

The investigation of relationship between preeclampsia and antiphospholipid antibody syndrome

Preeklampsi ve antifosfolipid antikor sendromu arasındaki ilişkinin incelenmesi

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Abstract

Aim. The aim of this study was evaluate the relationship between preeclampsia and antiphospholipid antibodies. **Methods.** A total of 116 pregnant women between 20th and 40th weeks of gestation admitted to our department were investigated. 63 of them were allocated our preeclampsia group and 53 of them were allocated our control group. Lupus anticoagulant, anti-cardiolipin antibodies (IG G ve M) and antiphosphatidylserine antibodies (IG G ve M) were measured. **Results.** There was no statistical significance between preeclampsia and control group for antiphospholipid antibodies but these were two times higher in preeclamptic group compared to control group. (22.2% in preeclampsia, 11.3% in control group p=0.193). **Conclusions.** In an unselected population we were not able to demonstrate an association between preeclampsia and antiphospholipid antibody syndrome but antiphospholipid antibody ratio elevated in women with preeclampsia. These findings show that, there is a need for large scale studies.

Keywords: Preeclampsia, antiphospholipid antibodies, pregnancy

Özet

Amaç. Bu çalışmanın amacı preeklampsi ve antifosfolipid antikor sendromu arasında ilişki olup olmadığının belirlenmesidir. **Yöntem.** Çalışmaya 20-40 hafta arasındaki toplam 116 gebe katılmıştır. Preeklampsi tanısı alan 63 hasta çalışma grubumuzu oluşturmuştur. Kontrol grubuna sağlıklı, normotensif ve sistemik hastalığı olmayan 53 gebe dahil edilmiştir. Çalışma ve kontrol grubunda bulunan gönüllülerden antifosfolipid antikorları olarak lupus antikoagülan, anti kardiolipin antikorları (IG G ve M) ve antifosfatidilserin antikorları (IG G ve M) çalışılmıştır. **Bulgular.** Preeklampsi ve kontrol grubu arasında antifosfolipid antikor sendromu açısından istatistiksel olarak anlamlı farklılık saptanmamıştır ancak bu antikorlar kontrol grubu ile karşılaştırıldığında, preeklamptik grupta iki kat daha yüksek olarak saptanmıştır. (preeklampside %22,2 kontrol grubunda %11,3) P=0,193. **Sonuç.** Bu çalışmada preeklampsi ve antifosfolipid antikor sendromu arasında ilişki gösterilememiştir ancak preeklamptik hastalarda antifosfolipid antikorlarının yüksek olarak saptanması daha geniş çaplı ve çalışmalara gereksinim olduğunu göstermektedir.

Anahtar sözcükler: Preeklampsi, gebelik, antifosfolipid antikor sendromu

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Introduction

Preeclampsia is a systemic disorder characterized by hypertension, edema and proteinuria in which a diffuse vascular damage with deposition of fibrin is well - recognised pathological feature. It is displayed that prevalence of preeclampsia is 5-7% of all pregnancies. It can have a major impact on both perinatal and maternal morbidity. It is one of the most causes of the direct maternal deaths throughout the world [1, 2].

Pregnancy is a hypercoagulability state. It is claimed that abnormality of natural coagulation inhibitor level, immunologic parameters and genetic parameters create a great tendency towards preeclampsia. [3]

Immunologic fragment of thrombophilia is associated with antiphospholipid antibodies (APA) that related to variety of medical problems including recurrent spontaneous abortion, foetal death, and arterial and venous thrombosis which is major cause of the acquired thrombophilia. A pregnant that carries characteristic clinical and biochemical features of preeclampsia with specified levels of APA is considered to have antiphospholipid syndrome (APAS) [4, 5].

APAS is an autoimmune condition in which venous or arterial thrombosis is a primary clinical feature. If this syndrome is associated with an autoimmune disease, called primary likewise systemic lupus erythematosus however not, called secondary disease and both of them have same clinical features for pregnancies [6].

Some studies have also detected elevated levels of APA in women with preeclampsia [7-8]. These antibodies are most likely to be present in patients with early-onset (before 34 weeks' gestation) severe preeclampsia [9]. However, others found no association between APA and preeclampsia [10, 11]. This situation shows that relationship between APA and preeclampsia remains uncertain.

During pregnancy, thrombosis and placental infarction have been implicated in some complications, for instance recurrent foetal wastage, idiopathic foetal growth restriction (FGR), and preeclampsia. Some of authors claim that this thrombotic predisposition is apparently linked to APA in women [12, 13].

It was important to test for those antibodies during complicated pregnancies, in particular during preeclampsia, to determine possible predictive or therapeutic effects. Despite contrasting results, some authors suggested thromboprophylaxis during APA-associated pregnancies [14].

This study is aimed to clarify relationship between preeclamptic pregnancies and APAS and evaluate the role of APA (anticardiolipin antibodies (ACA), antiphosphatidylserine antibodies and lupus anticoagulant (LA) in preeclamptic and eclamptic pregnancies.

