



# Relationship between serum cadherin 6 and 11 levels and severe and early-onset preeclampsia: A pilot study

## Erken başlangıçlı ve ağır preeklampsi ile serum kaderin 6 ve 11 seviyeleri arasındaki ilişki: Bir pilot çalışma

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### Abstract

**Objective:** Preeclampsia is a highly morbid disease of placental origin, life-threatening condition for both a pregnant woman and her fetus. Cadherin 6 and 11 are adhesion molecules that play an important role in trophoblastic development and placentation. In our study, we investigated the change in serum cadherin 6 and 11 levels in pregnant women with preeclampsia.

**Materials and Methods:** Pregnant women with preeclampsia were selected and compared with healthy women (as a control group) for a one-year study. The serum alanine aminotransferase, aspartate aminotransferase, and cadherin levels 6 and 11 of participants were analyzed and compared.

**Results:** A total of 189 pregnant women were subdivided into 2 groups as preeclamptic (n=94) and women with healthy pregnancy (n=95). The cadherin 6 and cadherin 11 levels of the preeclamptic patients were significantly higher than those in the control group (p=0.001), and they were found to be significantly higher mainly in patients with early-onset and severe preeclampsia group (p=0.001). The cut-off cadherin 6 and 11 values for severe preeclampsia were found as 98.174 ng/mL and 1.92 ng/mL; with sensitivity of 88.3% and 84% respectively (p=0.001).

**Conclusion:** The data analysis showed elevated serum cadherin 6 and 11 levels associated with the severity and early onset of pre-eclampsia. Serum cadherin 6 and 11 levels can be a candidate marker for the prediction of preeclampsia.

**Keywords:** Cadherin 6, cadherin 11, preeclampsia, severe preeclampsia, early-onset preeclampsia

### Öz

**Amaç:** Preeklampsi, plasenta kaynaklı oldukça morbid bir hastalık olup, hem gebe hem de fetüs için hayatı tehdit edici bir durumdur. Kaderin 6 ve 11, plasenta oluşumu ve trofoblastik gelişimde önemli bir rol oynayan adezyon molekülleridir. Çalışmamızda, preeklampsi olan gebe kadınlarda serum kaderin 6 ve 11 seviyelerindeki değişimleri incelemeyi amaçladık.

**Gereç ve Yöntemler:** Bir yıllık bir çalışma çerçevesinde preeklampsi olan gebeler seçildi ve kontrol grubu olarak sağlıklı gebelerle karşılaştırıldı. Katılımcıların serum alaninaminotransferaz, aspartate aminotransferaz, kaderin 6 ve 11 seviyeleri analiz edildi ve karşılaştırıldı.

**PRECIS:** In this study, we evaluated and found higher levels of serum cadherin levels 6 and 11 levels of pregnant women with preeclampsia than in healthy pregnant women.

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**Received/Geliş Tarihi:** 11.05.2022 **Accepted/Kabul Tarihi:** 06.06.2022

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Turkish Journal of Obstetrics and Gynecology published by Galenos Publishing House.

**Bulgular:** Toplam 189 gebe, preeklampitik (n=94) ve sağlıklı gebeliği olan (n=95) olmak üzere iki gruba bölünmüştür. Preeklampitik hastaların kaderin 6 ve kaderin 11 düzeyleri kontrol grubuna göre anlamlı olarak yüksekti ( $p=0,001$ ) ve özellikle erken başlangıçlı ve şiddetli preeklampsili hastalarda anlamlı olarak yüksek bulundu ( $p=0,001$ ). Şiddetli preeklampsisi için cut-off kaderin 6 ve 11 değerleri sırasıyla %88,3 ve %84 duyarlılıkla, 174 ng/mL ve 1,92 ng/mL olarak bulundu ( $p=0,001$ ).

**Sonuç:** Verilerin analizi, yüksek serum kaderin 6 ve 11 seviyelerinin preeklampsinin şiddeti ve erken başlangıcı ile ilişkili olduğunu gösterdi. Serum kaderin 6 ve 11 seviyeleri, preeklampsinin öngörülmesi için aday birer belirteç olabilir.

