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ORIGINAL ARTICLE

Investigation of plasminogen activator inhibitor-1 4G/5G gen polymorphism in Turkish preeclamptic patients

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ABSTRACT

Objective: The plasminogen activator inhibitor type-1 (PAI-1) is a genetic risk factor that plays a role in the pathogenesis of pre-eclampsia and elevated levels of PAI-1 may lead to an increased risk of thrombosis. At preent, there is considerable controversy about the association between PAI-1 gene polymorphism and preeclampsia. The aim of this study is to investigate whether the pattern of PAI-1 gene polymorphism is a useful marker for preeclampsia or not.

Material and Methods: Our study included 83 hypertensive pregnant women (64 preeclamptic women, 12 pregnant women with HELLP syndrome, and 7 eclamptic women) genotyped for PAI-1 gene polymorphism (4G/4G, 4G/5G, and 5G/5G) and 20 healthy pregnant women. The Chi-square analysis was used to evaluate the differences in genotype and allele frequencies between hypertensive pregnant women and healthy controls.

Results: The highest PAI-1 gene polymorphism rate was found in the hypertensive group and healthy controls in the 4G/5G allele distribution. No significant difference was determined between the hypertensive group and healthy controls regarding the distribution of PAI-1 4G/4G, 4G/5G, and 5G/5G polymorphic alleles.

Conclusion: According to the results obtained from present study, we think that PAI-1 gene polymorphism does not contribute to individual differences for the sensitivity of preeclampsia development. However, prospective cohort studies with larger sample sizes are needed to clearly demonstrate the contribution of PAI-1 gene polymorphism to serious pregnancy complications such as preeclampsia.

Keywords: PAI-1 gene polymorphism, preeclampsia, eclampsia, HELLP syndrome.

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INTRODUCTION

Preeclampsia is one of the leading causes of maternal and fetal morbidity and mortality in developed countries. It is considered that there is a deficiency in the natural anticoagulant pathway of patients with preeclampsia.[1] The addition of acquired or hereditary coagulopathies to the hypercoagulopathy state already present in the pregnancy increases the predisposition to preeclampsia and complications of preeclampsia. Early diagnosis of preeclampsia and to be able to perform the appropriate treatment is quite important for reducing maternal and fetal morbidity and mortality. In recent studies, it is aimed to be able to make a diagnosis of the disease well before the presentation of clinical symptoms of preeclampsia.

The plasminogen activator inhibitor type 1 (PAI-1) is mainly synthesized by endothelial cells and considered as a marker of endothelial cell dysfunction in preeclampsia.[2,3] PAI-2 is mainly synthesized by placental tissue and considered as a marker of placental function in pregnancy.[3,4] PAI-1 is responsible for approximately 60% of the PAI activity in the plasma[5] and it is the key inhibitor of fibrinolysis in the pregnancy when it is compared with PAI-2 and PAI-3.[6] It has been shown in many studies that PAI-1 was associated with many diseases such as severe hypertension, myocardial disease, deep venous thrombosis, malignancy, obesity, type 2 diabetes mellitus, polycystic ovary syndrome, and acute infection.[7]

The 4G polymorphism includes the deletion of a single guanine residue which is placed in the promoter region of the PAI-1gene located on chromosome 7q, 675 base pairs upstream from the transcriptional start site. This regulatory polymorphism does not alter the structure or function of the gene. But instead of this, it alters the expression of the gene and so it leads to higher circulating levels of PAI-1, which may increase the risk of thrombosis.[8]

The plasma level of PAI-1 in individuals with 4G/4G genotype (homozygous mutant) is approximately 25% higher than the individuals with 5G/5G genotype (homozygous normal).[9]

In this study, we aimed to investigate the contribution of genetic polymorphisms increasing the production of PAI-1 to serious pregnancy complications such as preeclampsia, eclampsia, and HELLP syndrome (hemolysis, elevated liver enzyme levels, and low platelet levels).

MATERIAL AND METHODS

Our study was performed with 83 preeclamptic, eclamptic pregnant women with HELLP syndrome more than 20 weeks of gestation, and 20 healthy pregnant women more than 20 weeks of gestation presenting to the Department of Obstetrics and Gynecology of Dicle University, Faculty of Medicine between January 2010 and January 2011. All participants gave signed informed consent. This study was conducted in accordance with the Declaration of Helsinki.

