Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2019;44(Suppl 1):547-554
DOI: 10.17826/cumj.558401

ARAŞTIRMA / RESEARCH

Is higher IgE levels in preeclamptic pregnancies suggest autoimmune pathophysiology?

Preeklamptik gebeliklerde yüksek IgE seviyeleri, otoimmün patofizyolojiye işaret ediyor mu?

Burak Elmas[1], Mehmet Ferdi Kıncı[2], İrem Eda Gök[3], Afra Alkan[4], Cihan Toğrul[5], Esma Sarıkaya[6]

[1]Etlik Zübeyde Hanım Education and Research Hospital, Department of Obstetrics and Gynecology, Ankara, Turkey
[2]Muğla Sıtkı Koçman University Education and Research Hospital, Department of Obstetrics and Gynecology, Muğla, Turkey
[3]Adatip Hospital, Department of Obstetrics and Gynecology Department, İstanbul, Turkey
[4]Ankara Yıldırım Beyazıt University, Department of Biostatistics, [6]Department of Obstetrics and Gynecology, Ankara, Turkey
[5]Hitit University - Erol Olçok Education and Research Hospital, Department of Obstetrics and Gynecology, Çorum, Turkey

Cukurova Medical Journal 2019;44(Suppl 1):547-554.

Abstract

Purpose: The aim of this study was to evaluate the role of potential autoimmune mechanisms in the pathogenesis of preeclampsia by investigating the coexistence of celiac disease in patients.

Material and Methods: Forty women diagnosed with preeclampsia and forty non-complicated pregnant women were enrolled in this prospective, cross-sectional, case-control study. Both groups were compared for any allergic disease symptoms, serological markers of celiac disease, total Ig A and total Ig E levels. Two years later, the mothers were questioned about the presence of allergic diseases in their babies.

Results: There was no statistically significant difference between the two groups for serological markers of celiac disease. However, total IgE levels of the preeclampsia group were significantly higher than that of the control group.

Conclusion: In this study, we did not ascertain any coexistence of celiac disease and preeclampsia. Nevertheless, we suggest that the increased IgE levels in the preeclampsia group might be accepted as an indicator of the immune pathogenesis of preeclampsia and a potential marker for coexisting allergic diseases.

Keywords: Preeclampsia, celiac disease, Ig E

Öz

Amaç: Bu çalışmada preeklampsi patogenezindeki potansiyel immun mekanizmaların, hastalarda çölyak hastalığı bulunup bulunmamasıyla değerlendirmesi amaçlanmıştır.

Gereç ve Yöntem: Kesitsel, vaka kontrolü ve prospektif çalışmaya preeklampsi tanısı konmuş 40 gebe ve 40 komplikasyonu olmayan gebe alındı. Her iki grup alerjik hastalık semptomları, çölyak hastalığına ait serolojik belirteçler, total Ig A ve total Ig E düzeyleri yönünden karşılaştırıldı. İki yıl sonra anneler bebeklerinde alerjik hastalık varlığı açısından sorgulandı.

Bulgular: Çölyak hastalığına özgü serolojik belirteçleri açısından karşılaştırıldığında iki grup arasında istatistiksel olarak anlamlı bir fark bulunmadı. Ancak, çalışma grubundaki toplam IgE düzeyleri kontrol grubununkilere göre anlamlı olarak daha yüksek olarak gözlendi.

Sonuç: Bu çalışmada, çölyak hastalığı ve preeklampsi birlikteliğine ait net olarak herhangi bir sonuç bulunmadı. Ancak, preeklampsi grubunda artmış IgE düzeylerinin, bu hastalığın immün patogenezine ait bir işaret olabileceğini ve eşlik eden alerjik hastalıklara ait potansiyel bir belirteç olarak kabul edilmesini öneriyoruz.