**Anahtar Kelimeler:** Kaderin 6, kaderin 11, preeklampsisi, ağır preeklampsisi, erken-başlangıçlı preeklampsisi

## Introduction

Preeclampsia is a disease characterized by hypertension (systolic blood pressure  $\geq 140$  mmHg, diastolic blood pressure  $\geq 90$  mmHg), proteinuria, or end-organ damage, occurring generally after 20 weeks of gestation<sup>(1)</sup>. According to the gestational week, it is classified as early-onset if diagnosed under 34 weeks, and late-onset preeclampsia if diagnosed at 34 weeks and above<sup>(2)</sup>. Worldwide, it complicates 4-5% of all pregnancies<sup>(3)</sup>, causing maternal deaths in more than 50.000 mothers per year<sup>(4)</sup>. Apart from maternal mortality, cerebrovascular events can lead to serious maternal complications, such as liver rupture, pulmonary edema, acute renal failure, or fetal complications, such as preterm labor, intrauterine growth restriction, and fetal death<sup>(5)</sup>.

Placental abnormalities are emphasized in the pathophysiology of preeclampsia. In the normal placental development process, cytotrophoblasts invade maternal spiral arteries at the myometrium level and form vascular spaces<sup>(6)</sup>. However, inadequate remodeling in the spiral arterioles leads to narrowing, ischemia, and, consequently, the development of preeclampsia<sup>(7)</sup>. During placental development, trophoblasts develop in two directions: villous trophoblasts that turn into syncytiotrophoblasts, responsible for the secretion of placental hormones, and extravillous trophoblasts (EVTs), responsible for the invasion of blood vessels in the uterus. EVT's destroy the media of the maternal spiral arterioles, displace them the endothelium and turn into endovascular trophoblasts<sup>(8)</sup>. Cytotrophoblasts must undergo several changes to transform from the epithelial form to the mesenchymal structure, forming the endothelium. Presenting epithelial structure, they are tightly linked to each other by desmosomes, tight junctions, and cadherins that receive support from cytoskeleton structures, such as the actin and catenin basement membrane by integrins<sup>(9)</sup>. However, in mesenchymal cells, either the inter-cell or inter-basal membrane adhesion molecule expression decreases. These cells are prone to migration and potentially invade the myometrium<sup>(10,11)</sup>.

Cadherins are a transmembrane protein family, provide cell communication with the microenvironment and regulate the structural microarchitecture of the cytoskeleton and cell<sup>(12)</sup>. Acting as biophysical and chemical sensors in the cell's microenvironment, cadherins also regulate cell growth and behavior<sup>(13)</sup>. Cadherin 6 is a protein in the class II cadherin group and is involved in the embryological development

of the kidney and central nervous system by triggering epithelial-mesenchymal transformation<sup>(14,15)</sup>. Despite this function in the embryonal period, cadherin 6 is also detected in renal carcinoma in adults and is considered a sign of a poor prognosis<sup>(16)</sup>. It has been shown that cadherin 6 is also expressed in the endometrial glandular epithelium and stroma in the follicular phase of the menstrual cycle and EVT's<sup>(17)</sup>. Furthermore, cadherin 11 belongs to the family class II cadherin, responsible for bone, cartilage, and neuronal development in embryonal life<sup>(18,19)</sup>. It is responsible for the terminal transformation of cytotrophoblasts into syncytiotrophoblasts in the human placenta<sup>(20)</sup>, regulates the relationship between maternal decidua and trophoblasts, and decreases trophoblast proliferation<sup>(17)</sup>.

In this study, considering the potential role of cadherin 6 and 11 in the development of pre-eclampsia condition due to their impact on placental development, we investigated the change in serum cadherin 6 and 11 in pregnant women with preeclampsia and the relationship with disease severity.

## Materials and Methods

### Study Design

A cohort of pregnant women was enrolled in a case-control study between February 2018 and February 2019. The study was conducted within the guidelines of Helsinki. The patients were all informed about the investigation and conditions for participation at the beginning of enrollment, after the local institutional review board (Committee on Human Research) had approved the study, by grant number KAEK2020/4/2. Written, informed consent was obtained from the participants. All potential enrolled subjects underwent a preliminary screening during pregnancy, a routine obstetric evaluation, and a biochemical routine test for complete blood count and urinalysis. The gestational week was calculated according to the first day of the last menstrual period or the first-trimester ultrasound.