Patient selection and classification were performed according to the ACOG criteria.[10] Accordingly, the diagnosis of preeclampsia was made with measurement of systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg in two measurements performed at least 4 h apart after 20th week of pregnancy in previously normotensive women and determination of proteinuria of ≥300 mg in 24-h urine collection or +1 proteinuria with urine dipstick test. The diagnosis of eclampsia was made with the observation of grand-mal convulsions in preeclamptic patients. The diagnosis of HELLP syndrome was made with determination of hemolysis (abnormal peripheral blood smear, serum bilirubin of >1.2 mg/dL, and lactic dehydrogenase of >600 IU/L), elevated liver enzymes (alanine aminotransferase or aspartate aminotransferase is more than 2 times the upper limit of normal), and low platelets (<100.000/mm^3).[11] Women who had multiple pregnancy, systemic diseases such as diabetes mellitus, autoimmune diseases, renal disease, chronic hypertension, using anticoagulant agents, pregnant women with a history of known thrombosis, and pregnant women who smoke were excluded from the study.

Patients in both groups were compared regarding demographic and clinical characteristics, blood pressures, laboratory values, gestational weeks at presentation, mode of delivery, the 1st- and 5th-min Apgar scores of neonates, birth weights of neonates, and PAI-1 gene polymorphism. Preeclamptic patients were compared regarding PAI-1 gene polymorphism in two groups as early-onset hypertensive disorder (24–32 weeks of gestation) and late-onset hypertensive disorder (35–42 weeks of gestation). In addition, all cases in the study group were compared regarding PAI-1 gene polymorphism according to their diagnoses (preeclampsia, eclampsia, and HELLP syndrome).

Hemogram has been studied in Cell–dyn 3700 device using the LYSE kit. Biochemical tests were studied in the ARCHITECT C 1600 device using the enzymatic method and ABBOTT kit. Proteinuria was measured in spot urine samples at Roche Urisys1800 device using Combur 10 Test S strips. Two milliliter of venous blood sample were taken into the EDTA tube for the determination of genetic polymorphism. DNA isolation was performed in the blood sample taken into the EDTA tube at Roche-Magna Pure Compact automated DNA isolation device using a ready-to-use isolation kit. Fifteen microliter of the mixed solution were taken into a capillary tube and 5 µL of DNA solution obtained previously was added onto it. A centrifugation procedure was performed for precipitation of master mix solution and DNA mixture onto the bottom of the capillary tube. The samples were studied in the Light Cycler 2.0 device. The 4G and 5G polymorphisms were amplified using previously defined primers. Amplification products obtained were evaluated using TIB Molbiol Light-Mix Kit Human.

Interpretation of Data

The samples were named according to temperatures at they were peaked using the melting curve. The samples peaked at 54.5°C were named as 4G/4G; the samples peaked at between 54.5°C and 62.0°C were named as 4G/5G; and the samples peaked at 62.0°C were named as 5G/5G. One peak was observed in homozygous samples and two peaks were observed in heterozygous samples.

Statistical Methods

The Statistical Package for the Social Sciences (SPSS Inc., version 15; Chicago, IL, USA) was used for statistical analyses. Data were expressed as numeric (%) or mean±standard deviation (SD) values, as appropriate. Kolmogorov–Smirnov test was performed for the distribution of continious data. Statistical analyses were performed by Student's t-test for normal distribution data and Mann–Whitney U-test for abnormal distribution data Chi-square and Fish-

er exact test were used for comparison of categorical variables. Statistical significance was set p≤0.05.

RESULTS

Eighty-three patients with diagnoses of preeclampsia, eclampsia, and HELLP syndrome were included in our study. The distribution of the patients in the study group was as follows: 64 (77.1%) preeclampsia, 7 (8.4%) eclampsia, and 12 (14.5%) HELLP syndrome. Twenty healthy pregnant women were evaluated in the control group.