Anahtar kelimeler: Preeklampsi, çölyak hastalığı, Ig E

Yazışma Adresi/Address for Correspondence: Dr. Burak Elmas, Etlik Zübeyde Hanım Education and Research Hospital, Department of Obstetrics and Gynecology, Ankara, Turkey e-mail: burak_elmas88@hotmail.com
Geliş tarihi/Received: 26.04.2019 Kabul tarihi/Accepted: 17.07.2019 Çevrimiçi yayın/Published online: 27.09.2019

INTRODUCTION

All over the world, hypertensive disorders complicate 5-10% of all pregnancies[1]. Preeclampsia in human pregnancies is a complex condition that is life-threatening both for the mother and the fetus. It is characterized by hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, arising after the 20th week of pregnancy in women, who were previously normotensive), proteinuria (≥300 mg/day), or occasionally end-organ damage. Although they increase the risk of materno-fetal morbidity and mortality, the majority of pregnant women with preeclampsia give birth at full term or near-term periods with favorable outcomes [2,3]. In developed countries, hypertensive diseases of pregnancy account for 16% of maternal deaths. For example, preeclampsia and eclampsia were found to be responsible from 12% of all pregnancy-associated maternal deaths in 2010 according to the USA data [4]. Several mechanisms, one of which is the immunological factors have been proposed to explain the pathophysiological background of preeclampsia. In an uncomplicated pregnancy, the predominant immune response depends on Th2, while Th1 predominance is observed in pregnancies complicated with preeclampsia.

Celiac disease is an autoimmune, genetic disorder that is characterized by sensitivity to gluten in grains. Malabsorption that causes characteristic intestinal lesions and improves with a gluten-free diet, occurs during the disease. Th1 dominant immune response has been emphasized in celiac disease[5,6]. The increase in the Th1/Th2 ratio in preeclampsia is similar to that of the celiac disease. Serological assays that are used for a diagnosis of celiac disease include testing for anti-gliadin antibodies IgG and IgA, anti-endomysial antibodies IgG and IgA, tissue transglutaminase antibodies IgG and IgA, and deaminase anti-gliadin antibody. Tests for tissue transglutaminase and anti-endomysial antibody IgA are more sensitive and specific for celiac than the other ones[7, 8]. Immunoglobulin E is the principal immunoglobulin in allergic reactions. In the pregnancy period, statistically non-significant minimal changes have been reported in maternal immunoglobulin E levels. Moreover, no significant difference has been observed between trimesters[9]. A study of pregnant women with preeclampsia revealed slightly increased IgE levels in preeclampsia complicated pregnancies compared to the levels in uncomplicated pregnancies [10].

In the current study, we aimed to evaluate the role of potential autoimmune mechanisms in the pathogenesis of preeclampsia by investigating the coexistence of celiac disease in patients.

MATERIALS AND METHODS

After obtaining the Local Ethics Committee (Date:30/04/2014, No:99950669/212) approval, 40 pregnant women with preeclampsia and 40 healthy pregnant women, who were between 30-40 weeks of gestation and admitted to Zekai Tahir Burak Training and Investigation Hospital between June 2014 and December 2014 were enrolled in the study.

The participants, who provided the informed consents and met the study criteria which were based on preeclampsia diagnostic criteria determined by American College of Obstetricians and Gynecologists in 2013 [11], were recruited in this prospective cross-sectional study. Gestational age was calculated using the date of the last menstrual period in addition to fetal biometric measurements obtained by gynecologic ultrasound (Aloka Co, Tokyo, Japan). Blood pressures were measured in all study participants, and any systemic symptoms such as headache, visual problems etc. present were noted.

Urinalysis was checked regarding the presence and amount of proteinuria. The presence of proteinuria (≥3 gr/day) with systolic or diastolic blood pressures equal to or above of 140 mmHg and 90 mmHg, respectively, or any sign of end-organ damage established the diagnosis for preeclampsia. Pregnant women, whose blood pressures were within the normal limits set forth and don't have proteinuria were enrolled in the control group. Pregnant women with multiple fetuses, history of autoimmune or chronic diseases such as renal disease, diabetes, and essential hypertension were excluded from the study. 2 pregnant women with preeclampsia were excluded from the study for the reasons described above.

Patients and controls were visited at postpartum 2nd year for physical examinations of the babies concerning any diagnosed disease or allergy symptoms. The presence of diarrhea, weight loss, sneezing attacks, eye redness, skin rash, and allergy history, post-vaccination fever and tooth decay were recorded and compared.

