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Research Article

Oxidative Stress and Anti-Carbonic Anhydrase Antibody Levels in Early Preeclampsia: A Clinical Investigation

Ayse Sebnem Erenler[1], Rauf Melekoglu[2], Tugba Raika Kiran[3], Feyza Inceoglu[4]

[1]Malatya Turgut Özal University, Faculty of Medicine, Department of Medical Biology, Malatya, Türkiye
[2]İnönü University, Faculty of Medicine, Department of Obstetrics and Gynecology, Malatya, Türkiye
[3]Malatya Turgut Özal University, Faculty of Medicine, Department of Medical Biochemistry, Malatya, Türkiye
[4]Malatya Turgut Özal University, Faculty of Medicine, Department of Biostatistics, Malatya, Türkiye

Abstract

Aim: Preeclampsia (PE) is a dangerous condition that affects 3–5% of pregnancies and has a substantial risk of death and morbidity for both mothers and newborns. The processes behind the etiology of PE are not entirely known, despite the fact that it is the primary cause of illness and death among mothers globally. In order to further understand the correlations between these parameters, this study will look at the levels and presence of anti-carbonicanhydrase (CA) I and II antibodies, total oxidant capacity (TOC), total antioxidant capacity (T-AOC), and malondialdehyde (MDA) in early PE.
Material and Method: The research analyzed 30 pregnant women with early PE and 30 normal pregnant women as the control group. Serum levels of anti-CAI (pg/mL), anti-CAII (ng/mL), MDA (nmol/mL), TOS (U/mL), T-AOC (U/mL) were measured and compared between the two groups.
Results: Significant variations were noted in the amount of anti-CA I, anti-CA II, MDA, TOS, and T-AOC (both $p<0.05$) between the control group and the early PE group. More specifically, oxidative stress indicators were changed and increased levels of anti-CA I and anti-CA II were seen in the early PE group in comparison with the control group.
Conclusion: The findings show that elevated amounts of anti-CAI and anti-CAII antibodies may serve as predictive markers for early PE. The significant differences in oxidative stress parameters further support the oxidative stress involvement in the pathogenesis of early PE. However, more extensive Research is required to validate these results and clarify the mechanisms underlying PE.

Keywords: Antioxidants, carbonic anhydrase, malondialdehyde, oxidants, oxidative stress, preeclampsia

INTRODUCTION

Preeclampsia (PE) is a hypertensive condition that affects 3-5% of women during the second half of pregnancy, posing significant risks to fetal, perinatal, and maternal health, especially in nations with poor and moderate incomes (1). Clinically, PE is categorized based on its onset: early PE, which happens before the thirty-fourth week of pregnancy, and late PE, which happens after the thirty-fourth week (2). Early PE, although less common, is a more severe form associated with abnormal placentation and intrauterine growth restriction (3). It affects approximately 0.5% of all pregnancies, accounting for 10% of all PE cases, and is linked to higher maternal and neonatal morbidity and mortality compared to late-onset PE.

Understanding the etiology of early PE is crucial due to its severity. The primary source of stress in early PE is uteroplacental malperfusion, which is secondary to abnormal remodeling of the uterine spiral arteries (4). Studies have shown that oxidative stress is more pronounced in early PE in comparison with late PE. The pathogenesis of PE is thought to originate in the utero-placental unit and is exacerbated by oxidative stress until it impacts the maternal endothelium (5). Free oxygen radicals and peroxides build up as a result of an imbalance between the body's natural antioxidant defense mechanisms and the oxidative chemicals that are produced. This imbalance is known as oxidative stress.

Oxidative stress evidences have been observed in both the placenta and the maternal circulation in cases of PE (6). It has been discovered that placentas from women with PE have lower antioxidant capacities than placentas from pregnancies that are typical. Additionally, blood tests on

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Corresponding Author: Ayse Sebnem Erenler, Malatya Turgut Özal University, Faculty of Medicine, Department of Medical Biology, Malatya, Türkiye
E-mail: serenler44@gmail.com

females with PE have shown increased levels of oxidative alterations of proteins and lipoprotein particles and decreased levels of antioxidants (7).