The study setup included a study cohort of patients with preeclampsia, aged between 17 and 44 years and between 26 and 38 gestational weeks of pregnancy, compared with a healthy cohort of pregnant women, matched for the same maternal and gestational age and from the same geographical area (as the control group). Patients with preeclampsia were further categorized as mild and severe, early and late onset preeclampsia according to the following criteria.

Mild preeclampsia was determined<sup>(1)</sup> when new onset of hypertension was measured twice, at least four hours apart: systolic blood pressure >140 mmHg or diastolic pressure >90 mmHg in a woman who was normotensive at <20 weeks of gestation. Urinary excretion of 300 mg in a 24-hour period or protein to creatinine ratio of 0.3 mg/dL was considered for diagnosis, and a dipstick reading of 1+ was used only if other quantitative methods were not immediately available at screening.

Severe preeclampsia was defined<sup>(1)</sup> based on additional signs and symptoms: 1) systolic blood pressure >160 mmHg or diastolic pressure >110 mmHg on two occasions at least four hours apart while the patient was on bed rest; 2) proteinuria of >5 g in a 24-hour period or 3+ on a urine dipstick; 3) hemolysis (peripheral blood smear or lactate dehydrogenase >480 U/L), elevated liver function (serum aspartate amino transferase >64 U/L or serum alanine amino transferase >80 U/L), thrombocytopenia (platelets <100.000), oliguria (<500 mL in 24 hours); 4) creatinine >1.1 mg/dL or a doubling of the serum creatinine concentration, with no known renal dysfunction or disease, cerebral or visual disturbances, or convulsions, with no history of seizure disorders. While early-onset pre-eclampsia was defined as pre-eclampsia occurring before 34 weeks, late-onset preeclampsia was defined as pre-eclampsia causing 34 weeks or latter.

Exclusion criteria for both enrolled groups were preexisting medical conditions, such as thyroid disorders, chronic hypertension, diabetes mellitus, multiple pregnancies, infection signs, and taking any medication.

Pregnant women whose gestational week was below 37 at delivery were administered two doses of betamethasone.

The following demographic, obstetric, and biochemical parameters were collected and compared for the pregnant women: age, gravida, parity, delivery type, alanine aminotransferase, aspartate aminotransferase, cadherin 6 and 11 levels, body mass index (BMI), birth weight of newborns, Apgar score at the fifth minute (min), and the need for a newborn intensive care unit (NICU).

### Biochemical Analysis

Five milliliters of blood was obtained from the antecubital vein of the pregnant women at the time of application and centrifuged (Shimadzu UV160A, S. No: 28006648, Japan) at 3,000 x g for 10 min, and the sera were stored at -80 °C. On the evaluation day, the samples were melted at room temperature. All assays were conducted according to the manufacturer's instructions. The samples, which had a higher concentration, were diluted and measured in duplicate.

The concentrations of cadherin 6 serum were measured using a commercially available Human Cadherin 6 Enzyme-Linked Immunosorbent Assay (ELISA) Kit (Bioassay Technology Laboratory, Cat No. E6937Hu, Shanghai, China). The concentrations of cadherin 11 in serum were measured, using a commercially available Human Cadherin 11 Enzyme-Linked

Immunosorbent Assay (ELISA) Kit (Bioassay Technology Laboratory, Cat No. E3272Hu, Shanghai, China). The enzymatic reactions were quantified in an automatic microplate photometer. The concentrations of cadherin 6 and 11 were determined by comparing the samples' optic density with the standard curve. All assays were conducted according to the instructions of the manufacturer. The mean inter-assay and intra-assay coefficients of variation percentage for cadherin 6 were <10% and <8%, respectively. The assay ranges of the kit are 10-2.000 ng/L. The sensitivity of the test is 4.93 ng/L for cadherin 6. The assay ranges of the kit are 0.05-20 ng/mL. The sensitivity of the test is 0.025 ng/mL for cadherin 11. The rest of the blood analyses were carried out within 2 h of blood sampling, using a hematology analyser (GEN-S; Beckman-Coulter Inc., USA).