The demographic characteristics of the patients are shown in Table 1. While the mean gestational week of the patients in the study group was 33.06±4.7 weeks, it was 34.05±4.7 weeks in the cases of the control group. No statistical difference was determined in this regard. When the study group and the control group were compared regarding the mode of delivery, while the delivery rate with caesarean section was 65% (n: 54) in the study group, it was found to be 40% (n: 8) in the control group. The difference was statistically significant.

The patients were compared regarding the 1st- and 5th-min Apgar scores, and mean birth weights of neonates after delivery. The 1st and 5th min Apgar scores of neonates in the study group were observed to be statistically significantly lower compared to the 1st and 5th min Apgar scores of neonates in the control group. Again, the mean birth weight of neonate in the study group was found to be statistically significantly lower compared to the mean birth weight of neonate in the control group.

When the patients in the study group and the control group were compared regarding PAI-1 gene polymorphism, no statistically significant difference was determined between groups (Table 2). However, when the patients in the study group were compared regarding PAI-1 gene polymorphism according to their pre-diagnoses; a statistically significant difference was determined between groups (p=0.005). While 17 (26.6%) of 64 preeclamptic patients had a mutation in the 4G/4G gene, 32 (50%) of them had a mutation in the 4G/5G gene, and 15 (23.4%) of 64 preeclamptic patients had a 5G/5G genotype. 4G/4G PAI-1 gene polymorphism was not found in any of the 7 eclamptic patients, while 2 (28.6%) of eclamptic patients had a mutation in the 4G/5G gene. Five (71.4%) of eclamptic patients had a 5G/5G genotype. While 1 (8.3%) of 12 patients with HELLP syndrome had 4G/4G genotype, 8 (66.7%) of them had 4G/5G genotype, and 3 (25.0%) of them had 5G/5G genotype (Table 3). While 4 (20%) of 20 control patients had a mutation in the 4G-4G gene, 13 (65%) of them had a mutation in the 4G-5G gene. Three (15%) of 20 control patients had a 5G-5G genotype. The patients in the study group were compared in two separate groups as early-onset hypertensive disorders (24–32 weeks of gestation) and late-onset hypertensive disorders (35–42 weeks of gestation) regarding PAI-1 gene polymorphism and no statistically significant difference was determined between groups (Table 4). Since 4 patients from the study group were seen during the postpartum period and their gestational weeks were not known, they were not included in the table.

Table 1: Demographic characteristics of the patient groups

	Study group (n=83)	Control group (n=20)	p
Maternal age	31.20±6.802	30.80±6.37	0.81
Gravida	4.40±3.268	4.15±2.943	0.75
Parity	2.98±3.044	2.80±2.64	0.81
Gestational age (wk)	33.06±4.759	34.05±4.718	0.40
SBP* (mm/Hg)	152.57±14.21	118.07±13.43	<0.001
DBP* (mm/Hg)	92.21±11.71	70.22±10.79	<0.001

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; *: Blood pressure at the time of diagnosis.

Table 2: Distribution of the patient and control groups regarding PAI-1 genotype

PAI-1 genotype	Study group		Control group		Total		p
	n	%	n	%	n	%	
4G/4G	18	21.7	4	20	22	21.4	0.43
4G/5G	42	50.6	13	65	55	53.4	
5G/5G	23	27.7	3	15	26	25.2	
Total	83	100	20	100	103	100	

Chi-Square=1.67.

DISCUSSION

It is considered that predisposition to endothelial cell dysfunction which triggers abnormal activation of hemostatic and/or inflammatory systems plays an important role in the pathogenesis of preeclampsia, eclampsia, and HELLP syndrome.[12,13] It remains uncertain whether increased PAI-1 levels are a primary mechanism leading to the development of preeclampsia or a consequence of the associated endothelial and placental damage.[8,14]