Materials and methods

A total of 116 pregnant women between 20th and 40th weeks of gestation admitted to our department were investigated. 53 pregnant women with uncomplicated healthy pregnancies constituted our control group and 63 women with undefined type of preeclampsia constituted our study group. This study was carried out within a year. Women who reported histories of preeclampsia were not eligible to be controls. Patients with multiple pregnancies, with chronic renal and vascular disease or previous thromboembolic complications were excluded and women who is taking anticoagulant therapy or having preeclampsia superimposed on chronic hypertension were not included in the study. None of the patients or controls was in labor at the time of sampling. All patients delivered in the Obstetrics Department of Erciyes University Faculty of Medicine and were followed until discharged from hospital. This study was approved by the ethics committee for human research at Erciyes University Kayseri/Turkey.

Diagnose of preeclampsia was done according to the criteria agreed by the National High Blood Pressure Education Program Working Group of National Institutes of Health (NIH) in 2000. Preeclampsia was defined as blood pressure (BP) of at least 140/90 mmHg after 20 weeks gestation on at least two occasions 6 hours apart when the absence of gestational trophoblastic disease or multiple pregnancies was confirmed by ultrasonographic examination, with proteinuria more than 0.3 g per 24 hours and edema < 1+ after bed rest. Blood was measured with a calibrated aneroid manometer in the spine position after five minutes rest. Absolute diastolic blood pressure of ≥ 110 mmHg and proteinuria ($\geq 2+$ [100mg/dL] on a chateterized specimen was diagnostic for severe preeclampsia at admission.

Patients who were diagnosed as preeclampsia and had grand-mal seizure were defined as eclampsia. Gestational age was estimated from the first day of last menstrual period and confirmed by ultrasonographic measurments. The APS is diagnosed by the presence of two major components, one clinical and the other a laboratory finding. At least one clinical occurrence of either vascular thrombosis, other than superficial venous thrombosis, or one of several pregnancy morbidities, such as preeclampsia. Persistent presence in the serum of at least one type of antiphospholipid antibody.

Participants were divided into four groups according to their gestational age. Control group allocated into two groups; the first group was constituted by uncomplicated healty pregnant with <34th (early onset) weeks of gestation and the second group was constituted by uncomplicated healty pregnant with >34th (late) weeks of gestation. Third group was constituted by <34th (early onset preeclampsia) weeks of gestation whose pregnancy was complicated with preeclampsia or eclampsia and fourth group had similar clinic features likewise third whose pregnancy were at the >34th weeks of gestation.

After all patients were informed about trial and got their constent, 20 mL of blood was taken from the antecubital vein into plastic tubes at admission. All samples were studied relevant laboratories by the same technician after 10 minutes from taking blood samples for avoid laboratory mistake. ACA IG G, M and APS IG G, M, (antiphosphatidylserine antibody) were measured by enzyme-linked immunoassay (ELISA) technique using the enzyme-linked immunoassay Euroimmun kit; a range between 0 and 12 iu/ml was considered as normal. The plasma LA was measured using Biomerux LA kit with photometric clot detection principle, considering normal a range of values between 0.6 - 1.2% / mL.

All of continuous variables were subjected to normality testing using the Kolmogorov-Smirnov method and data were expressed as mean \pm S.D. and median (min-max). Continuous variables were analyzed with non-parametric methods. Differences between control and preeclamptic groups were evaluated with Mann Whitney U test and chi-square was used for comparing catagoric values. P values by Fischer exact test were reported for 2 \times 2 tables when the assumptions for the chi-square analysis were not met. Data were stored and analyzed with The Statistical Package for Social Sciences (SPSS), relase 13.0 (Chicago IL) for Windows. Statistical significance was defined as $p < 0.05$.

Results

Charasteristics of patients in study and control groups are listed on table 1. There was no statistical significance between control and study group for parity ($p > 0.05$). Nineteen (35.8%) patients of 53 healty pregnant were primigravid and 34 (64.2%) of them were multigravid. Twenty-three (36.5%) patients of 63 preeclamptic pregnant were primigravid and 40 (63.5%) of them were multigravid.

We did not detect difference between control and study groups for APA, <34 weeks of gestation and >34 weeks gestation and totally evaluated preeclamptic and healthy groups.

As illustrated in table 2; there was no statistical significance between control and study group for every stage of gestation but antibodies were seen in preeclamptic group two times more than control group ($p = 302$ and 490).

Table 1. Characteristics of the early onset, late onset preeclamptic pregnant and gestational week matched control groups.

Groups	Age $\bar{x} \pm SD$	1. min. apgar score $\bar{x} \pm SD$	5. min. apgar score $\bar{x} \pm SD$	IU EX $\bar{x} \pm SD$
Early onset preeclampsia (<34 weeks of gestation) (n=28)	27.86± 5.63	4.14±2.22	5.71±2.69	0.29±0.46
Healthy control (< 34 weeks of gestation) (n=23)	27.72±5.84	7.40±1.47	9.36±1.63	0.24±0.6
P value	0.929	<0.001	<0.001	0.378
Late onset preeclampsia (> 34 weeks of gestation)(n=35)	29.72± 6.93	6.09±2.44	7.89±2.82	0.63±1.9
Healthy control > 34 weeks of gestation (n=28)	28.04±5.52	7.68±0.99	9.68±0.98	0.21±0.42
	0.309	0.002	0.002	0.423

Table 2. Comparing APA results among early onset preeclampsia (<34th weeks of gestation), late onset preeclampsia and healthy pregnancies.

