terms of age, gravidity, parity, weight, birth weight, birth length, birth week, hemoglobin, platelets, alanine transaminase (ALT), and aspartate transaminase (AST), and it was observed that the two groups showed similar characteristics ($p>0.05$) (Table 1). Regarding the FGF-21 values, a statistically significant difference was found between the group diagnosed with gestational diabetes and the group without ($p<0.001$) (Table 1). The mean FGF-21 level was higher in the group with gestational diabetes. Table 1 presents the general characteristics of the study participants for both the GDM and non-GDM groups.

When the participants in our study were evaluated in terms of those with and without gestational diabetes and their laboratory parameters were compared, no statistically significant difference was detected in terms of hemoglobin, platelet, ALT, and AST levels, and it was observed that the two groups showed similar characteristics ($p>0.05$) (Table 2).

The mean FGF-21 level was 26.7 pg/mL (11.5-110.8) in the GDM group and 17.2 pg/mL (11-28) in the control group (Figure 1). Compared with the control group, the FGF-21 level was significantly higher among GDM cases ($p<0.001$) (Figure 1).

As a result of the receiver operating characteristic analysis performed for the use of the FGF-21 level in the diagnosis of

GDM, the area under the curve was 0.838 (95% confidence interval: 0.746-0.930). When the FGF-21 cut-off value was selected as 22.75, the specificity value for the diagnosis of GDM was found to be 94.44%, sensitivity was 61.11%, positive predictive value was 91.7%, and negative predictive value was 70.8% (Figure 2).

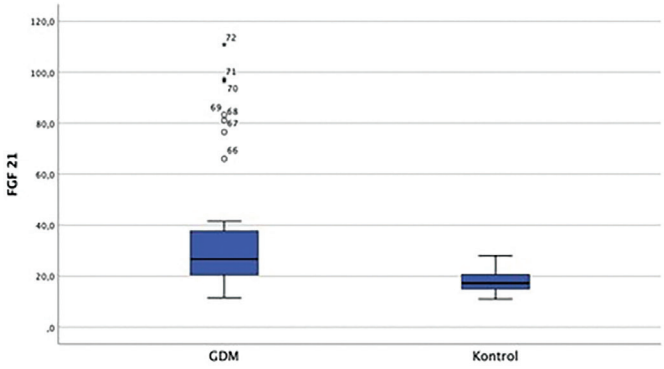

Figure 1. Graphical representation of the distribution of serum FGF-21 levels in the GDM and control groups

GDM: Gestational diabetes mellitus, FGF-21: Fibroblast growth factor-21

When the FGF-21 values of the participants and their diet, medication, and neonatal intensive care unit admission were examined, no statistically significant relationship was detected (p>0.05)(Table 3). A statistically significant difference was detected between the FGF-21 level and AFI increase (p=0.003) (Table 3). The mean FGF-21 level was higher in individuals with increased AFI than in those with normal AFI. The results are shown in Table 3.

Discussion

GDM causes serious maternal and fetal complications. Therefore, diagnosis and treatment are important. The most commonly used method is the oral glucose tolerance test. The American Diabetes Association and the International Association of Diabetes and Pregnancy Study Groups accept the one-step 75-g test. In a study conducted by

Table 1. Comparison of demographic characteristics between the GDM and non-GDM groups

	GDM	Non-GDM		Total
	Median (min-max)	Median (min-max)		Median (min-max)
	Mean ± SD	Mean ± SD	p	Mean ± SD
FGF-21	26.7 (11.5-110.8)	17.2 (11-28)	<0.001*	20.6 (11-110.8)
Age	34.5±5.86	31.3±4.57	0.198**	32.11±5.28
Gravidity	3 (1-8)	2 (1-5)	0.138*	3 (1-8)
Parity	2 (0-7)	1 (0-4)	0.430*	1 (0-7)
Kg	78.5±8.7	76±7.1	0.162**	77.4±7.97
Height	160.8±5.85	160.1±5.32	0.600**	160.4±5.56
Birth weight	3415±538	3220±570	0.139**	3318±559
Birth length	49.2±2.17	48.5±2.74	0.257**	48.9±2.48
Birth week	38.1±1.41	38.1±1.69	1**	38.1±1.53

*: Mann-Whitney U test result, **: t-test results, SD: Standard deviation, GDM: Gestational diabetes mellitus, FGF-21: Fibroblast growth factor-21