It is known that PAI-1 provides a contribution to the formation of thrombus and the development and the clinical course of acute and chronic cardiovascular diseases.[15] It has been suggested that PAI-1 gene polymorphism (4G or 5G) plays a role in the regulation of the synthesis of the inhibitor 4G allele which is associated with the enhanced gene expression and plasma PAI-1 levels.[15–17] Glueck et al.[18] investigated the effect of PAI-1 gene polymorphism and they reported that the frequency of PAI-1 4G/4G polymorphism was increased in the presence of severe preeclampsia and the other obstetric complications (stillbirth, fetal growth restriction, and detachment of the placenta). In the study performed by Yamada et al.[19] in 115 preeclamptic patients and 210 healthy pregnant women, it was determined that an increase occurred in the quantity of PAI-1 due to an increase of mRNA expression in the placenta and plasma of preeclamptic women. It has been reported that the presence of the

Table 3: Comparison of the patient group according to prediagnosis regarding PAI-1 genotype

Diseases	PAI-1						Total		p
	4G/4G		4G/5G		5G/5G				
	n	%	n	%	n	%	n	%	
Pre-eclampsia	17	26.6	32	50	15	23.4	64	100	0.04
HELLP syndrome	1	8.3	8	66.7	3	25	12	100	
Eclampsia	0	0	2	28.6	5	71.4	7	100	
Total	18	21.7	42	50.6	23	27.7	83	100	

Chi-Square=9.76.

Table 4: Comparison of the patient group regarding PAI-1 genotype according to be early-onset hypertensive disorder and late-onset hypertensive disorder

	Early-onset hypertensive disorder		Late-onset hypertensive disorder		Total		p
	n	%	n	%	n	%	
4G/4G	6	15.4	12	30	18	22.8	0.28
4G/5G	21	53.8	19	47.5	40	50.6	
5G/5G	12	30.8	9	22.5	21	26.6	
Total	39	100	40	100	79	100	

Chi-Square=2.52.

4G/4G genotype of the PAI-1 gene could be a risk factor for preeclampsia in Japan population.

Wu et al.[20] suggested that even if it was combined with the other genetic risk factors associated with thrombogenesis when it was compared with the established clinical factors such as previous or familial history of preeclampsia, cigarette smoking, or elevated body mass index, PAI-1 4G/4G gene polymorphism would be insufficient to predict individual disease.

Conflicting findings were reported in genetic epidemiological studies investigating the association between PAI-1 (–675 4G/5G) polymorphism and preeclampsia. The majority of meta-analyses investigating the genetic and non-genetic risk factors for preeclampsia have warning that threatens their validity. The systematic review and meta-analysis performed by Giannakou et al.[21] provided strong evidence for an association between PAI-1 4G/5G polymorphism (recessive model) and preeclampsia. In the meta-analysis performed by Wiwanitkit investigating the correlation between the pattern of PAI-1 4G/5G polymorphism and preeclampsia in 880 patients and 810 controls, case–control studies of six different countries (Finland, Japan, South Africa, Germany, Scotland, and Italy) were evaluated and the authors suggested that the pattern of PAI-1 4G/5G polymorphism might represent a useful marker of increased risk for preeclampsia.[17] Whereas, in the study performed by Hakli et al.[22] in an eastern Finland population including 133 preeclamptic and 115 healthy control pregnant women, the authors found no difference regarding the allelic distribution of 4G/5G polymorphism between preeclamptic women and healthy control pregnant women.

de Maat et al.[23] compared 157 preeclamptic and 157 healthy control pregnant women and they determined the frequencies of the 4G/4G allele, the 4G/5G allele, and the 5G/5G allele in preeclamptic and healthy control pregnant women to be 34%, 51%, 15%, and 28%; 55%, 17%; respectively. As a result of the study, the authors reported that there was no difference between the frequency distribution of the 4G/4G allele in women with severe preeclampsia and in healthy control pregnant women.

In the systematic review of Morgan et al.,[24] a total of 1511 women with preeclampsia, eclampsia, and HELLP syndrome and 3492 healthy controls participating in 12 genetic association studies meeting all criteria were evaluated and although several potential sources of bias could not be neglected, it was reported that the fibrinolytic pathway regulated by the PAI-1 (4G/5G) gene might contribute to the pathogenesis of preeclampsia and related conditions. However, the authors supported that this genetic association did not justify screening pregnant women for PAI-1 (4G/5G) polymorphism but this condition might help to prioritize therapeutic targets that merit evaluation in randomized clinical trials.