Measurements

Blood pressure was measured on the left arm in the sitting position with the cuff at the level of the heart at least six hours apart by using with a standard sphygmomanometer. In the measurement of diastolic pressure, Korotkoff phase 5 sounds were accepted. The amount of proteinuria in urine samples was evaluated by using H (Lapstrip) neg/+1/+2/+3 with a dipstick, and estimations were converted into mg/dl (between 0 to +1: 30-100 mg/dl, +1 to +2: 100-300 mg/dl, +2 to +3: 300-1000 mg/dl) values with device analyzer (Labumat). +1 value evaluated with dipsticks roughly corresponded to 300 mg/day proteinuria in 24 hours of urine. In order to examine total immünglobulin A, total immunoglobulin E, anti-gliadin antibody Ig A, anti-transglutaminase antibody Ig A, and anti-endomysial antibody IgA kits 4cc whole blood was drawn from the antecubital vein with vacutainer under sterile conditions and transferred to red-capped biochemistry tube. After serum samples were centrifuged for 10 minutes at 4000 rpm, they were stored at -20 °C in the freezer until analysis was performed. Total immunoglobulin A (Sunderibo), total immunoglobulin E (Diametra), anti-endomysial antibody IgA (GenericAssay), anti-gliadin antibody IgA, and anti-transglutaminase antibody IgA were examined with ELISA method using platinum kits (Immco) following the instructions of the manufacturer.

Results were calculated as EU/ml for anti-gliadin antibody and anti-transglutaminase antibody, U/ml for the anti-endomysium antibody, IU/ml for total immunoglobulin E, and mg/ml for total immunoglobulin A level. For anti-gliadin antibody IgA and anti-transglutaminase antibody IgA, values at or above 25 EU/ml were considered as positive, and those less than 25 EU/ml were as negative. For anti-endomysial antibody IgA, values of ≧ at or above 20 U/ml were considered as positive, and those less than 20 U/ml were as negative [12].

Statistical analysis

For statistical analysis of data, IBM SPSS Statistics 21.0 version (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) software package and R program "*ltm*" was used. Graphics were drawn with Microsoft Excel 2013. The conformity of continuous measurements to the normal distribution was examined by the Shapiro Wilk test. Normally distributed variables are expressed as mean ± standard deviation (mean ± S); the non-normally distributed variables are expressed as median (IQR: Inter-quartile range). Minimum-maximum (Min-Max) values are given for all continuous variables. The categorical variables are presented as number (%). Mann-Whitney U test or independent sample t-test was used for comparing numerical variables such as results of biochemical and serological assays that were obtained from patient and control groups. The categorical variables were examined using the Chi-square tests. More than two numerical variables were compared using the Kruskal-Wallis Test. The Mann-Whitney U test with Bonferroni correction was used for multiple pairwise comparisons. The correlations between serological markers and laboratory measurements were tested by calculating the Spearman rho coefficient or point double line correlation coefficient. A p value less than 0.05 was considered statistically significant. Although the statistical power of this study was low for serologic markers except for Ig E, we used a two-way ANOVA test while calculating the power analysis. In order to estimate the statistical power, we used the mean total serum IgE levels (100.93±121.92 IU/ml in the patient group, and 43.65±69.07 IU/ml in the control group) on a sample size of n=40 for each group, and accepting 95% confidence interval with an α error value of 0.05. The resulting P (Statistical Power) was found to be 0.7235531.

RESULTS

Mean age of patients and controls included in the study were similar (28.40±4.67 years vs. 28.28±5.08 years, respectively, t=0.115, p=0.909, Table 1). The study groups were similar regarding median body mass index (BMI) (30.82 (IQR=6.02) vs. 29.83 (IQR=5.54). respectively, Z=0.669, p=0.504). There was no difference in the rates of smoking between the patient and the control groups. The rate of smoking was similar between the patient and control groups (n=5, 12.5% and n=4,10.0%, p=1,00).

When the study groups were compared for clinical parameters, such as celiac symptoms, allergy status, screening test results, and comorbid diseases, no significant differences were observed between study groups (p>0.05, for each parameter). The number of leukocyte subtypes, such as neutrophils, monocytes, eosinophils, and basophils was counted, and no significant difference was observed between the patient and control groups (Table 2).

