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Evaluation of first- and third-trimester afamin levels in preeclampsia

Selim Gülücü[1*], Sebahattin Çelik[2], Gökhan Unver[3]

SUMMARY

OBJECTIVE: The aim of this study was to investigate serum afamin levels in the first and third trimesters in preeclampsia.

METHODS: Serum samples from 118 patients in the first and third trimesters were analyzed. Serum samples were collected from pregnant women who had enrolled in the first trimester. Blood was then collected from pregnant women who had developed preeclampsia and from healthy controls in the third trimester. The collected blood samples were resolved for analysis, and serum afamin concentrations were measured in the first and third trimesters. Preeclampsia and healthy controls were compared.

RESULTS: There was no significant difference between the control and preeclampsia groups in terms of age, body mass index, and smoking. Afamin levels in the first and third trimesters were higher in the preeclampsia group than in the control group ($p<0.05$). In the subgroup analysis of the preeclampsia group, afamin levels were higher in the early-onset preeclampsia group than in the late-onset preeclampsia group in the first and third trimesters ($p<0.05$). In the receiver operating characteristic analysis afamin levels were 96.23 ng/mL in the first trimester and 123.57 ng/mL in the third trimester as cut-off values for preeclampsia.

CONCLUSION: Serum afamin levels are useful for predicting preeclampsia in the first trimester in pregnant women and can be used in clinical practice as a supportive biomarker for the diagnosis of preeclampsia in the third trimester. Meta-analyzes are needed to investigate the effect of afamin levels in the prediction and diagnosis of preeclampsia and to determine the cut-off value.

KEYWORDS: Pre-eclampsia. Proteinuria. Hypertension. Biomarker. Pregnancy trimester, first.

INTRODUCTION

Preeclampsia (PE) is a hypertension [blood pressure (BP) ≥140/90 mmHg] disorder that occurs after 20 weeks of gestation (but no hypertension before pregnancy) and also causes proteinuria (proteinuria≥300 mg/24 h), but the presence of proteinuria is not always observed for PE[1]. The presence of systemic findings along with hypertension (liver dysfunction, renal failure, presence of hemolysis and thrombocytopenia, pulmonary edema, and visual and cerebral findings) indicates PE without proteinuria[1]. Although it is thought to be caused by PE trophoblast invasion disorder and impaired placental blood supply, the pathogenesis is not fully understood. Impaired placental development, increased placental oxidative stress, apoptosis, and necrosis cause endothelial dysfunction, proteinuria, and maternal hypertension[2].

Afamin (also called α-albumin), which is a vitamin E-binding glycoprotein, has been identified as the fourth member of the human albumin gene family after albumin, α-fetoprotein, and vitamin D-binding protein[3]. Vitamin E is an important protective lipophilic antioxidant that protects against oxidative stress during pregnancy and postpartum[4]. Serum afamin concentrations have previously been reported to increase in response to high oxidative stress[3].

During normal pregnancy, plasma afamin concentration approximately increases two times and decreases to pre-pregnancy levels soon after delivery[5]. High afamin concentrations have been associated with insulin resistance (IR) and components of metabolic syndrome[6]. In the literature, there are few studies on the association between PE and afamin. To the best of our knowledge, in English literature, there is no study that examined afamin, which is associated with oxidative stress, in both the first and third trimesters.

The aim of this study was to evaluate the role of afamin in predicting PE by comparing afamin levels in the first and third trimesters of the PE and control groups.

METHODS

Pregnant patients who presented to the Obstetrics and Gynecology Outpatient Department of Samsun Training and Research Hospital between January 2021 and January 2022

[1]Gaziosmanpaşa University, Department of Obstetrics and Gynecology – Tokat, Turkey.
[2]Balikesir State Hospital, Department of Obstetrics and Gynecology – Balıkesir, Turkey.
[3]Samsun Training and Research Hospital, Department of Obstetrics and Gynecology – Samsun, Turkey.
*Corresponding author: selim.gulucu@gop.edu.tr
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were enrolled in the study. Prior to the study, approval was obtained from the ethics committee of our hospital (Dated September 23, 2021/No. KAEK 2021/418).