Groups	(ACA IG G,IG M or APS IG G, IG M or LA)		Total	P
	Positive n (%)	Negative n (%)		
Preeclampsia (Pregnancies <34th weeks of gestation)	7 (25.0)	21 (75.0)	28	0.302
Control (Pregnancies <34th weeks of gestation)	3 (12.0)	22 (88.0)	25	
Preeclampsia(Pregnancies >34th weeks of gestation)	7 (20.0)	28 (80.0)	35	0.490
Control (Pregnancies >34th weeks of gestation)	3 (10.7)	25 (89.3)	28	

Table 3. Total evaluation of APA for both groups.

Groups	(ACA IG G,IG M or APS IG G, IG M or LA)		Total	P
	Positive n (%)	Negative n (%)		
Preeclampsia	14 (22.2)	49 (77.8)	63 (54.3)	0.193
Control	6 (11.3)	47 (88.7)	53 (45.7)	
Total	20 (17.2)	96 (82.8)	116 (100.0)	

Discussion

The presence of APA significantly increases the risk of developing pre-eclampsia [7, 8]. However, when women who developed pre-eclampsia were matched with women who didn't, there are some conflicting among authors. Many of the authors have described increased rates of APA, ranging between 10% and 20%, among women with preeclampsia, [15-17] severe preeclampsia, [18-19] or eclampsia [20]. On the other hand some of investigators have found no increased rate of APA among women with preeclampsia [21, 22].

The APS is diagnosed by the presence of two major components, one clinical and the other a laboratory finding. Clinical finding include; occurrence of either vascular thrombosis, other than superficial venous thrombosis, or one of several pregnancy morbidities, such as preeclampsia. Laboratory finding include; persistent presence in the serum of at least one type of antiphospholipid antibody. Participants were divided into four groups according to their gestational age. Control group allocated into two groups; the first group was constituted by uncomplicated healthy pregnant with <34th (early onset) weeks of gestation and the second group was constituted by uncomplicated healthy pregnant with >34th (late) weeks of gestation. Third group was constituted by <34th (early onset preeclampsia) weeks of gestation whose pregnancy was complicated with preeclampsia or eclampsia and fourth group had similar clinic features likewise third whose pregnancy were at the >34th weeks of gestation. In our unselected population we

were unable to demonstrate an association between APAS and preeclampsia. On the other hand we detected similar ratios as many authors who found positive correlation preeclampsia and antiphospholipid antibodies. One of the possible discrepancy mechanism is size of control and study groups. For instance Van Pampus et al. [19] studied 345 patients with a history of severe preeclampsia, compared with 67 women who remained healthy and normotensive during pregnancy. This study suggested that elevated levels of APA were more common in women with a history of severe preeclampsia compared with controls (20.9% versus 7.5%). They reported that there were APAS in 20.9% of patients with a history of preeclampsia therefore they recommended that patients with preeclampsia or with a history of preeclampsia should be tested for acquired thrombophilia because of the high prevalence of thrombophilia in such woman. Thus thrombophilias may be a cause or an outcome of pregnancy associated hypertensive disorders. Despite our study did not demonstrate statistically significant APA in preeclampsia, we demonstrated similar ratios with Van Pampus et al. [19] (22.2% versus 11.3%). Redman et al. [23] suggested that preeclampsia is an extreme form of a universal maternal response to pregnancy whereby a systemic inflammatory response characteristic of normal pregnancy becomes excessive, causing a degree of decompensation in some maternal systems. In contrast Dreyfus et al. [24] claimed that APA were not capable of activating the coagulation cascade that already had been activated by another mechanism during preeclampsia such as abnormalities of other thrombophilia markers. Therefore, they consider that these APAs were natural nonpathogenic, innocent autoantibodies. Their study group was constituted from 180 pregnant with first incidents of preeclampsia and no histories of thrombosis or systemic autoimmune diseases.

Although we did not classified patients on this type and we did not find any statistically significant increase in APAs, we detected that incidence of APAs were two times higher in preeclamptic group so this situation might be a result of excessive response in women with pregnancy associated hypertensive disorders [24].

In conclusion; despite contrasting results, some authors suggested thromboprophylaxis during antiphospholipid antibody-associated pregnancies. APA is positive for one of five pregnant whose pregnancy is complicated with preeclampsia. This study didn't prove statistical significance between preeclampsia and antiphospholipid antibodies however situation might arise from small size of groups. These findings show that, there is a need for large scale studies. Another study will have to determine the treatment strategies and predictive effect of anticoagulants, antiplatelets or steroids in antiphospholipid positive preeclamptic pregnant.

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