The carbonic anhydrase (CA) enzyme, which plays a versatile role in metabolism, has been identified as a potential contributor to the pathogenesis of adverse prenatal outcomes. The CA enzyme (EC 4.2.1.1) is a zinc-containing metallo enzyme. Antibodies against CA-I and CA-II enzymes have been proved to inhibit CA catalytic activity and disrupt placental and endometrial functions, potentially contributing to PE (8,9). Despite the importance of CA in metabolic processes, there are few studies investigating its role in the etiopathogenesis of hypertensive diseases in pregnancy.

In this study, we measured oxidative stress markers and levels of anti-CAI and anti-CAII antibodies in pregnant females with early PE to explore potential correlations. The focus is to find out if anti-CA I and II antibodies are present in PE and to examine the connections between these autoantibodies and parameters measuring MDA, TOC and T-AOC. This study aims to provide insight into the role of CA and oxidative stress in the pathogenesis of early PE, potentially contributing to better understanding and management of the condition.

MATERIAL AND METHOD

Ethical Approval

The Inonu University Faculty of Medicine Clinical Research Ethics Committee granted the project approval (Approval No. 2021/113). The research adhered to the World Medical Association Declaration of Helsinki (including the amendments made in 2013) and followed Good Clinical Practices (GCP) guidelines throughout the study.

Study Population

All pregnant women who attended the Prenatal Diagnosis and Treatment Unit of the Department of Gynecology and Obstetrics at Inonu University Faculty of Medicine Hospital between May 1, 2021, and May 1, 2022, and were diagnosed with early preeclampsia were included in the research. The research group was made up of 30 individuals having early preeclampsia, while 30 normotensive pregnant females, matched for age, gestational week, and body mass index (BMI), set up the control group. Gestationaliage was confirmed by first-trimester ultrasonography measurements.

Exclusion and Inclusion Criteria

Inclusion criteria for the research were as follows:

- Pregnant females aged 18-45,
- Singleton, live pregnancies,
- Diagnosed with early-onset PE,
- BMI; 35kg/m^2,
- Normal medical and obstetric history.

Exclusion criteria were as follows:

- Multiple pregnancies,
- Gestational diabetes,
- Preterm premature rupture of membranes,
- Presence of maternal systemic diseases (dyslipidemia, asthma, malignancy, chronic renal failure, chronic hypertension, pulmonary or cardiac diseases),
- Abnormali karyotype or fetal malformations,
- Alcohol and tobacco use.

Diagnosis of Preeclampsia

PE was diagnosed following the criteria established by the American College of Obstetricians and Gynecologists (ACOG). PE was defined as high blood pressure (140/90 mmHg) beginning after the 20th week of pregnancy in a previously normotensive female who also had proteinuria and/or end-organ dysfunction (ACOG Practice Bulletin, Number 222).

Blood Sample Collection and Processing

Following an overnight fast, participants; blood samples were drawn in the morning and placed into gel separator (serum) tubes. After 30 minutes of clotting at room temperature, the samples were centrifuged for 10 minutes at 1200 g. The serum was then separated and transferred to micro-volume eppendorf tubes and kept at -80°C until biochemical analysis.

Biochemical Analysis

ELISA for serum anti-CA I and II antibodies: Serum levels of anti-CA I and anti-CA II antibodies were determined using commercial enzyme-linked immunosorbent assay (ELISA) kits (Bioassay Technology Laboratory, Cat. No: E1371Hu, China). Total Antioxidant Capacity (T-AOC): T-AOC levels in serum samples were measured using a commercial ELISA kit (Sunredbio, Cat. No: 201-12-2200, China). Total Oxidant Capacity (TOC): TOC levels were measured using a commercial ELISA kit (Sunredbio, Cat. No: 201-12-5539, China). Malondialdehyde (MDA): MDA values were measured using a commercial ELISA kit (Bioassay Technology Laboratory, Cat. No: E1371Hu, China).