Routine evaluations were performed on the pregnant women who presented to the outpatient clinic in the first trimester. Serum samples taken from the pregnant women for the study were stored at -80°C for subsequent biochemical analyses. Patients were followed until delivery, and pregnancy outcomes were recorded. Prenatal serum samples were collected from the patients who developed PE in the third trimester. The control group consisted of pregnancies whose blood was collected and stored in the first trimester, who did not develop PE or any complications during pregnancy follow-up, and who delivered at term (37–41 weeks). Multiple pregnancies, fetal anomalies, and patients with systemic diseases (chronic hypertension, vascular diseases, and diabetes mellitus) diagnosed before or after pregnancy were accepted as criteria for exclusion from the study.

It was planned to include age, gravidity, parity, body mass index (BMI), smoking, type of delivery (cesarean section/normal vaginal delivery), presence of meconium, neonatal intensive care unit (NICU) requirement, systolic blood pressure (SBP), diastolic blood pressure (DBP), birth weight, APGAR 0 min, APGAR 5 min, serum afamin level in the first and third trimesters, and birth weight. Week of gestation was confirmed by ultrasound using the first day of the last menstrual period (LMP) or first-trimester ultrasound measurements in patients whose LMP was unknown.

Preeclampsia was defined as BP ≥140/90 mmHg associated with proteinuria in two separate measurements of at least 4 h after the 20th week of gestation in a woman whose BP was previously within normal limits. Proteinuria was detected in ≥+1 protein by dipstick test or ≥300 mg in a 24-h urine test. The study included 2,852 pregnant women in the first trimester. Serum samples from 118 patients in the first and third trimesters were analyzed in the study. Of the patients whose serum samples were taken, 74 patients were diagnosed with PE and these patients were included in the study group, while 44 pregnant women were included in the control group.

A subgroup analysis of the PE group was performed. The PE group was divided into two groups according to the week of delivery: less than 34 weeks (early-onset) and 34 weeks and more (late-onset). Stored serum samples were measured for serum afamin concentrations using a commercially available kit. Afamin levels were expressed in ng/mL.

Statistical analyses were performed using SPSS 22 (IBM SPSS Statistics 22, an IBM Co, Somers, NY). The continuous variables were reported as mean and standard deviation. The categorical variables were expressed as percentage and frequency. The chi-square test was used to compare categorical data between groups. The independent samples t-test was used to compare the distribution of variables between groups. Receiver operating characteristic analysis (ROC) was used to evaluate the diagnostic performance of afamin in the first and third trimesters in PE. The p-value<0.05 was considered significant.

RESULTS

There was no significant difference between the control and PE groups in terms of patient age, BMI (p=0.059), and smoking (p=0.458). Gravida and parity numbers were lower in the PE group than in the control group. SBP, DBP, and cesarean section rates were lower in the control group than in the PE group. As for neonatal outcomes, the presence of meconium and the need for NICU were lower in the control group, while APGAR first-fifth min scores and birth weight were higher. Afamin levels in the first and third trimesters were lower in the control group than in the PE group. The demographic characteristics and serum analysis results of the patients are shown in Table 1.

Table 1. Demographic characteristics of the patients and results of serum analysis.

	Preeclampsia (n=74)	Control (n=44)	p-value
Age (year)	27.31±4.88	29.23±6.03	0.062
Gravida	1.99±1.03	2.7±1.44	**0.002**
Parity	0.68±0.72	1.18±1.19	**0.005**
Type of birth			
C/S	44 (59.5%)	15 (34.1%)	**0.008**
VD	30 (40.5%)	29 (65.9%)	
Presence of meconium	17 (23%)	3 (6.5%)	**0.024**
NICU	17 (23%)	3 (6.5%)	**0.036**
SBP (mmHg)	155±21.03	117.27±8.99	**<0.001**
DBP (mmHg)	97.43±17.23	65.45±6.97	**<0.001**
Birth weight	2899.26±787.71	3349.89±316.75	**<0.001**
Week of birth	36.61±2.99	39.14±0.88	**<0.001**
Apgar 1 min	7.53±1.67	9.2±1.02	**<0.001**
Apgar 5 min	8.2±1.52	9.7±1.02	**<0.001**
First trimester afamin	217.47±231.72	53.57±23.37	**<0.001**
Third trimester afamin	467.08±359.76	79.38±26.25	**<0.001**

Data are presented as mean±standard deviation or as numbers and percentages. The significance test of the difference between the two means or the Pearson chi-square test was used. BMI: body mass index; C/S: cesarean section; VD: vaginal delivery; NICU: neonatal intense care unit; SBP: systolic blood pressure; DBP: diastolic blood pressure. Bold indicates statistically significant p-values.