Furthermore, in our study, we determined the highest rate of PAI-1 gene polymorphism in either hypertensive group or healthy controls regarding the distribution of 4G/5G allele. There was no significant difference between the hypertensive group and healthy controls regarding the distribution of PAI-1 4G/4G, 4G/5G, and 5G/5G polymorphic alleles.

As it is known, there are significant differences between early- and late-onset preeclampsia. At present, it is suggested that the role of the placenta in the development of these forms of the disease is different and therefore it is recommended that early- and late-onset preeclampsia should be evaluated as separate conditions while investigating pathophysiological factors and biochemical markers of preeclampsia.

Normally, the PAI-1 level increases beginning from 20 weeks of gestation. This increase is earlier and higher in preeclampsia.[14,25] Wikström et al.[26] compared early-onset (24–32 weeks of gestation) and late-onset (35–42 weeks of gestation) preeclamptic patients with healthy pregnant women and determined that placental oxidative stress was increased in women with early-onset preeclampsia secondary to this an increase occurred in PAI-1/PAI-2 ratio. Furthermore, in the study of Udenze et al.,[27] it has been shown that plasma levels of PAI-1 were increased in preeclamptic women, however, since there was no correlation between this marker and the severity of preeclampsia, the opinion was reported that its clinical benefit would be limited.

In our study, we evaluated the frequency of PAI-1 gene polymorphism among early- and late-onset hypertensive disorders and no significant difference was determined between early- and late-onset groups. Preeclampsia and HELLP syndrome among its more severe forms is characterized by increased placental thrombosis based on a procoagulatory state in the mother. While most of the studies have investigated the role of the PAI-1 4G/5G polymorphism in preeclampsia, very few studies have focused especially on HELLP syndrome. In the study performed by Muetze et al.[28] on this subject comparing 102 pregnant women with HELLP syndrome and 102 healthy pregnant women, the 4G/4G gene polymorphism was found to be more frequent in women with HELLP syndrome than in healthy controls (35.3% vs. 22.5%, respectively), but this difference was not significantly different (p=0.129). As the result of the study, the authors reported that women carrying a 4G/4G genotype of the PAI-1 gene were not at increased risk for developing HELLP syndrome and this condition was consistent with the majority of the previous studies investigating the association between the PAI-1 4G/5G polymorphism and preeclampsia. In the systematic review performed by Morgan et al.,[24] the authors reported that the frequency of 4G/5G polymorphism was not different between groups in the subgroup analysis of six studies in which participants were women with severe preeclampsia, eclampsia, and HELLP syndrome.

In our study, we determined 4G/4G genotype, 4G/5G genotype, and 5G/5G genotype in 8.3%, 66.7%, and 25% of 12 patients with HELLP syndrome; respectively. In addition, while 4G/4G genotype was encountered in none of 7 eclamptic patients, we determined 4G/5G genotype and 5G/5G genotype in 28.6% and 71.4% of the patients. Most of the studies in the literature investigate the relationship between PAI-1 gene polymorphism and preeclampsia. We think that the fact that we investigated the relationship between PAI-1 gene polymorphism and other hypertensive diseases (eclampsia and HELLP syndrome) besides preeclampsia makes our study different and powerful.

CONCLUSION

In summary, according to the results obtained from present study, we think that PAI-1 gene polymorphism does not contribute to individual differences for the sensitivity of preeclampsia development. However, prospective cohort studies with larger sample sizes are needed to clearly demonstrate the contribution of PAI-1 gene polymorphism to serious pregnancy complications such as preeclampsia.

Statement

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – ÖT, ME; Design – ÖT, ME; Supervision – ÖT, ME; Data Collection and/or Processing – ÖT, ME; Analysis and/or Interpretation – ÖT, ME; Literature Search – EÇ; Writing – EÇ; Critical Reviews – EÇ.

Conflict of Interest: The authors have no conflict of interest to declare.