Table 2. Comparison of laboratory parameters between the GDM and non-GDM groups

	GDM	Non-GDM		Total
	Median (min-max)	Median (min-max)		Median (min-max)
	Mean ± SD	Mean ± SD	p	Mean ± SD
Hgb	11.6±0.97	11.9±1.37	0.194**	11.7±1.19
PLT	210±2±63.37	219.7±77.54	0.579**	214.8±70.23
ALT	12 (6-25)	9 (5-53)	0.065*	11 (5-53)
AST	16 (8-30)	17 (9-78)	0.316*	16.5 (8-78)
Urea	14±3.94	13.8±4.66	0.839**	13.9 ±4.27
Uric acid	3.4 (1.4-6.8)	3.7 (2.4-5.8)	0.328*	3.5 (1.4-6.8)
Creatinine	0.47 (0.34-0.79)	0.51 (0.37-0.77)	0.059*	0.48 (0.34-0.79)

*: Mann-Whitney U test result, **: t-test results, AST: Apartate transaminase, ALT: Alanine transaminase, SD: Standard deviation, GDM: Gestational diabetes mellitus, PLT: Platelet, Hgb: Hemoglobin

ElSayed et al. (18) in 2023, the importance of the 75-g OGTT approach was emphasized. Therefore, in our study, 75-g OGTT results were examined. Treatment of the diagnosed pregnant woman should be started immediately based on the test results. This treatment consists of diet, exercise, and medical treatment. Treatment should be decided by the clinician according to the patient's condition. Studies have shown that treatment initiation improves maternal and fetal outcomes. The main findings of our study are as follows. FGF-21 serum levels were found to be significantly higher in pregnant women diagnosed with GDM than in normal pregnant women without GDM diagnosis. A significant relationship was found between serum FGF-21 levels and AFI in pregnant women. No significant relationship was found between serum FGF-21 levels and fetal outcomes (birth weight, birth length, need for neonatal intensive care).

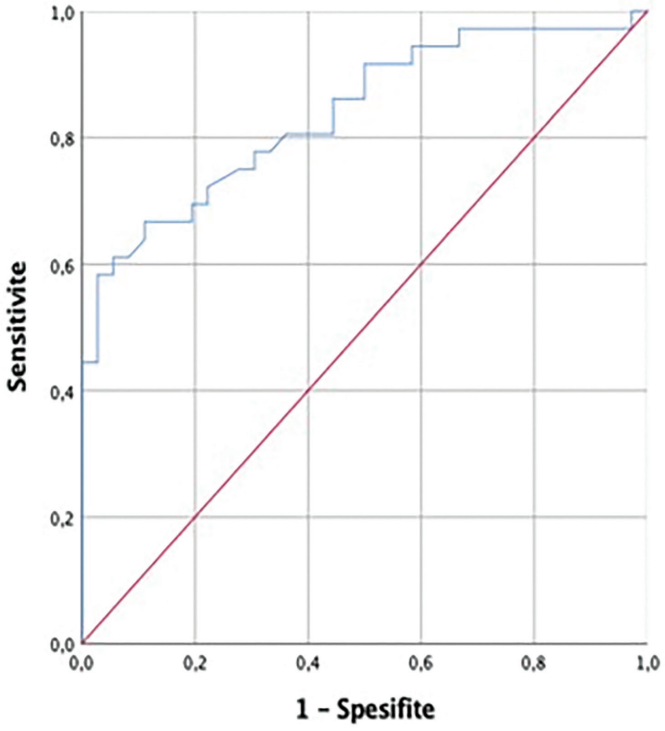

Figure 2. ROC curve showing the ability of FGF-21 level to distinguish GDM

GDM: Gestational diabetes mellitus, FGF-21: Fibroblast growth factor-21, ROC: Receiver operating characteristic

When the general characteristics of the people participating in our study were evaluated in terms of those with and without gestational diabetes mellitus, no statistically significant difference was detected in terms of age, gravidity, parity, weight, birth weight, birth length, birth week, hemoglobin, platelet, alanine aminotransferase, and aspartate aminotransferase, and the two groups were observed to have similar characteristics.

In our study, serum FGF-21 levels were found to be significantly higher in the GDM group than in the non-GDM group. In a study conducted in the Caucasus by Tan et al. (15), the relationship between GDM and FGF-21 was investigated. In the study conducted with a total of 24 patients 12 diagnosed with GDM and 12 in the control group, samples were collected before elective cesarean section between 39 and 40 weeks. FGF-21 was found to be significantly higher in the GDM group. High FGF-21 levels were found to be similar to those in our study (15). In the study conducted by Wang et al. (16) in China, with a control group of 60 people and 30 patients with GDM, samples were collected between 24-28 gestational weeks after OGTT. FGF-21 levels were found to be significantly higher. In our study, samples were collected between 28 and 40 gestational weeks. Similar to this study, serum FGF-21 levels were found to be significantly higher than those in the control group (16). In a study conducted in China by Li et al. (19) with a total of 101 patients 51 diagnosed with GDM and 50 in the control group, FGF-21 serum values

Table 3. Comparison of the effect of FGF-21 on maternal and fetal outcomes between the GDM and non-GDM groups