Sample Size Calculation

A power analysis was conducted to ascertain the necessary sample size for the research. The investigation was predicated on the finding that pregnant women with early PE had a statistically significant drop in the anti-carbonic anhydrase II ratio of 1.0 pg/mL with a 1.7 standard deviation. The calculation indicated that to achieve 80% statistical power at a 5% significance level (two-tailed), a minimum of 30 participants per group was required.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) software, version 22.0 (SPSS Inc., New York, USA), was used to conduct statistical analyses. Means, standard deviations, minimum and maximum values were used to describe continuous variables, while medians with interquartile ranges were used to show baseline characteristics of the study and control groups. The distribution of the data was examined for normalcy using

the Shapiro-Wilk test. Two-sample t-tests were used to examine differences between the study and control groups for normally distributed data. The Mann-Whitney U test was applied to data that were not regularly distributed. Frequencies and percentages were used to summarize the categorical variables, and Pearson exact chi-square test and continuity-corrected chi-square test were used to make comparisons. A p-value of less than 0.05 on both sides was deemed statistically significant.

RESULTS

Demographic and Clinical Characteristics

The demographic and clinical characteristics of the participants are summarized in Tables 1 and 2. There were no statistically significant differences between the control and study groups regarding parity, gravidity, BMI, maternal age, ethnicity, and smoking habits (Table 1).

Obstetric History and Placenta-Mediated Disease

A statistically significant difference was observed among the study and control groups with regard to early PE and the presence of placenta-mediated diseases in the obstetric history ($p<0.05$). Additionally, a significant difference was observed in the need for neonatal intensive care unit (NICU) admission between the groups ($p<0.05$) (Table 1).

Maternal and Fetal Characteristics

Table 2 presents maternal and fetal characteristics. No significant differences were found between groups concerning gestational age, number of pregnancies, parity, weight, height, BMI, 24-hour urine protein, platelet count (PLT), alanine amino transferase (ALT), cord blood pH value, and cord blood base excess ($p>0.05$).

Table 1. Demographicand clinical characteristics

Variable	Group	n/%	Groups		Total	p value
			Study	Control		
Early PE	(-)	n	26	30	56	0.016*
		%	86.7	100.0	93.3	0.016*
	(+)	n	4	0	4	0.016*
		%	13.3	0.0	6.7	0.016*
The presence of placenta-mediated diseases in the obstetric history	(-)	n	12	17	29	0.005*
		%	40.0	56.7	48.3	0.005*
	IUGR	n	15	6	21	0.005*
		%	50.0	20.0	35.0	0.005*
	PE	n	0	1	1	0.005*
		%	0.0	3.3	1.7	0.005*
	OLIGO	n	0	4	4	0.005*
		%	0.0	13.3	6.7	0.005*
	PPROM	n	0	2	2	0.005*
		%	0.0	6.7	3.3	0.005*
	LGA	n	2	0	2	0.005*
		%	6.7	0.0	3.3	0.005*
	IUEF	n	1	0	1	0.005*
		%	3.3	0.0	1.7	0.005*
Gender	Female	n	11	13	24	0.598*
		%	36.7	43.3	40.0	0.598*
	Male	n	19	17	36	0.598*
		%	63.3	56.7	60.0	0.598*
Need for neonatal intensive care unit (NICU)	(-)	n	4	20	24	0.001*
		%	13.3	66.7	40.0	0.001*
	(+)	n	26	10	36	0.001*
		%	86.7	33.3	60.0	0.001*
Total		n	**30**	**30**	**60**	
		%	**100.0**	**100.0**	**100.0**	

n: number of samples, %: percent, test value: chi-square test value ($\chi 2$), p value: statistical significance, *p<0.05: There is a statistically significant difference between the groups

