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Prognostic effect of factor V Leiden mutation in pregnant women with preeclampsia, eclampsia and chronic hypertension

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Abstract

Aim: To investigate the effect of factor V Leiden mutation on neonatal and maternal morbidity and mortality in hypertensive pregnant groups.

Materials and Methods: The study was carried out as a prospective case-controlled study with 108 pregnant women who applied to the Gynecology and Obstetrics Outpatient Clinic of Karadeniz Technical University, Faculty of Medicine within 2 years. Patients were divided into four groups: mild preeclampsia (n=20), severe preeclampsia (n=54), chronic hypertension (n=14), and normal pregnant women as a control group (n=20). Since superimposed preeclampsia (n=6), eclampsia (n=23), and HELLP syndrome (n=27) are variants of severe preeclampsia, these patients were included in the severe preeclampsia group. The clinical study aimed at investigating whether FVL mutation has any significant correlation with neonatal morbidity (IUGR, 1st and 5th minute $<$ 7 Apgar score), intrauterine fetal death, neonatal mortality, maternal morbidity (ablatio placenta, deep vein thrombosis, intracranial hemorrhage, cesarean section rate) and mortality risk in hypertensive pregnant women.

Results: Factor V Leiden mutation was most common in the severe preeclampsia group. Maternal and neonatal outcomes of pregnant women with and without FVL mutations were similar in all study groups ($p > 0.05$).

Conclusion: Although FVL mutation was more common than usual in severe preeclamptic pregnant women, it did not affect maternal and neonatal outcomes. Prospective studies with larger patient populations investigating the effects of FVL mutation in preeclampsia are needed.

Introduction

Hypertension occurs in 6-20% of all pregnancies [1]. Comorbid diseases of hypertension (preeclampsia, eclampsia, and chronic hypertension) observed in pregnancy are the second most important cause of maternal mortality after embolism and the mortality rate is approximately 15%. These patients may have potentially fatal complications such as HELLP syndrome, ablatio placenta, disseminated intravascular coagulation (DIC), venous thrombosis, brain hemorrhages, liver and kidney failure, and increased cesarean section (C/S) rates [2]. In cases where the disease is severe, intrauterine fetal death may occur. Due to prematurity, it can lead to neonatal mortality and morbidity (necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), respiratory distress syndrome (RDS), intrauterine growth retardation (IUGR) and low Apgar score) [3].

Factor V Leiden (FVL) mutation has an autosomal dominant transmission and is the most common cause of primary and recurrent venous thromboembolism in pregnancy. It leads to the development of resistance to active protein C (APC), increasing the tendency to thrombosis. The FVL mutation prevalence was found to be high in women with a history of venous thromboembolism during pregnancy and postpartum period [4]. In addition, due to increased thrombotic risk, the incidence of pregnancy complications such as severe and early onset preeclampsia, recurrent pregnancy losses, intrauterine growth retar-

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dation and ablatio placenta are high in individuals with FVL mutation [5]. There are reports indicating that the pregnant women with early onset and severe preeclampsia should be screened for FVL mutation, protein C, protein S deficiency and antiphospholipid antibody [6,7]. However, there are also some studies with opposite conclusions [8,9].

The aim of the present study was to investigate whether FVL mutation is associated with neonatal morbidity (IUGR, 1st and 5th minute < 7 Apgar score), intrauterine fetal death, neonatal mortality, maternal morbidity (ablatio placenta, deep vein thrombosis, intracranial hemorrhage, cesarean section rate) and mortality risk in hypertensive pregnant women.