Table 1. Distribution of demographic characteristics

	Patient group (n=40)	Control group (n=40)	Test statistics	P
Age *[year]*				
mean±S	28.40±4.67	28.28±5.08	t=0.115	0.909
Min – Max	19.00 – 40.00	19.00 – 42.00		
BMI *[kg/m²]**			Z=0.669	0.504
median (IQR)	30.82 (6.02)	29.83 (5.54)		
Min – Max	23.23 – 37.78	23.60 – 45.70		
LMP *[week]***			Z=0.087	0.930
Median (IQR)	36.00 (4.00)	36.00 (4.00)		
Min – Max	30.00 – 40.00	30.00 – 40.00		
LMP [n (%)]			0.000	1.000[2]
≤ 34weeks	14 (35.0)	14 (35.0)		
> 34 weeks	26 (65.0)	26 (65.0)		
Smoking [n (%)]	5 (12.5)	4 (10.0)	-	1.000[1]
Celiac symptom [n (%)]	10 (25.0)	5 (12.5)	χ^2=1.313	0.252[2]
Allergy [n (%)]	3 (7.5)	2 (5.0)	-	1.000[1]
Comorbid disease [n (%)]	5 (12.5)	2 (5.0)	-	0.432[1]

[1]Fisher Exact test result [2]Yates chi square test result
*BMI: Body Mass İndex, **LMP: Last Menstruation Period, ***IQR: Inter Quartile Range

Table 2. Distribution of blood pressure values and laboratory findings in groups.

	Patient Group	Control Group	Test statistics	P
Systolic blood pressure [mm-Hg]			Z=7.756	<0.001
Median (IQR)	160.00 (13.00)	110.00 (10.00)		
Min – Max	140.00 – 199.00	90.00 – 120.00		
Diastolic blood pressure [mm-Hg]			Z=6.828	<0.001
Median (IQR)	100.00 (17.00)	70.00 (0.00)		
Min – Max	68.00 – 139.00	60.00 – 80.00		
Amount of Proteinuria [mg/dl]			Z=8.143	<0.001
Median (IQR)	100.00 (470.00)	0.00 (0.00)		
Min – Max	0.00 – 500.00	0.00 – 0.00		
Hemoglobulin [g/dl]			t=-1.076	0.285
mean±S	12.17±1.62	11.81±1.34		
Min – Max	9.10 – 15.60	9.10 – 15.60		
NLR*			Z=0.828	0.408
Median (IQR)	3.80 (2.26)	4.32 (2.03)		
Min – Max	2.25 – 11.23	1.50 – 11.12		
Eusinophil[n/uL]			Z=1.144	0.253
Median (IQR)	0.00 (100.00)	0.00 (100.00)		
Min – Mxk	0.00 – 400.00	0.00 – 200.00		
Basophil [n/uL]			Z=1.103	0.270
Median (IQR)	0.00 (100.00)	0.00 (0.00)		
Min – Mak	0.00 – 200.00	0.00 – 100.00		

*NLR: Neutrophil Lymphocyte Ratio

The patients and control subjects were comparable in terms of the median value of anti-gliadin levels (6.82 EU/ml, IQR=7.60 vs. 8.96 EU/ml, IQR=7.87, respectively, Z=0.707, p=0.479) (Table 3). Similarly, anti-endomysium, anti-transglutaminase, and total IgA levels results were comparable between the study

groups (p>0.05, for each). The median value of total IgE was 17.87 and 52.49 IU/ml in control (IQR=48.36) and the patient (IQR=102.88) groups, respectively. Total IgE values were significantly higher in the patient group compared to healthy controls (Z=2.771, p=0.006). Antitransglutaminase antibody, antiendomysial antibody, antigliadin antibody, total IgA, and total IgE levels were similar between preeclampsia, severe preeclampsia and HELLP groups (p>0.05, Table 4).