### Statistical Analysis

The sample size was calculated according to a medium effect size, 80% power, and a significance level of 0.05. IBM SPSS 21 software (SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was used for statistical analysis. Descriptive statistical methods (median, frequency, percentage, minimum, maximum) were used to evaluate the study data. The suitability of quantitative data for normal distribution was tested by the Kolmogorov-Smirnov and Shapiro-Wilk tests and graphical evaluations. The Kruskal-Wallis test was used to compare three groups of non-normally distributed data Pearson chi-square and Yates chi-square tests were used to examine the relationship between cadherin 6, 11 and preeclampsia and control group. Diagnostic screening tests (sensitivity, specificity, positive predictive value, negative predictive value) and the receiver operating characteristic (ROC) curve analysis assessed the cadherin 6 and 11 cutoff. Significance was evaluated at the level of  $p < 0.05$ .

### Results

At the beginning of the study, 108 pregnant women with preeclampsia and 103 healthy pregnant women agreed to participate, but 14 pregnant women were excluded from the preeclampsia group (two women refused to participate, six had chronic hypertension, four had thyroid disorders, and two had signs of infection). Furthermore, eight pregnant women were excluded from the control group (three refused to participate, two were expecting twins, and three had gestational diabetes). Finally, 94 pregnant women with preeclampsia and 95 healthy pregnant women were included in the study (Figure 1).

The control, mild, and severe preeclampsia groups were similar in median maternal age ( $p=0.867$ ), gravidity ( $p=0.150$ ), and parity ( $p=0.173$ ). The BMI values of the women with severe preeclampsia ( $p=0.003$ ) and mild preeclampsia ( $p=0.004$ ) were significantly higher than those of the controls, and the BMI values of women with severe and mild pre-eclampsia were similar ( $p=0.857$ ).

The birth weight and Apgar score at the fifth min of the women with severe ( $p=0.001$ ) and mild preeclampsia ( $p=0.001$ ) were significantly lower than the controls. Also, the birth weight ( $p=0.001$ ) and Apgar score at the fifth min ( $p=0.02$ ) of the subjects with severe preeclampsia was significantly lower than those with mild pre-eclampsia.

The NICU admission ( $p=0.001$ ) and cesarean section rates ( $p=0.001$ ) of the women with severe preeclampsia were higher than those of the women with mild preeclampsia and the controls. While the CS rates of the women with mild preeclampsia were higher than those of the controls ( $p=0.001$ ), the NICU admission rates were similar ( $p=0.165$ ).

All maternal and neonatal characteristics according to the severity of preeclampsia are shown in Table 1.

The median serum cadherins 6 and 11 levels of the participants with severe preeclampsia were higher than those of the pregnant women with mild preeclampsia and the controls ( $p=0.001$ ). The median serum cadherins 6 and 11 of pregnant women with mild preeclampsia were higher than those of controls ( $p=0.001$ ). The median serum cadherins 6 and 11 levels of the study groups concerning the severity of preeclampsia are shown in Table 2.

As presented in Table 3, the median serum cadherin 6 and 11 levels of the women with early-onset pre-eclampsia ( $n=32$ ) were higher than those of the controls and women with late-onset pre-eclampsia ( $n=62$ ) ( $p=0.001$ ). The median serum cadherins 6 and 11 of pregnant women with late-onset preeclampsia were also higher than those of the control subjects ( $p=0.001$ ).

The ROC curve analysis of serum cadherin 6 and 11 data revealed that for preeclampsia prediction, with a cut-off value of more than 98.174 ng/mL, cadherin 6 had a sensitivity and specificity of 92% and 91.4%, respectively ( $p=0.001$ ). It also showed that above 98.174 ng/mL, the risk of severe preeclampsia increased 121.71 fold. Moreover, for predicting preeclampsia, with a cut-off value of more than 1.92 ng/mL, cadherin 11 had a sensitivity and specificity of 86% and 88.5%, respectively ( $p=0.001$ ), and above 1.92 ng/mL, severe pre-eclampsia risk increased 47.22 fold (Figure 2 and Figure 3).

## Discussion

In this study, it was shown that serum cadherin 6 and 11 levels increased with the severity and onset of pre-eclampsia.

Both severe and early-onset preeclampsia caused a meaningful increase in the level of these biomarkers, and clinical and obstetric variables were in accordance with the clinical presentation of preeclampsia.