Table 2. Maternal and fetal characteristics

Variable	Study		Control		Sig. (p)
	Mean±SD	M (Min-Max)	Mean±SD	M (Min-Max)	
Number of pregnancies	32±2.96	31.5 (28-37)	32.57±4.08	32 (24-40)	0.721[a]
Age	31.83±5.98	31 (20-42)	29.33±5.8	29.5 (18-41)	0.125a
G	2.7±1.34	2.5 (1-6)	2.73±1.57	3 (1-6)	0.964[a]
P	1.13±1.2	1 (0-4)	1.2±1.19	1 (0-4)	0.799[a]
A	0.57±0.86	0 (0-4)	0.53±0.94	0 (0-4)	0.607[a]
Weight	77.03±16.41	77 (52-110)	69.45±15.62	73.25 (8-90)	0.216[a]
Height	161.8±5.71	162 (150-175)	160.4±5.86	160 (145-170)	0.238[a]
BMI	29.37±5.83	29.73 (20.83-42.97)	27.02±6.1	26.98 (3.13-35.16)	0.304[a]
PE diagnosis pregnancy week	32±2.96	31.5 (28-37)	0±0	0 (0-0)	
Systolic blood pressure	157±23.84	159.5 (109-207)	110.97±11.55	107.5 (90-135)	**<0.001*[a]**
Diastolic blood pressure	99.03±13.29	100 (70-130)	72.93±8.59	72.5 (60-89)	**<0.001*[a]**
24 H MTP	3371.31±5009.35	1170 (150-21986.25)	210.7±62.6	215 (70-310)	**<0.001*[a]**
PLT	219.37±78.65	222 (83-383)	232.33±77.23	221.5 (95-364)	0.549[a]
AST	46.07±55.18	22 (9-240)	19.57±5.96	18 (13-35)	**0.038*[a]**
ALT	36.53±48.93	15.5 (6-236)	14.67±5.86	13 (3-34)	0.177[a]
BUN	12.06±6.29	10.64 (3-29.91)	7.43±2.58	7.01 (3.74-14.95)	**0.001*[a]**
CRE	0.7±0.16	0.68 (0.44-1.19)	0.6±0.13	0.6 (0.4-1.1)	**0.002*[a]**
LDH	350.6±168.15	293 (163-886)	210.81±75.23	202.5 (7.4-403)	**<0.001*[a]**
Uric acid	5.82±1.4	5.71 (3.1-8.6)	4.41±1.12	4.2 (2.7-7.8)	**<0.001*[a]**
Birth weight	1818.17±603.27	1780 (500-3240)	2755.9±640.35	2851 (850-3700)	**<0.001*[a]**
Cord blood PH	7.27±0.12	7.3 (6.9-7.38)	7.31±0.1	7.33 (7.1-7.56)	0.222[a]
Cord blood LB	-5.93±5.24	-6.15 (-22.4-2.6)	-4.91±2.8	-4.4 (-13.6--1)	0.460[a]
Birth type	Cesarean (n/%)		Vaginal (n/%)		0.236[b]
	30 (100.0)	0(0.0)	27 (90.0)	3 (10.0)	

Cover: mean, sd: standard deviation, min: the smallest value taken is max: the highest value taken, a: Mann Whitney Test Value p value, n: number of samples, %: percent, a: chi-square test($\chi 2$) p value, *p<0.05; There is a statistically significant difference between the groups.

Blood Pressure and Biochemical Parameters

Significant differences were detected between the groups regarding systolic and diastolic blood pressure, as well as levels of aspartate amino transferase (AST), blood urea nitrogen (BUN), lactate dehydrogenase (LDH), creatinine (CRE), uric acid, and birth weight (p<0.05) (Table 2).

OxidativeStress Markers and Anti-CA Antibodies

The oxidative stress markers and values of anti-carbonic anhydrase (CA) antibodies were significantly different between the groups. anti-CA I (pg/mL) (Figure 1) and anti-CA II (ng/mL) antibodies (Figure 2), MDA (nmol/mL) (Figure 3), TOC (U/mL) (Figure 4), and T-AOC (U/mL) (Figure 5) were significantly greater in the study group in comparison with the controlgroup (Both p<0.05) (Table 3).