Materials and Methods

The study was carried out as a prospective case-controlled study and included 108 pregnant women who applied to the outpatient clinic of the Department of Obstetrics and Gynecology within 2 years and who met the study criteria. The study was approved by the Ethics Committee of Karadeniz Technical University, Faculty of Medicine (No: 2003/38, Date: 15.05.2003). Oral and written consents of patients between the ages of 16 and 44 were obtained. The pregnant women included in the study were divided into four groups: mild preeclampsia, severe preeclampsia, chronic hypertension and normal pregnancy as control. Since superimposed preeclampsia, eclampsia and HELLP syndrome are variants of severe preeclampsia, these patients were included in the severe preeclampsia group. The definitions in the groups were made based on the classification made by the American National High Blood Pressure Education Program, High Blood Pressure in Pregnancy Working Group in their 2000 report [10]. Pregnant women were divided into 4 groups based on the severity of hypertensive disease and these definitions. Information about age, gravida, parity, obstetric history and systemic diseases of all pregnant women were recorded. Blood pressure measurement was recorded [3]. AST, ALT, LDH (IU/L) values, bilirubin (mg/dL), platelet (x103/mm^3) measurements, creatinine (mg/dL) and Hb (g/dL) levels, proteinuria (more than 300 mg in 24-hour urine) levels were studied and recorded. Fetal ultrasonography measurements were made and recorded. All pregnant women diagnosed with severe preeclampsia were hospitalized and followed up until birth. All pregnant women delivered in our hospital, and newborns were evaluated in our neonatal unit in terms of gestational week, birth weights, the first and fifth minute < 7 Apgar scores. Those with a history of diabetes, Cushing's syndrome, lupus, renal disease, those with a history of venous thrombosis in themselves or family, those with known thrombophilia disease (protein C-S deficiency, antithrombin III deficiency, MTHFR carriership, prothrombin II deficiency) and smokers were not included in the study. In addition, pregnant women who were under 20 weeks, who had twin pregnancies, major fetal anomaly, and abortus, stillbirth, preeclampsia and HELLP syndrome in their obstetric history were excluded. In all cases, presence of IUGR was determined based on gestational age through making measurements by ultrasonography and examining the percentile charts after birth. The IUGR diagnosis was calculated according to the 10th percentile value of the weight in that gestational age. After the 20th gestational week, intrauterine fetal death diagnosis was made when fetal cardiac activity was absent based on ultrasonography. Infant mortality within seven days of birth was considered as early neonatal mortality [11]. Ablatio placenta diagnosis was made clinically and with ultrasonography using the pre- and postnatal findings. Venous thrombosis and cesarean deliveries were recorded in all pregnant women. Intracranial bleeding findings were recorded by taking computed tomography and/or magnetic resonance imaging (MRI) in patients who had convulsions. Maternal mortality was defined as deaths during pregnancy or within 42 days of birth irrespective of the time and localization of pregnancy due to a pregnancy-related or pregnancy-aggravated disease or during the treatment of such a disease [12].

Two ml venous blood was taken from each patient, FVL gene mutation was detected by Light Cycler PCR (polymerase chain reaction) method [13]. The results were obtained as negative, heterozygous and homozygous. Heterozygous and homozygous results were considered positive.

In this study, an evaluation was made considering the checklist in The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE 2007) guidelines for reporting observational studies [14].

Statistical analysis

Descriptive statistics of quantitative data were summarized using mean and standard deviation for continuous variables and frequency counts and percentages for qualitative data. Normality of distribution was assessed using Kolmogorov-Smirnov test. Contingency tables and chi-square tests were used for comparison of categorical variables.

For normally distributed quantitative data, differences between groups were assessed using the Kruskal-Wallis test (a nonparametric analysis of variance) and post-hoc Mann-Whitney U tests for pairwise comparisons. For non-normally distributed quantitative data, the Mann-Whitney U test was used. Spearman's rank correlation coefficient was used to investigate the correlation between variables.

All statistical tests were two-sided and a p value of less than 0.05 was considered statistically significant. Analyses were performed using SPSS 11.5 (Statistical Package for Social Sciences, Licensed by Karadeniz Technical University).

Experimental (post hoc; retrospective; posterior) power analysis was performed in the study to justify the sample size. With alpha (the probability of a Type I error)= 0.05 significance level and w=0.3 effect size, the power of the study (1-β) was calculated as 0.80. The power of the sample was calculated in the G*Power 3.1.9.7 program environment.

Results

The study group included a total of 108 patients. Characteristics of patient groups are given in (Table 1). Systolic and diastolic TA were higher in the severe preeclampsia group than in the other groups (Table 1). AST,

Table 1. Characteristics of different pregnancy groups.