In placental development, cadherins play an important role<sup>(21)</sup>, and it is therefore vital that experimental studies be conducted to examine the relationship between cadherin 6 and 11 and preeclampsia, as none currently exist. Cadherin 6 affects the prognosis of pregnancies, starting from the preimplantation period. In the endometrium, expression of cadherin 6 predominates in the follicular phase of the menstrual cycle, whereas expression of cadherin 11 predominates in the luteal phase and prepares the endometrium for implantation. However, if the cadherin 6 to 11 change cannot be achieved

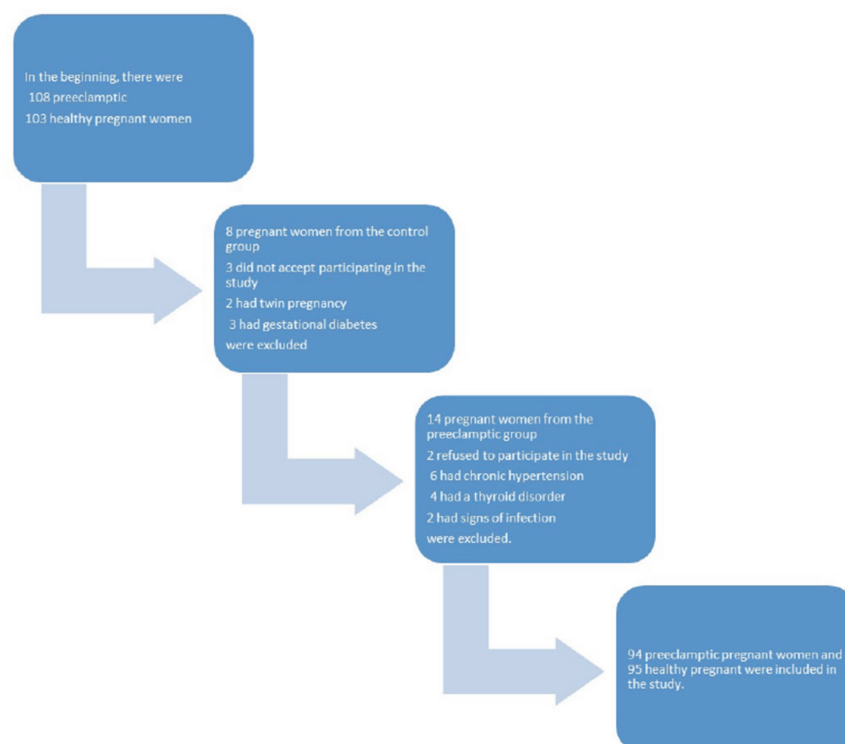


Figure 1. Study flowchart

and cadherin 6 continues to be expressed in high amounts, an accurate implantation cannot succeed and adverse pregnancy outcomes, such as miscarriage, preeclampsia, and intrauterine growth retardation, may occur<sup>(22)</sup>.

In our study, we found that cadherin 6 levels were higher in pregnant women severe and early pre-eclampsia. Cadherin 6 is the dominant marker in invasive EVT and regulates the

communication between maternal blood vessels, myometrium, and EVT. Furthermore, Dunne et al.<sup>(23)</sup> showed that cadherin 6 is expressed on the platelet surface and supports platelet adhesion, aggregation, and thrombus formation. Additionally, when the integrin  $\alpha$ IIb $\beta$ 3 receptor, which cadherin 6 is related, is blocked, platelet aggregation is inhibited<sup>(23)</sup>. Bouck et al.<sup>(24)</sup> showed in mice that cadherin 6 expression in

**Table 1.** Maternal and neonatal characteristics according to the severity of preeclampsia status

		Preeclampsia status			p
		Controls	Mild	Severe	
		(n=95)	(n=44)	(n=50)	
Age (year)	Min-Max (Median)	17 - 40 (27)	19 - 43 (26.5)	19 - 40 (28)	<sup>a</sup> 0.867
BMI (kg/m <sup>2</sup> )	Min-Max (Median)	18 - 34.77 (23.12)	20 - 36.77 (23.885)	18.12 - 37 (25.165)	<sup>a</sup> 0.009*
Gravidity	Min-Max (Median)	1 - 7 (2)	1 - 5 (2)	1 - 6 (2.5)	<sup>a</sup> 0.150
Parity	Min-Max (Median)	0 - 6 (1)	0 - 3 (1)	0 - 5 (1)	<sup>a</sup> 0.173
Birth weight (gr)	Min-Max (Median)	1500 - 5200 (3200)	2040 - 4100 (2900)	950 - 4500 (1800)	<sup>a</sup> =0.001*
Apgar score at 5 <sup>th</sup> minute	Min-Max (Median)	7 - 9 (9)	0 - 9 (9)	4 - 9 (8)	<sup>a</sup> =0.001*
NICU admission	No	88 (58.2%)	38 (25.16%)	25 (16.55%)	<sup>b</sup> =0.001*
	Yes	7 (18.42%)	6 (15.78%)	25 (65.78%)	
Delivery type	Vaginal	94 (71.21%)	23 (17.42%)	15 (11.36%)	<sup>b</sup> =0.001*
	Cesarean section	1 (1.75%)	21 (36.84%)	35 (61.40%)	