Table 3. Oxidative stress markers and anti-CA antibodies

Valuable	Study		Control		Mann Whitney Sig. (p)
	Mean ±SD	M (Min-Max)	Mean±SD	M (Min-Max)	
Anti-CAI (pg/mL)	23797.1±7503.95	22889.82 (14903.33-40890.61)	11977.99±2998.27	11108.87 (8440.97-18696.39)	<0.001*
Anti-CAII (ng/mL)	24.47±9.2	26.7 (12.05-37.81)	20.06±7.93	19.49 (9.46-35.91)	0.037*
MDA (nmol/mL)	64.64±9.9	65.09 (42.75-94.61)	20.83±8.13	19.2 (10.55-45.62)	<0.001*
TOC (U/mL)	287.46±62.3	289.44 (146.25-373.4)	50.41±14.02	48.47 (25.02-91.94)	<0.001*
T-AOC (U/mL)	14.67±3.98	13.8 (8.72-25.46)	50.48±9.08	49.77 (36.18-77)	<0.001*

Cover: mean, sd: standard deviation, *p<0.05: There is a statisticallysignificant differenc between the groups

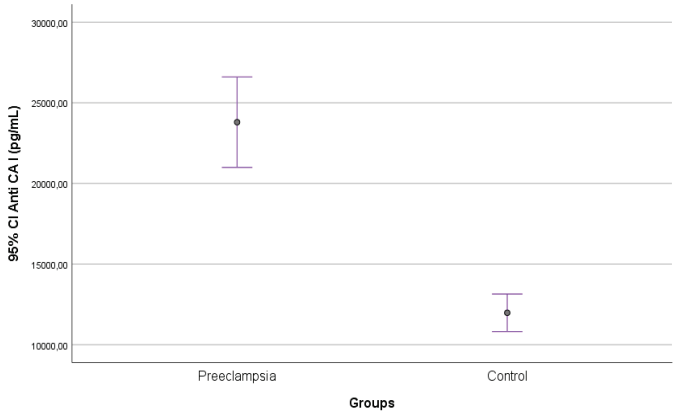

Figure 2. Boxplot in groups for Anti CA I (pg/mL)

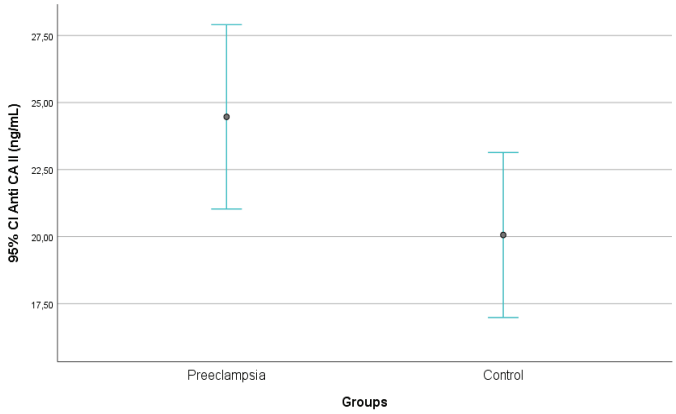

Figure 3. Boxplot in groups for Anti CA II (ng/mL)

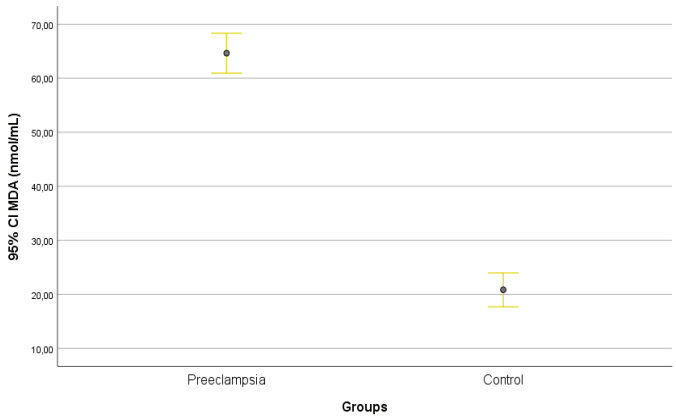

Figure 4. Boxplot in groups for MDA (nmol/mL)