	Normal pregnancy (n: 20)	Mild preeclampsia (n: 20)	Severe preeclampsia (n: 54)	Chronic hypertension (n: 14)	P					
					p^a	p^b	p^c	p^d	p^e	p^f
Age (years)	28±5.7	30±5.7	28±6.4	36±5	>0.05	>0.05	<0.05	>0.05	<0.05	<0.001
Gestation period (weeks)	38±1.4	34±3.7	32±3.9	34±3.7	<0.05	<0.001	<0.05	>0.05	>0.05	>0.05
Systolic blood pressure (mmHg)	116±9.3	153±11	175±20	140±9	<0.001	<0.001	<0.001	<0.001	<0.05	<0.001
Diastolic blood pressure(mmHg)	78±6	95±9	113±9	89±3	<0.001	<0.001	<0.001	<0.001	<0.05	<0.05
AST (IU/L)	14±3	20±6.5	168±271	18±6	<0.05	<0.001	>0.05	<0.001	>0.05	<0.001
ALT (IU/L)	17±5	16±6.7	119±194	23±3.7	>0.05	<0.001	<0.05	<0.001	<0.001	>0.05
Bilirubin (mg/dL)	0.8±0.17	0.7±0.07	1.2±1.4	0.6±0.05	>0.05	>0.05	<0.001	>0.05	<0.001	<0.05
LDH (IU/L)	236±17	348±132	849±487	374±139	>0.05	<0.001	>0.05	<0.001	>0.05	<0.001
Thrombocyte (x10^3/mm^3)	321±101	226±64	185±107	216±38	<0.05	<0.001	<0.05	>0.05	>0.05	>0.05
Creatinine (mg/dL)	0.6±0.1	0.7±0.3	1.1±1.1	0.8±0.1	<0.001	<0.001	<0.001	>0.05	>0.05	>0.05
Hb (g/dL)	11±0.9	12±1	12±1	11±1.3	<0.05	>0.05	>0.05	>0.05	<0.05	<0.05
Nulliparity (%)	70	45	57	14	>0.05	>0.05	<0.05	>0.05	>0.05	<0.05

Data is given as mean ± standard deviation and %. AST: Aspartate transferase, LDH: Lactic dehydrogenase, Hb: Hemoglobin, ALT: Alanine transferase.
p^a: Comparison between normal pregnancy and mild preeclampsia groups; p^b: Comparison between normal pregnancy and severe preeclampsia groups
p^c: Comparison between normal pregnancy and chronic hypertension groups; p^d: Comparison between mild preeclampsia and severe preeclampsia groups
p^e: Comparison between mild preeclampsia and chronic hypertension groups; p^f : Comparison between severe preeclampsia and chronic hypertension groups.

Table 2. Factor V Leiden mutation frequencies in pregnancy groups.

Factor V Leiden	Normal pregnancy (n: 20)	Mild preeclampsia (n: 20)	Severe preeclampsia (n: 54)	Chronic hypertension (n: 14)	P p^a, p^b, p^c, p^d, p^e, p^f
Heterozygous (n, %)	1 (5%)	2 (10%)	6 (11%)	1 (7%)	>0.05
Homozygous (n, %)	–	–		–	>0.05
Negative (n, %)	19 (95%)	18 (90%)	47 (87%)	13 (93%)	>0.05

Data is given as mean ± standard deviation and %.
p^a: Comparison between normal pregnancy and mild preeclampsia groups; p^b: Comparison between normal pregnancy and severe preeclampsia groups
p^c: Comparison between normal pregnancy and chronic hypertension groups; pd: Comparison between mild preeclampsia and severe preeclampsia groups
p^e: Comparison between mild preeclampsia and chronic hypertension groups; p^f: Comparison between severe preeclampsia and chronic hypertension groups.

ALT, bilirubin, LDH, and creatinine levels were elevated in the severe preeclampsia group, whereas they were normal in the other groups (Table 1). The highest decrease in platelet count was detected in the severe preeclampsia group (Table 1). The nulliparity rate was found to be lowest in the chronic hypertension group (Table 1).