<sup>a</sup>Kruskal-Wallis H test, <sup>b</sup>Pearson ki-kare test, \*p<0.05  
NICU: Newborn Intensive Care Unit, BMI: Body mass index, Min: Minimum, Max: Maximum, Data are expressed as range (median) and number (line percentage) as appropriate

**Table 2.** Laboratory findings according to the severity of preeclampsia status

		Preeclampsia status			p
		Controls	Mild	Severe	
		(n=95)	(n=44)	(n=50)	
Cadherin 6	Min-Max (Median)	67.15 - 2553.4 (81.26)	73.44 - 146.7 (92.83)	81.24 - 2090.49 (202.75)	<sup>a</sup> =0,001*
Cadherin 11	Min-Max (Median)	0.35 - 14.91 (0.99)	0.57 - 12.32 (1.45)	0.88 - 21.78 (3.51)	<sup>a</sup> =0,001*

<sup>a</sup>Kruskal-Wallis H test, \*p<0.05, Min: Minimum, Max: Maximum

**Table 3.** Laboratory findings according to onset of preeclampsia status

		Preeclampsia status			p
		Controls	Early onset preeclampsia	Late onset preeclampsia	
		(n=95)	(n=32)	(n=62)	
Cadherin 6	Min-Max (Median)	67.15 - 2553.4 (81.26)	81.24 - 2090.49 (265.63)	73.44 - 996.19 (94.03)	<sup>a</sup> =0,001*
Cadherin 11	Min-Max (Median)	0.35 - 14.91 (0.99)	0.88 - 21.78 (4.62)	0.57 - 19.46 (1.82)	<sup>a</sup> =0,001*

<sup>a</sup>Kruskal-Wallis H test, \*p<0.05, Min: Minimum, Max: Maximum



platelets contributes to thrombus formation. Considering that preeclampsia causes widespread endothelial damage in many organs and atherosclerosis development in the placental vessels<sup>(25)</sup>, the prothrombotic state, due to high levels of cadherin 6, could contribute to the aggravation of the disease and the course of eclampsia. Also, MacCalman et al.<sup>(17)</sup> showed that the lack of cadherin 6 expression in invasive EVT may result in excessive trophoblast invasion into the maternal tissue. Considering the opposite of this physiological situation, that is, when cadherin

6 is at a high level, an inadequate invasion may develop and pre-eclampsia may occur.

Cadherin 11 is responsible for the terminal transformation of cytotrophoblasts into syncytiotrophoblasts into the placenta, reducing cell proliferation<sup>(20)</sup>. The trophoblast assumes critical tasks in decidual development and early implantation by arranging the decidua and trophoblast communication through the growth factor  $\beta$ -1 (TGF $\beta$ -1). Finally, when placental development is completed, cadherin 11 expression decreases<sup>(17)</sup>. Garrido-Gomez et al.<sup>(26)</sup> evaluated the microenvironment during pregnancy in the culture medium and the decidualisation of the cells derived from placental tissue of pregnant women with severe preeclampsia and endometrial stromal cells of women with a history of severe preeclampsia. In the Gomez study, although the transcription profile was the same as the healthy control group, the cells of the patients with severe pre-eclampsia and a history of severe pre-eclampsia had undergone defective decidualization and cytotrophoblast invasion. While defective decidualization is the basis of preeclampsia, it can be prevented with preventative therapies.