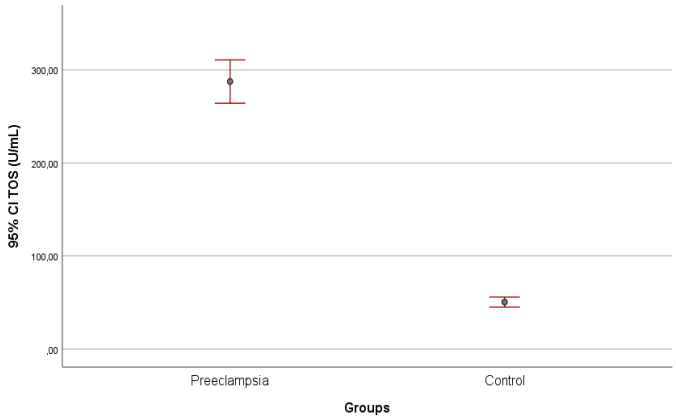

Figure 5. Boxplot in groups for TOC (U/mL)

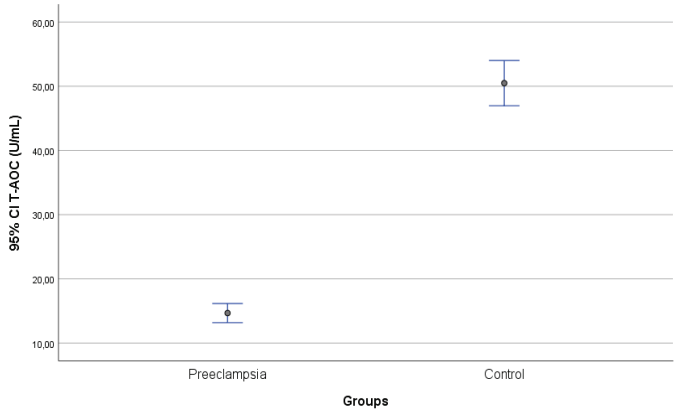

Figure 6. Boxplot (U/mL) in groups for T-AOC

DISCUSSION

In this research, we investigated the existence of CA I and II antibodies in early PE and examined the relation between these auto antibodies and various oxidative stress parameters, including T-AOC, TOC and MDA. Our results demonstrated significant differences between pregnant females with early PE and healthy pregnant females across all measured values. These findings are crucial as they provide a comprehensive evaluation of the antioxidant system and oxidative stress, which are integral to understanding the pathogenesis of early PE.

Our study revealed significantly higher levels of anti-CA I and anti-CA II auto antibodies in pregnant women with early PE in comparison with the control group. This result shows that the autoimmune response against CA I and CA II enzymes may have a part in the pathogenesis of early PE. The presence of CA autoantibodies is known to be linked with auto immune diseases, but there are limited studies focusing on their presence in early PE patients (10). The relationship between early PE and oxidative stress has been well-documented, with several studies indicating that uteroplacental hypoxia/reoxygenation during PE elevation maternal and fetal oxidative stress. Free radicals stemming from an inadequately perfused fetoplacental unit trigger oxidative stress in placental cells, further exacerbating the condition (11).

MDA, a product of lipid peroxidation, acts as a marker for oxidative stress. Our study found elevated MDA levels in the early PE group, indicating on going excessive lipid peroxidation, a marker of oxidative stres (12). This finding is consistent with previous research that have reported higher plasma MDA levels in women with PE compared to normal pregnancies. Lipid peroxidation, driven by free radicals attacking poly unsaturated fatty acids in cell membranes, leads to increased membrane fluidity and permeability (13). This process is toxic and damages endothelial cells, increasing peripheral vasoconstriction, promoting thromboxane synthesis, and decreasing prostacyclin synthesis, all of which are critical for the pathogenesis of PE (14).

Our research also revealed lower T-AOC and higher TOC

levels in pregnant women with early PE compared to normal pregnant women. This imbalance indicates that oxidative stress has a significant part in PE pathogenesis. Previous studies have reported similar findings, suggesting that decreased antioxidant capacity and increased oxidant levels contribute to the development of PE. The relationship between serum T-AOC and PE has been extensively investigated, with studies suggesting that decreased T-AOC is linked with a higher rate of maternal complications and PE (15). The imbalance between free radical production and the antioxidant defense system appears to play a crucial role in PE's pathogenesis, as indicated by lower T-AOC activity in our research in the early PE group in comparison with the normal group (16,17).