FVL mutation was detected in 11 of 108 patients (10%) (Table 2). Although the frequency of FVL mutation was highest in the preeclampsia group, there was no significant difference in FVL mutation frequency based on heterozygosity or homozygosity between the groups (p>0.05) (Table 2).

In terms of gestational weeks at birth, birth weight, the first- and fifth-minute Apgar scores (<7), IUGR rates, stillbirth and early neonatal mortality frequency, C/S rates, ablatio placenta, intracranial hemorrhage (ICH) and maternal mortality rates did not significantly differ between pregnant women with and without FVL mutation in normal pregnancy, mild preeclampsia, severe preeclampsia, and chronic hypertension groups (p>0.05) (Table 3). In hypertensive group, FVL mutations did not have significant correlations with birth weight, the first- and fifth-minute Apgar score <7, IUGR, stillbirth, early neonatal mortality, C/S frequency, ablatio placenta, ICH rates, and maternal mortality variables (p>0.05), p>0.05), p>0.05, p>0.05, p>0.05, p>0.05, p>0.05 , p>0.05 , p>0.05 , respectively) (Table 4).

Table 3. Effect of FVL mutation on neonatal and maternal morbidity and mortality in different pregnancy groups.

	Normal pregnancy (n: 20)		Mild preeclampsia (n: 20)		Severe preeclampsia (n: 54)		Chronic hypertension (n: 14)	
	FVL (+) (n: 1)	FVL (–) (n: 19)	FVL (+) (n: 2)	FVL (–) (n: 18)	FVL (+) (n: 7)	FVL (–) (n: 47)	FVL (+) (n: 1)	FVL (–) (n: 13)
Gestational period at birth (weeks)	38±0	38±1	34±5	34±4	31±5	33±4	29±0	34±4
Birth weight (g)	4200±0	3194±350	2000±1400	2266±1154	1264±600	1589±784	1040±0	2525±851
Apgar 1 (<7), (%)	0	0	50	33	86	55	39	100
Apgar 5 (<7), (%)	0	0	0	0	29	30	8	0
IUGR (%)	0	0	0	39	28	34	100	92
Stillbirth (%)	0	0	0	0	15	0	0	8
Early neonatal mortality	0	0	0	6	29	23	0	0
C/S (%)	0	37	100	89	86	72	100	39
Ablatio placenta (%)	0	0	0	0	0	13	0	0
ICH	0	0	0	0	0	9	0	0
Maternal mortality (%)	0	0	0	0	14	0	0	0

Data is given as mean ± standard deviation and %. FVL: Factor V Leiden IUGR: intrauterine growth retardation C/S: C section ICH: Intracranial hemorrhage.

Table 4. Correlation of FVL mutation with neonatal and maternal morbidity and mortality in different pregnancy groups.

	Normal pregnancy (n: 20)		Mild preeclampsia (n: 20)		Severe preeclampsia (n: 54)		Chronic hypertension (n: 14)	
	r	p	r	p	r	p	r	p
Birth weight (g)	0.380	>0.05	−0.087	>0.05	−0.161	>0.05	−0.379	>0.05
Apgar 1 (<7), (%)	–	–	−0.105	>0.05	−0.208	>0.05	0.320	>0.05
Apgar 5 (<7), (%)	–	–	–	–	0.009	>0.05	0.077	>0.05
IUGR (%)	–	–	−0.245	>0.05	−0.039	>0.05	−0.077	>0.05
Stillbirth (%)	–	–	–	–	0.039	>0.05	–	–
Neonatal mortality (%)	–	–	–	–	0.244	>0.05	–	–
C/S (%)	−0.168	>0.05	0.111	>0.05	0.103	>0.05	0.320	>0.05
Ablatio placenta (%)	–	–	–	–	−0.136	>0.05	–	–
ICH	–	–	–	–	−0.109	>0.05	–	–
Maternal mortality (%)	–	–	–	–	–	–	–	–

Discussion

Thrombophilia mutations increase the susceptibility to thrombosis in preeclamptic patients, disrupting maternal and fetal circulation and contributing to the development of preeclampsia. Role of FVL mutation in preeclampsia pathogenesis has been investigated since 1994. FVL mutation leads to APC resistance and increases the risk of thrombosis [15,16]. In many studies, the role of APC resistance and FVL mutation in preeclampsia pathogenesis has been investigated, but contradicting results were obtained [17-19]. Factor V Leiden mutation rate in hypertensive patients was found as 16% by Dekker GA et al. [17], 22% by Lindoff C et al. [18], and 7% by Benedetto C et al. [19]. In the present study, FVL mutation rate was 5% in normal pregnant women, 10% in mild preeclampsia, 13% in severe preeclampsia and 7% in chronic hypertension.