Table 3. Distribution of antigliadin antibody, anti-endomysial antibody, anti-transglutaminase antibody, total IgA ve total IgE values in patient and control groups

	Patient group	Control Group	Test statistics (Z)	P
Anti-gliadin antibody Ig A [EU/ml]			0.707	0.479
Median (IQR)	6.82 (7.60)	8.96 (7.87)		
Min – Max	1.63 – 78.62	2.98 – 69.08		
Ant-endomisyum antibody IgA [U/ml]			1.511	0.131
Median (IQR)	6.88 (6.19)	5.96 (3.52)		
Min – Max	1.00 – 52.39	1.91 – 19.00		
Anti-transglutaminase antibody IgA [EU/ml]			0.933	0.351
Median (IQR)	6.26 (3.92)	6.08 (3.05)		
Min – Max	1.23 – 152.13	3.27 – 14.13		
Total IgA [mg/ml]			1.910	0.056
Median (IQR)	2.07 (1.20)	2.26 (0.73)		
Min – Max	0.50 – 8.00	0.50 – 8.00		
Total IgE [IU/ml]			2.771	0.006
Median (IQR)	52.49 (102.88)	17.87 (48.36)		
Min – Max	0.01 – 392.17	0.95 – 381.45		

Table 4. In patients diagnosed with preeclampsia, severe preeclampsia and HELLP, the comparison of anti-transglutaminase antibody, anti-endomysium antibody, anti-gliadin antibody, Total IgA and Total IgE levels.

	Preeclampsia Group	Severe Preeclampsia Group	HELLP Group	P
(n=40)	(n=10)	(n=25)	(n=5)	
Anti-gliadin antibody IgA [EU/ml]				
Median	6.34	6.22	8.52	0.376
Min – Max	1.63 – 25.31	2.82 – 46.00	5.43-78.62	
Anti-endomysial antibody IgA [U/ml]				
Median	6.53	6.96	7.31	0.793
Min – Max	1.00 – 12.54	2.55 – 15.72	3.51-52.39	
Anti-transglutaminase antibody IgA [EU/ml]				
Median	6.86	6.00	8.73	0.654
Min – Max	1.23 – 13.61	2.92 – 11.75	3.85-152.13	
Total IgA [mg/ml]				
Median	1.83	2.76	2.36	0.886
Min – Max	0.63 – 8.00	0.50 – 8.00	1.23-4.22	
Total IgE [IU/ml]				
Median	42.97	53.69	51.50	0.862
Min – Max	1.50 – 161.25	0.01 – 392.17	4.35-373.90	

p<0.05

Patients and control groups were divided into four subgroups according to the presence of gastrointestinal symptoms of the celiac disease. The subgroups were compared in terms of serum markers (Table 5). While there was no statistically significant difference between groups in terms of anti-gliadin, anti-endomysial and anti-transglutaminase antibodies ($p>0.05$); there was a significant difference in serum total IgA and total IgE values ($p<0.05$, for both). In pairwise comparisons, we found that the serum total IgA values were lower in ten patients with celiac symptoms compared to patients without celiac symptoms and also controls with or without celiac symptoms. Besides, serum total IgE values were significantly higher in patients without celiac symptoms than those of the healthy controls without celiac symptoms ($p<0.05$). There was no significant difference in other pairwise comparisons for other parameters.

Table 5. The comparison of celiac markers, and total IgA and total IgE values in terms of celiac symptoms