In the subgroup analysis of 74 patients in the PE group, 23 patients delivered below 34 weeks of gestation (early-onset PE), and 51 patients delivered at or above 34 weeks of gestation (late-onset PE). There was no significant difference between the early and late PE groups in terms of patient age, parity (p=0.058), BMI (p=0.065), and smoking (p=0.122). Gravida was lower in the early PE group compared to the late PE group. SBP, DBP, and cesarean section rates were found to be lower in the late-onset PE group than in the early-onset PE group. When neonatal outcomes were evaluated, the presence of meconium and the need for NICU were higher in the early PE group, while APGAR 1–5 min scores and birth weight were significantly lower. Afamin levels in the first and third trimesters were lower in the late-onset PE group than in the early-onset PE group. Demographic characteristics and serum analysis results of PE patients are given in Table 2.

In the ROC, an afamin level of 96.23 ng/mL [sensitivity (59%) and specificity (95%)] in the first trimester and 123.57 ng/mL [sensitivity (81%) and specificity (99%)] in the third trimester was set as the cutoff value for PE. The area under the curve (AUC) was 0.73 (95%CI 0.64–0.81) in the first trimester and 0.90 (95%CI 0.84–0.95) in the third trimester. ROC curves are shown in Figure 1.

Table 2. Demographic characteristics and serum analysis results of the preeclampsia patients.

	<34 weeks (early-onset PE) (n=23)	34 weeks and above (late-onset PE) (n=51)	p-value
Age (year)	28.65±4.95	26.71±4.77	0.113
Gravida	2.52±1.12	1.75±0.89	**0.002**
Type of birth			
C/S	23 (100%)	21 (41.2%)	
VD	0 (0%)	30 (58.8%)	**<0.001**
Presence of meconium	11 (47.8%)	6 (11.8%)	**0.001**
NICU	17 (47.8%)	6 (11.8%)	**0.001**
SBP (mmHg)	169.78±12.66	148.33±20.73	**<0.001**
DBP (mmHg)	110.22±9.83	91.67±6.97	**<0.001**
Birth weight	2054.57±624.26	3280.2±508.15	**<0.001**
Week of birth	33.22±2.54	38.14±1.60	**<0.001**
Apgar 1 min	6.57±1.62	7.96±1.52	0.001
Apgar 5 min	7.43±1.59	8.55±1.36	0.003
First-trimester afamin	377.33±264.16	145.38±175.03	**<0.001**
Third-trimester afamin	800.43±261.73	316.75±290.96	**<0.001**

Data are presented as mean±standard deviation or as numbers and percentages. The significance test of the difference between the two means or the Pearson chi-square test was used. BMI: body mass index; C/S: cesarean section; VD: vaginal delivery; NICU: neonatal intense care unit; SBP: systolic blood pressure; DBP: diastolic blood pressure. Bold indicates statistically significant p-values.

DISCUSSION

This study compared serum afamin levels in the first and third trimesters between patients with and without PE in predicting PE. This is the first study that we know of that evaluated both first- and third-trimester afamin levels in PE patients. Serum afamin levels were found to be higher in patients with PE compared to patients without PE in both first and third trimesters. For patients with PE, 96.23 ng/mL in the first trimester and 123.57 ng/mL in the third trimester were set as cut-off values. In the PE subgroup analysis, higher serum afamin levels were found in both first and third trimesters in early-onset (<34 weeks) PE compared with late-onset (≥34 weeks) PE.