The reasons for the differences in the incidence of FVL in different studies are ethnic differences in the groups studied and differences in the definition of preeclampsia. Pregnant women in our study group are Caucasians, and FVL carriership rate in the Caucasians is 4-5% [20]. In the European race, FVL carriership in preeclamptic women rate is 10-22% [17,18]. Therefore, we considered the lower frequency of FVL mutations in our study group as normal due to its racial characteristics. In addition, different definitions and classifications are used for preeclampsia in studies [1-3,21]. In our study, we used the classification made by the American National High Blood Pressure Education Program Working Report in 2000 on Group High Blood Pressure in Pregnancy [20]. Thus, Dekker GA et al. [17] and Lindoff C et al. [18], who used different diagnostic criteria in their studies, may have found the incidence rate of FVL mutation higher.

In the present study, the earliest gestational week at birth was in severe preeclamptic pregnant women with the FVL mutation. In addition, the first- and fifth-minute Apgar scores were lower than 7 in severe preeclamptic pregnant women with the FVL mutation and in chronic hypertensive pregnant women without the FVL mutation. The birth weight of patients with FVL mutation was lower than those of those with mild or severe preeclampsia and chronic hypertension groups. As a result, prematurity, low Apgar scores and low birth weights were more common in pregnant women with FVL mutations. The reason for this

could be that FVL mutation does not pose a risk in normal pregnant women, but in preeclamptic and chronic hypertensive pregnant women, it further disrupts the already impaired placental perfusion. Besides, reason for the lowest birth weight in pregnant women with chronic hypertension could be that sustained hypertension further increases the risk of microvascular thrombosis. Likewise, as shown in some studies, FVL mutation in these patients could negatively affect fetal development [22,23]. The prematurity rate in severe preeclamptic pregnant patients was reported as 52% by Osmanağaoglu T. et al. [22] and 55% by Kesim M. et al. [23]. Like previous studies, highest premature birth frequency was observed in the severe preeclampsia group in the present study. There was no significant correlation between FVL mutation and severe preeclampsia. Therefore, we hypothesized that the premature birth frequency in pregnant women with FVL mutation increased in proportion to the severity of preeclampsia, rather than the FVL mutation.

Martinelli P et al. [24] and Alfirevic Z et al. [25] reported an increased risk of IUGR in those with FVL mutations. Kupferminc MJ at al. and Rigo J at al. [26,27] did not find an association IUGR in those with FVL mutations. In accordance with the previous studies, FVL mutation was not significantly associated with IUGR in the study groups of the present study [26-27]. Besides, consistent with the results of previous studies, no significant difference was observed between the FVL mutation and IUGR in the study groups. Nevertheless, severe preeclampsia and chronic hypertension were more common in pregnant women with FVL mutation.

Rai R. et al. [28] found that 20-50% of the pregnant women with stillbirths were FVL carriers compared to 5% in the controls. There are other studies supporting these findings [29,30]. In some studies, on the other hand, no relationship was found between FVL and stillbirth rates [27,31]. Although stillbirth rates were more common in pregnant women with FVL mutation in the present study, the difference was not significant ($p>0.05$). In our study groups, stillbirths were observed in severe preeclampsia and chronic hypertension groups. All stillbirths in the severe preeclampsia group were in pregnant women with FVL mutation. However, in the chronic hypertension group, the stillbirth rate was higher in pregnant women without FVL mutation. These results suggest that when hypertension develops during pregnancy, the risk of stillbirth increases in the presence of additional factors such as FVL mutation, which increases susceptibility to thrombosis (leading to the deterioration of placental microvascular circulation and ultimately fetal circulation).