	Patient + GIS symptom (n=10)	Patients – GIS symptom (n=30)	Control + GIS symptom (n=5)	control – GIS symptom (n=35)	Test statistics (χ^2)	p
Antigliadin antibody IgA [EU/ml]					2.485	0.478
Median (IQR)	6.78 (9.27)	7.02 (7.88)	4.80 (6.85)	9.07 (7.60)		
Min – Max	4.64 – 25.31	1.63 – 78.62	3.61 – 11.77	2.98 – 69.08		
Antiendomysial anti body IgA [U/ml]					4.540	0.209
Median (IQR)	6.25 (6.17)	7.02 (6.21)	3.73 (3.79)	6.27 (3.23)		
Min – Max	3.51 – 13.26	1.00 – 52.39	1.91 – 7.43	2.28 – 19.00		
Antitransglutaminase anti body IgA [EU/ml]					2.272	0.518
median (IQR)	5.68 (3.50)	6.69 (4.36)	4.83 (3.54)	6.17 (3.08)		
Min – Max	3.85 – 13.61	1.23 – 152.13	4.14 – 10.41	3.27 – 14.13		
Total IgA [mg/ml]					11.727	0.008
Median (CIQR)	1.65 (0.31)*∫‡	2.18 (1.49)*	2.32 (1.11) ‡	2.25 (0.75)ļ		
Min – Max	1.23 – 3.45	0.50 – 8.00	2.17 – 3.93	0.50 – 8.00		
Total IgE [IU/ml]					8.641	0.034
Median (IQR)	37.63 (80.77)	54.99 (148.30)*	30.38 (52.52)	16.92 (44.31)*		
Min – Max	4.35 – 136.76	0.01 – 392.17	6.14 – 60.20	0.95 – 381.45		

*∫‡ $p<0.05$

While diagnosis and symptoms of celiac disease, allergic dermatitis, and allergic rhinitis were present in none of the babies; there were wheezing in the offspring of the women in control groups, but the difference was not statistically significant ($p=0.241$).

DISCUSSION

Preeclampsia is a disease of pregnancy leading to maternal and fetal complications. Since the only treatment of preeclampsia is delivery, studies about the physiopathology and predicting factors of the disease are still ongoing. We hypothesized that allergic and autoimmune disorders could occur together with preeclampsia, so we explored the signs and symptoms of allergic disease in preeclampsia patients [10]. Th1/Th2 ratio increase, which is also a finding in celiac disease, is also reported in preeclampsia patients. Based on this similarity between the two diseases, we specifically chose to examine the symptoms and findings of celiac disease in preeclampsia patients; however, we also evaluated the presence of other autoimmune, allergic diseases, such as allergic rhinitis, allergic conjunctivitis, allergic asthma, and atopic dermatitis, in the current study.

No significant difference was found between patient and control groups in terms of serum markers of celiac disease including anti-gliadin IgA, anti-endomysial antibody IgA, anti-transglutaminase IgA, and total IgA. The IgG fraction of serological markers was not evaluated since none of the subjects had low serum IgA levels. We found that total serum IgE level was significantly higher in the patient group. When we tested the correlation between some biochemical measurements and markers, we found a weak negative relationship between the amount of proteinuria and total serum IgA level. On the contrary, there was a weak positive correlation

between the amount of proteinuria and total serum IgE level. Furthermore, a weak positive correlation was found between the presence of celiac gastrointestinal symptoms and the serum levels of total IgA and total IgE.

IgE, which represents the main immunoglobulin of allergic reactions, was significantly higher in the preeclampsia group[13]. We suppose that preeclampsia risk might be increased in allergic individuals. However, as emphasized in a study comparing total serum IgE levels of pregnant women carrying male fetuses with those carrying female fetuses, maternal IgE levels were higher in pregnant women compared to non-pregnant women [13]. Moreover, in the context of immunological hypothesis in preeclampsia pathophysiology, it is not clear whether an increase in serum IgE level is a response of the immune system in preeclamptic pregnant, or not. In a case-control study conducted in Norway, it was demonstrated that total IgE level in maternal serum had a weak positive relationship with the risk of preeclampsia development [10]. Since it was a weak relation, it might be due to variations in the storage conditions of participants' sera [14]. In the current study, we paid full attention to maintain appropriate storage conditions for samples and analyzed them in the possible shortest time, so the significant relationship we found in the current study carries none to negligible technical bias.

Based on our study results, rather than concluding associations between increased serum total IgE levels in preeclamptic patients with potential asthma or atopy, advancing our studies for investigating mechanisms of the multi-directional relationships among allergy, preeclampsia, and IgE would be more of benefit for elucidating the pathogenesis of preeclampsia.

In our study, we did not find an increase in the number of allergic disease in the off-springs of women with preeclampsia. In a previous study, atopy in the adolescent period was investigated in children ~~of~~ born to preeclamptic women, and it was found that the risk of severe atopy was increased particularly in boys [15].