Early PE is mostly dependent on the placenta, and increasing oxidative stress during pregnancy may cause tissue damage (18). When oxidative stress in the placenta exceeds antioxidant defenses, oxidative damage can spread to distal tissues, contributing to the pathogenesis of PE. Placentas from women with PE have been shown to have lowered antioxidant capacity in comparison with normal placentas, and females with PE have lower blood levels of antioxidants and oxidatively modified proteins and lipoprotein particles (19). The placental barrier may burst due to oxidative stress and tissue damage, enabling fetal and placental-derived substances to enter the mother's blood and causing endothelial damage in the mother as well as increased oxidative stress and systemic inflammation (15). These findings highlight the importance of further research into the potential effects and mechanisms of antioxidant treatments in early PE.

Evaluating the carbonic anhydrase enzyme, which has a versatile effect on metabolism, alongside oxidative stress markers can significantly contribute to the literature on PE. Our study found that anti-CA I and anti-CA II autoantibody levels were significantly higher in pregnant women with early PE compared to the control group, suggesting an autoimmune response against CA I and CA II enzymes may play a role in early PE's pathogenesis. MDA values were also observed to be geater in the early PE group, indicating increased lipid peroxidation and oxidative stress. These results confirm that increased lipid peroxidation may be associated with the pathogenesis of PE. The imbalance between T-AOC and TOC further supports the notion that oxidative stress is a critical factor in early PE.

Strengths and Limitations

Our research has many strengths. Firstly, it provides a comprehensive analysis of the relationships between auto antibodies and oxidative stress parameters in early PE, offering valuable insights into the pathogenesis of the condition. Secondly, by investigating novel biomarkers (anti-CA I and anti-CA II antibodies) that have not been extensively studied in the context of early PE, we contribute to the limited literature on this topic. This novel approach can help in understanding the potential role of autoimmunity in PE and open new avenues for research.

However, there are limitations to our study that should be acknowledged. The relatively small sample size may limit the generalizability of our findings. Larger studies with more participants are needed to validate our results and confirm the observed associations. Additionally, as a single-center study, our findings may not be representative of the broader population. Multi-center studies would enhance the external validity of our results and provide a more comprehensive understanding of early PE. Furthermore, our study did not include molecular analyses, which could provide deeper insights into the mechanisms underlying the observed associations. Future research incorporating molecular techniques is warranted to elucidate the etiopathogenesis of early PE further.

CONCLUSION

Our study found that anti-CA I and anti-CA II antibody levels, along with oxidative stress markers, were significantly higher in pregnant women with early PE compared to healthy controls. These results suggest that the autoimmune response against CA I and CA II enzymes and increased oxidative stress play crucial roles in the pathogenesis of early PE. Understanding these mechanisms could lead to the development of new diagnostic and therapeutic strategies for early PE. Future studies should focus on larger, multi-center cohorts and incorporate molecular analyses to further elucidate the etiopathogenesis of this complex condition. The presence and levels of anti-CA I and II antibodies and antioxidant parameters discussed in our study highlight the need for further research in this field. Our findings underscore the importance of comprehensive maternal-fetal health approaches to minimize the risks associated with early PE for maternal, fetal, and neonatal individuals. As PE's prevalence and high treatment follow-up and costs necessitate biomarker studies, it seems possible that panels consisting of both biochemical and molecular markers may be clinically useful in predicting this disease.

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Conflict of interest: *The authors have no conflicts of interest to declare.*

Ethical approval: *Ethical approval for the study was obtained from the İnönü University Faculty of Medicine Clinical Research Ethics Committee (ethical approval number: 2021/113). The researchers committed to comply with the principles of the World Medical Association Declaration of Helsinki (including the recruitments adopted in 2008) and the Good Clinical Practice (GCP) Guide, which was enacted on December 29, 1995, as an annex to the circular numbered 51748 by the Turkish Ministry of Health.*

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