Afamin, a plasma glycoprotein, belongs to the albumin gene family and has been identified as an alternative carrier protein for vitamin E[7]. In addition, it functions as a transfer protein responsible for the exchange of lipoproteins such as cholesterol, triglycerides, and ApoB[8]. It has also been found to correlate highly with the prevalence of metabolic syndrome[9]. Köninger et al., found an association between afamin and gestational diabetes mellitus[6]. A meta-analysis found a high correlation between afamin and type 2 diabetes mellitus[10]. According to Hubalek et al., maternal serum afamin concentrations increase

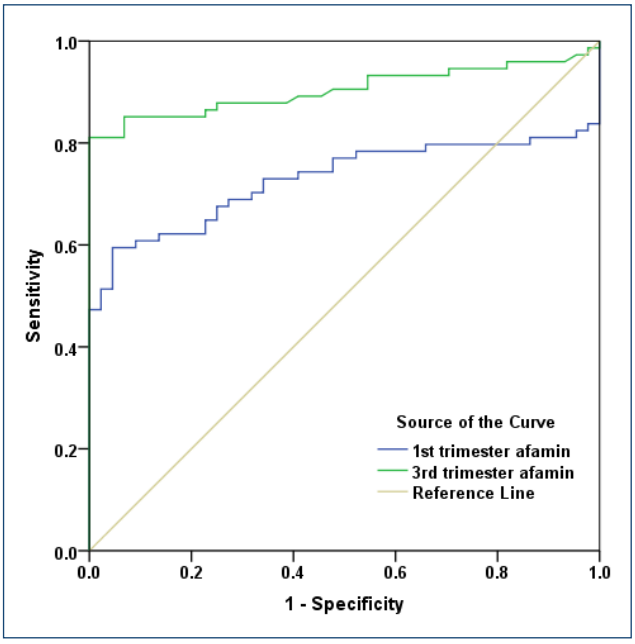

Figure 1. Receiver operating characteristic analysis curves.

linearly during the three trimesters in uncomplicated pregnancies[5]. It is not clear why serum afamin concentrations increase as pregnancy progresses. There are few studies of afamin in PE.

Tramontana et al., involving 30 PE patients and Köninger et al., involving 39 PE patients in their studies found that the first-trimester afamin levels were lower in patients in control compared to the PE group[11,12]. Caliskan et al., in a study of 39 PE patients found that PE developed in those who had high second-trimester afamin levels[3]. Our study differs from other studies in that it detects and reveals high levels of afamin in both first and third trimesters. Although early diagnosis is important for predicting PE, detection of high afamin levels in the third trimester may be useful in diagnosing PE cases that cannot be definitively diagnosed. Caliskan et al., found no difference in serum afamin levels in early-onset and late-onset patients with PE[3]. Köninger et al., detected higher afamin levels in the first trimester in the late-onset patients with PE compared with the early-onset patients with PE, but there was no difference in afamin levels in the early-onset patients with PE compared with the control group[7]. In our study, afamin levels were lower in patients with the early-onset PE compared with patients with the late-onset PE. This result is consistent with the literature. Although increased maternal serum afamin concentrations have been described in patients with PE, the mechanism of any causal relationship is not clear.

The strengths of our study are that afamin levels were not checked in the second trimester, afamin levels were not checked in the cord blood of patients with PE, the number of patients with PE was higher than in other studies, and 2,852 pregnant women were followed until delivery.

CONCLUSION

Serum afamin levels are useful for predicting the first-trimester PE in pregnant women and can be used in clinical practice as a supportive biomarker in the diagnosis of third-trimester PE. Prospective studies with larger patient groups and meta-analyses will be necessary to investigate the effect of serum afamin level on the prediction and diagnosis of PE and to determine the cut-off value.

ETHICAL APPROVAL

Prior to the study, approval was obtained from the Ethics Committee of Samsun Training and Research Hospital (September 23, 2021//No. KAEK 2021/418).

AUTHORS' CONTRIBUTIONS

SG: Conceptualization, Formal Analysis, Investigation, Resources, Writing – original draft, Writing – review & editing. **SÇ:** Conceptualization, Formal Analysis, Writing – original draft. **GU:** Data curation, Formal Analysis, Writing – original draft, Writing – review & editing.

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