The course of pregnancy in celiac disease has been addressed in previous studies. Some of them have reported higher termination rates, abortion, low birth weight, intrauterine growth retardation compared to healthy pregnancies[16, 17]. In a study on celiac serology in small for gestational age (SGA) and preeclamptic pregnancies, both transglutaminase and endomysium antibody positivity were observed in SGA and preeclampsia groups in only one patient, and no significant relationship could be demonstrated [18]. In this respect, this result was in accordance with the celiac data in our study. In another study evaluating the pregnancy and fertility status of women with celiac disease, it was shown that maternal age was significantly high, and abortion and cesarean rates were slightly increased. However, the rates of operative delivery, breech presentation, preeclampsia, postpartum hemorrhage, ectopic pregnancy, stillbirth, and termination were reported to be similar to the proportions of the normal population [19]. In a meta-analysis from Italy, the reproductive status of celiac patients was decreased, and the risk of unexplained infertility, recurrent abortion and intrauterine growth retardation (IUGR) was significantly higher in celiac patients. In addition, the rates of preterm labor and SGA were increased compared to the healthy population. However, there was no increase in the risk of stillbirth and preeclampsia. Anti-transglutaminase antibody screening in unexplained infertility, IUGR, and recurrent abortion might be recommended, but there was not sufficient evidence to justify serology screening in preeclampsia and SGA deliveries [20].

In the metanalysis published by Saccone et al. in 2015, it was demonstrated that preterm delivery, IUGR, and SGA risks were significantly higher in pregnant women with celiac disease compared to healthy population, while there was no difference in the incidence of preeclampsia [21]. In a study from Turkey, antithyroglobulin, antimicrosomal anti-smooth muscle, antimitochondrial, antinuclear, anti-gastric parietal call and anti-thrombocyte antibodies were investigated in 49 cases with pregnancy-associated hypertension, 8 of whom had antibody positivity (16.3%), which was a rate lower than reported in the literature. And it was reported that according to these results, autoantibodies have no prognostic significance in pregnancy-associated hypertension and treatment was not warranted for them [22]. In the present study that assessed celiac serological markers in preeclamptic pregnant women, there was no relationship between celiac disease and pregnancy, which is a consistent finding with the literature. In the power analysis of the relationship between celiac serological markers and total IgA, statistical power was found to be low due to the small number of cases. As it is a screening study, it should be supported with further, large-scale studies.

In the present study, our results regarding biological markers support immunopathogenesis in preeclampsia and draw attention to the possible coexistence of preeclampsia and autoimmune diseases indicating the potential common immunological pathways in pathophysiology. Although these findings are promising, further large-scale, randomized controlled clinical studies would clarify the role, reliability, and efficacy of these markers in the pathogenesis of preeclampsia.

Yazar Katkıları: Çalışma konsepti/Tasarımı: BE, ES; Veri toplama: BE, ES; Veri analizi ve yorumlama: AA, CT; Yazı taslağı: BE, MFK; İçeriğin eleştirel incelenmesi: ES, CT; Son onay ve sorumluluk: BE, MFK, İEG, AA, CT, ES; Teknik ve malzeme desteği: AA; Süpervizyon: ES, İEG; Fon sağlama (mevcut ise): yok.
Bilgilendirilmiş Onam: Katılımcılardan yazılı onam alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

Author Contributions: Concept/Design : BE, ES; Data acquisition: BE, ES; Data analysis and interpretation: AA, CT; Drafting manuscript: BE, MFK; Critical revision of manuscript: ES, CT; Final approval and accountability: BE, MFK, İEG, AA, CT, ES; Technical or material support: AA; Supervision: ES, İEG; Securing funding (if available): n/a.
Informed Consent: Written consent was obtained from the participants.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support