		FGF-21	
		Mean (min-max)	**p**
Medication use*	Yes	25.5 (15.9-110.8)	0.570
	No	28.2 (11.5-96.5)	
Diet*	Yes	28.2 (11.5-96.5)	0.570
	No	25.5 (15.9-110.8)	
AFI	Normal	18.8 (11-76.5)	0.003
	Increased	25.5 (12.6-110.8)	
Newborn intensive care unit admission	Yes	19.5 (11-110.8)	0.720
	No	20.8 (11.5-96.5)	

*: Only the GDM group, GDM: Gestational diabetes mellitus, FGF-21: Fibroblast growth factor-21, AFI: Amniotic fluid index

were compared between the GDM and non-GDM groups at the 28th gestational week and the 7th postpartum day. The serum FGF-21 level in the GDM group was significantly higher. A decrease in serum concentrations was observed in both groups. This indicates that studies can be conducted to determine whether the FGF-21 level in both patient groups may increase with conditions such as insulin resistance and carbohydrate intolerance during pregnancy and that it may return to normal after birth. The finding that FGF-21 levels are high during pregnancy is consistent with our study (19). No significant difference was found between FGF-21 levels in studies conducted by Dekker Nitert et al. (20) in Australia and Wang et al. (21) in China. However, the number of cases in these studies was limited to 45 and 38 patients. The higher number of cases in both our study and the other studies suggests that the results are stronger (20,21).

In our study, a significant relationship was found between AFI and FGF-21, but the relationship between them was not mentioned in previous studies. Our study revealed that this problem should be investigated in new studies.

In studies on GDM and fetal outcomes, when case and control groups are compared, a significant difference is detected in fetal outcomes and baby birth weight. Patients with GDM are more likely to experience macrosomia. In a study conducted by Kc et al. (22), a relationship was shown between macrosomic babies and GDM. In our study, when birth weight was compared, the average birth weight of the GDM group was 3415±538 g, and that of the control group was 3220±570 g. Although the average birth weight was higher in the GDM group, there was no significant difference between the two groups. The reason for this was thought to be the fact that the patients diagnosed with GDM in our study were monitored by gynecologists, obstetricians, and endocrinologists after diagnosis and were treated with diet, exercise, and medical treatment options.

In the GDM group, the treatment type (diet-medical treatment) and FGF-21 serum levels were compared. No correlation was found between elevated serum FGF-21 levels and planned treatment.

Since our study was a prospective study, all the parameters evaluated in the patients were collected completely. This feature was one of the strengths of our study. No significant differences were detected between the groups in terms of age, body mass index, gravidity, parity, and laboratory parameters. Pregnant women with genetic diseases, endocrine disorders, liver diseases, kidney failure, a history of diabetes, cardiovascular disease, or hypertension were not included in the study. This indicates that there is no difference between our case and control groups other than GDM, and that both groups have similar characteristics. The fact that the case and control groups had similar characteristics was another strength of our study.

Study Limitations

There are some limitations in our study. Blood samples were collected from the case and control groups. No opinions can be expressed on whether the results will be affected by repeated sampling. All samples were collected after performing the OGTT on the patient. This means that serum FGF-21 levels could not be compared with those obtained weeks before the diagnosis and prior to the OGTT. In addition to these, the fact that our study was single-centered was another limitation.

Conclusion

In conclusion, our study found that serum FGF-21 levels were significantly higher in the GDM group. This indicates that FGF-21 can be used as a GDM diagnostic test if supported by studies conducted in the coming years. This test can be used in the diagnosis of GDM in the following years in centers where OGTT cannot be performed or for patients who do not want to undergo testing by performing a glucose challenge. It may be easier and more accessible for patients to undergo testing. FGF-21 can be used in the diagnosis and treatment of GDM, but further studies are needed to understand whether this parameter can be used.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, approved the study (02.07.2021/43991-62/21).

Informed Consent: Informed consent forms were obtained from all pregnant women included in the study

Authorship Contributions

Concept: N.Ç.Ç., H.Ö.Ç., V.M., Design: N.Ç.Ç., H.Ö.Ç., V.M., Data Collection or Processing: N.Ç.Ç., S.G., E.A., Analysis or Interpretation: N.Ç.Ç., H.Ö.Ç., Drafting Manuscript: N.Ç.Ç., H.Ö.Ç., S.G., Critical Revision of Manuscript: N.Ç.Ç., E.A., V.M., Final Approval and Accountability: N.Ç.Ç., H.Ö.Ç., E.A., S.G., V.M., Technical or Material Support: N.Ç.Ç., H.Ö.Ç., V.M., Supervision: N.Ç.Ç., S.G., E.A., Writing: N.Ç.Ç., H.Ö.Ç., E.A., S.G., V.M.

Conflict of Interest: No conflict of interest was declared by the authors.

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