Neonatal mortality rates in those with preeclampsia and FVL mutations were reported to increase due to prematurity [32]. It was reported that 20-25% of all perinatal deaths is due to pregnancy-induced hypertension [22]. As known, prematurity, along with placental insufficiency and ablatio placenta, which can occur in this disease, also negatively affects fetal health. In our study, no direct relationship was found between neonatal mortality and FVL mutation, but prematurity rates were high due to earlier birth in patients with severe preeclampsia and FVL mutation. We also think that early neonatal mortality rates were higher because of high prematurity rates.

FVL mutation had no effect on birth method in normal pregnancy, but C/S rates were higher in pregnant women with mild or severe preeclampsia, chronic hypertension and FVL mutation. This was because most of these patients had IUGR. Therefore, since the fetal distress rate increases earlier in pregnancy and these patients deliver by C/S, we think that C/S rates were indirectly high in those with FVL mutation.

In a study evaluating the relationship between placental infarcts and FVL mutation, an increased risk of placental infarction was reported in FVL mutation carriers [33]. In another study, no increase of ablatio placenta was observed with FVL mutation [34]. In our study, ablatio placenta was not detected in pregnant women with FVL mutation.

In our study, ICH frequency was higher in patients without FVL mutation in the severe preeclampsia group. However, the differences between the groups were not significant. We have not come across any study showing an association of FVL mutation with ICH in preeclamptic pregnant women. The presence of ICH in the group without FVL mutation suggested that it was the acute hypertensive crisis, rather than the FVL mutation, which caused intracranial bleeding.

In patients with preeclampsia, a maternal mortality rate of 14% was observed among the patients with FVL mutation. There were no maternal deaths in those without FVL mutation. The death of this only patient, whose FVL mutation was homozygous, because of multiple organ failure could be attributed to the fact that the clinical progression is much more severe in homozygous cases. The risk of venous thrombosis increases 5-10 times in those with heterozygous FVL mutation, which could be 50-100 times higher in those with homozygous mutation [35,36]. In our study, deep venous thrombosis or pulmonary embolism was not observed. However, the rapid and severe progression of the preeclampsia clinic, the development of multiorgan failure and the formation of multiple microvascular thrombosis in this patient aggravated the prognosis. The diagnosis of homozygous FVL mutation carriership was made while the patient was in the intensive care unit and antithrombotic treatment was started immediately. However, the negative clinical table progressed fast and the patient became exitus. We are of the opinion that studies are needed to investigate the effect of antithrombotic therapy.

Women who had venous thromboembolism during pregnancy or in the puerperium was reported to have higher FVL prevalence [4]. There were no cases of venous thrombosis or thromboembolism in our study group. Routine screening of all pregnancies for thrombophilia mutations is not recommended [8,9]. Future studies should aim to determine which subgroups need FVL mutation screening. In addition, it is also recommended to investigate whether the anticoagulant therapy used in pregnant women with FVL mutation reduces maternal and neonatal morbidity in pregnant women with preeclampsia [37].

Conclusion

Our results did not suggest routine screening of pregnant women for FVL mutation. However, due to the higher inci-

dence of FVL mutation in pregnant women with low Apgar scores, prematurity, intrauterine growth retardation, stillbirth, cesarean section, maternal and neonatal mortality as a result of preeclampsia and eclampsia, thrombophilia mutations can be investigated individually.

In the present study, FVL mutation was not associated with pregnancy complications such as the development of severe preeclampsia and ablatio placenta, intrauterine growth retardation, venous thromboembolism, ICH, maternal and neonatal mortality pregnancy. This could be due to small study population, use of different classifications for hypertensive diseases observed during pregnancy, the different numbers of study groups, and different inclusion criteria. Future studies should aim to reveal for which subgroups FVL mutation screening are necessary. In addition, potential benefit of anticoagulant therapy in preeclamptic pregnant women with FVL mutation should be investigated. Prospective case-controlled studies with larger patient populations are needed.

Conflict of interest

There is no conflict of interest in the preparation of this article.

Ethical approval

The study was approved by the Ethics Committee of Karadeniz Technical University, Faculty of Medicine (No: 2003/38, Date: 15.05.2003).

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