REFERENCES

1. Gökdemir İE, Evliyaoğlu Ö, Çoşkun B. The role of ADAMTS genes in preeclampsia. Turk J Obstet Gynecol. 2016;13:149-53.
2. Sibai BM, Caritis S, Hauth J. What we have learned about preeclampsia. Semin Perinatol. 2003;27:239-46.
3. Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol. 2011;25:391-403.
4. Cunningham FG. Hypertensive Disorders. In: F Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, et al., editors. Williams Obstetrics. 24th ed. New York: McGraw-Hill. 2014;728–79.
5. Müller B, Gimsa U, Mitchison NA, Radbruch A, Sieper J, Yin Z. Modulatin the Th1/Th2 balance in inflammatory arthritis. Springer Semin Immunopathol. 1998;20:181-96.
6. Auricchio S, Troncone R, Maurano F. Celiac disease in the year 2000. Ital J Gastroenterol Hepatol, 1999;31:773-80.
7. Bürgin-Wolff A, Gaze H, Hadziselimovic F, Huber H, Lentze MJ, Nussle D, Reymond-Berthet C. Antigliadin and antiendomysium antibody determination for celiac disease. Arch Dis Child. 1991;66:941-7.
8. Sulkanen S, Halttunen T, Laurila K, Kolho KL, Korponay-Szabó IR, Sarnesto A et al. Tissue transglutaminase autoantibody enzyme-linked immunosorbent assay in detecting celiac disease. Gastroenterology. 1998;115:1322-8.
9. Bahna SL, Woo CK, Manuel PV, Guarderas JC. Serum total IgE level during pregnancy and postpartum. Allergol Immunopathol (Madr). 2011;39:291-4.
10. Eskild A, Nilsen TI, Jeansson S, Jenum, PA, Vatten LJ. Serum levels of immunoglobulin E and the subsequent risk of pre-eclampsia: a population-based study. Acta Obs Gyn Scandinavica. 2008;87:373-6.
11. The American College of Obstetricians and Gynecologists (ACOG). Hypertension in pregnancy 2013. http://www.acog.org/ Resources_And_ Publications/
12. Sulkanen, S. (2000). Serum antibodies in coeliac disease. Tampere University Press.
13. Loken MO, Jeansson S, Jenum PA, Eskild, A. Serum level of immunoglobulin E during pregnancy- Does offspring sex matter? Paediatr Perinat Epidemiol. 2010;24:75-7.
14. Henderson CE, Ownby D, Klebanoff M, Levine RJ. Stability of immunoglobulin E (IgE) in stored obstetric sera. J Immunol Methods. 1998;213:99-101.
15. Keski-Nisula L, Heinonen S, Remes S, Pekkanen J. Pre-eclampsia, placental abruption and increased risk of atopic sensitization in male adolescent offspring. Am J Reprod. Immunol. 2009;62:293-300.
16. Rostami K, Steegers EA, Wong WY, Braat DD, Steegers-Theunissen RPM. Celiac disease and reproductive disorders: a neglected association. Eur J Obstet Gynecol Reprod Biol. 2001;96:146–9.
17. Smecuol E, Maurino E, Vazquez H, et al. Gynaecological and obstetric disorders in celiac disease: frequent clinical onset during pregnancy or the puerperium. Eur J Gastroenterol Hepatol. 1996;8:63–89.
18. Wolf H, Ilsen A, van Pampus MG, Sahebdien S, Pena S, Von Blomberg ME. Celiac serology in women with severe preeclampsia or delivery of a small for a gestational neonate. Int J Gynaecol Obstet. 2008;103:175–7. doi:10.1016/j.ijgo.2008.05.024.
19. Tata LT, Card TR, Logan RF, Hubbard RF, Smith CJP, West JB. Fertility and pregnancy related events in women with celiac disease: a population-based cohort study. Gastroenterology. 2005;128:849-5.
20. Tersigni C, Castellani R, De Waure C, Fattorossi A, De Spirito M, Gasbarrini A. Celiac disease and reproductive disorder: a meta-analysis of epidemiologic associations and potential pathogenic mechanisms. Hum Reprod Update. 2014;20:582-93.
21. Saccone G, Berghella V, Sarno L, Maruotti GM, Cetin I, Greco L, et al. Celiac disease and obstetric complications: a systematic review and meta-analysis. Obstet Gynecol. 2015;4:225-4.
22. Uncu G, Demirtürk M, Macit A, Cengiz C. Gebeliğe bağlı hipertansiyon olgularında otoantikorlar. Perinatoloji Dergisi. 1996;4:121-2.