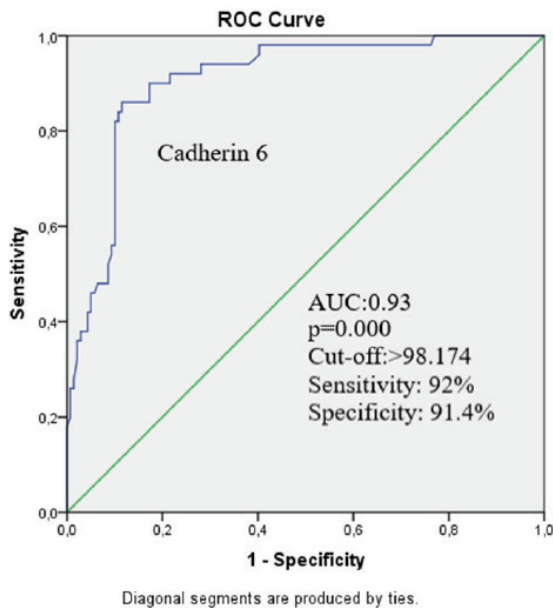
Our results showed that the cadherin 11 level was higher in pregnant women with severe and early onset preeclampsia. There is some evidence in the literature that supports our outcome. Cadherin 11 induces the formation of large cellular aggregates and multinucleated cells from EVT by inducing through TGF $\beta$ -1 in cell culture medium<sup>(27)</sup>. Thus, when the cadherin 11 level is higher than it should be, uncontrolled cellular aggregates may affect placental perfusion. Also, it was shown that cadherin 11 is predominantly expressed in complete hydatidiform mole<sup>(20,28)</sup> and preeclampsia can be seen in the first trimester in hydatidiform mole. Similarly, the risk of preeclampsia in the second trimester in triploidy pregnancies is 35%<sup>(29)</sup>. It could be speculated that the relationship between preeclampsia risk and hydatidiform mole might be due to the cadherin 11 protein.

### Study Limitations

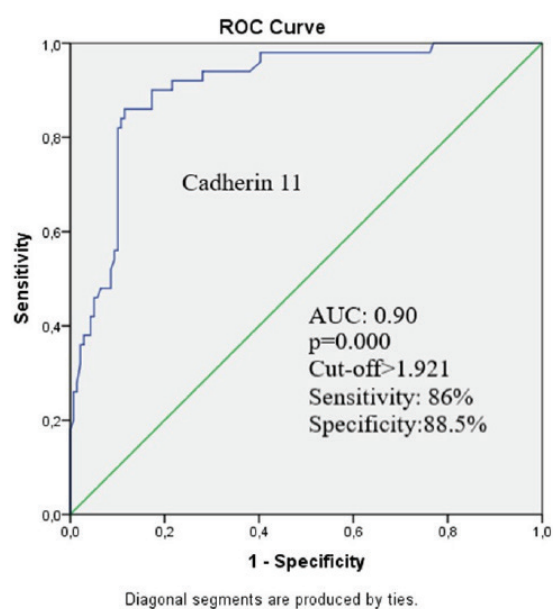
The limitations of the authors' investigation are that the study was conducted in a single centre and the samples were taken from confirmed cases of pre-eclampsia, not randomly during pregnancy; and not just in the suspected cases of pre-eclampsia to confirm the progressive increase in biomarkers, depending on the severity of the disease. In future studies, to clarify the cause-effect relationship between preeclampsia and cadherin 6 and 11 level, changes of these markers at the tissue levels will be examined.

### Conclusion

The authors detected a significant relationship between the increases in cadherins 6 and 11 with pre-eclampsia development, promoting both biomarkers as tools for the diagnosis and severity of the disease. These findings could contribute to the elucidation of the pathogenesis, screening, and diagnosis of preeclampsia, even if larger studies must determine the roles



**Figure 2.** Receiver operating characteristic curve of serum cadherin 6 in women with severe preeclampsia



**Figure 3.** Receiver operating characteristic curve of serum cadherin 11 in women with severe preeclampsia

of these cadherins during placentation and the course of pre-eclampsia.

### Ethics

**Ethics Committee Approval:** The study was approved by the the local institutional review board by grant number KAEK2020/4/2 (Samsun Training and Research Hospital).

**Informed Consent:** Written informed consent was obtained from the participants.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Supervision: Ş.H., A.T., Concept: S.Ç., Ş.H., Design: H.G., C.S.Ç., Data Collection or Processing: C.S.Ç., S.Ç., Analysis or Interpretation: H.G., N.Y., B.A., Literature Search: N.Y., B.A., Writing: H.G., A.T.

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

**Financial Disclosure:** The authors declared that this study received no financial support.

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