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REFERENCES

1. Brenner B, Blumenfeld Z. Thrombophilia and fetal loss. Blood Rev 1997;11(2):72–9.
2. Chappell LC, Seed PT, Briley A, Hunt BJ, Charnock-Jones DS, Kelly FJ, et al. A longitudinal study of biochemical variables in women at risk of preeclampsia. Am J Obstet Gynecol 2002;187(1):127–36.
3. Mayer M. Biochemical and biological aspects of the plasminogen activation system. Clin Biochem 1990;23(3):197–211.
4. Halligan A, Bonnar J, Sheppard B, Darling M, Walshe J. Haemostatic, fibrinolytic and endothelial variables in normal pregnancies and pre-eclampsia. Br J Obstet Gynaecol 1994;101(6):488–92.
5. Kluft C, Jie AF, Sprengers ED, Verheijen JH. Identification of a reversible inhibitor of plasminogen activators in blood plasma. FEBS Lett 1985;190(2):315–8.
6. Jørgensen M, Philips M, Thorsen S, Selmer J, Zeuthen J. Plasminogen activator inhibitor-1 is the primary inhibitor of tissue-type plasminogen activator in pregnancy plasma. Thromb Haemost 1987;58(3):872–8.
7. Ye Y, Vattai A, Zhang X, Zhu J, Thaler CJ, Mahner S, et al. Role of plasminogen activator ınhibitor type 1 in pathologies of female reproductive diseases. Int J Mol Sci 2017;18(8):1651–68.
8. Said JM, Tsui R, Borg AJ, Higgins JR, Moses EK, Walker SP, et al. The PAI-1 4G/5G polymorphism is not associated with an increased risk of adverse pregnancy outcome in asymptomatic nulliparous women. J Thromb Haemost 2012;10(5):881–6.
9. Dellas C, Loskutoff DJ. Historical analysis of PAI-1 from its discovery to its potential role in cell motility and disease. Thromb Haemost 2005;93(4):631–40.
10. ACOG Committee on Obstetric Practice. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet 2002;77(1):67–75.
11. Ditisheim A, Sibai BM. Diagnosis and management of HELLP syndrome complicated by liver hematoma. Clin Obstet Gynecol 2017;60(1):190–7.
12. Roberts JM, Cooper DW. Pathogenesis and genetics of pre-eclampsia. Lancet 2001;357(9249):53–6.
13. Williams PJ, Broughton Pipkin F. The genetics of pre-eclampsia and other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol 2011;25(4):405–17.
14. De Boer K, Lecander I, ten Cate J, Borm JJ, Treffers PE. Placental-type plasminogen activator inhibitor in preeclampsia. Am J Obstet Gynecol 1988;158(3 Pt 1):518–22.
15. Francis CW. Plasminogen activator inhibitor-1 levels and polymorphisms. Arch Pathol Lab Med 2002;126(11):1401–4.
16. Banfi C, Mussoni L, Tremoli E. PAI-1, the primary plasmatic inhibitor of

fibrinolysis. Physiopathologic role and molecular mechanisms. Minerva Endocrinol 2002;27(3):181–91.

17. Wiwanitkit V. Correlation between plasminogen activator inhibitor-1 4G/5G polymorphism and pre-eclampsia: An appraisal. Arch Gynecol Obstet 2006;273(6):322–4.
18. Glueck CJ, Kupferminc MJ, Fontaine RN, Wang P, Weksler BB, Eldor A. Genetic hypofibrinolysis in complicated pregnancies. Obstet Gynecol 2001;97(1):44–8.
19. Yamada N, Arinami T, Yamakawa-Kobayashi K, Watanabe H, Sohda S, Hamada H, et al. The 4G/5G polymorphism of the plasminogen activator inhibitor-1 gene is associated with severe preeclampsia. J Hum Genet 2000;45(3):138–41.
20. Wu O, Robertson L, Twaddle S, Lowe GD, Clark P, Greaves M, et al. Screening for thrombophilia in high-risk situations: Systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. Health Technol Assess 2006;10(11):1–110.
21. Giannakou K, Evangelou E, Papatheodorou SI. Genetic and non-genetic risk factors for pre-eclampsia: Umbrella review of systematic reviews and meta-analyses of observational studies. Ultrasound Obstet Gynecol 2018;51(6):720–30.
22. Häkli T, Romppanen EL, Hiltunen M, Helisalmi S, Punnonen K, Heinonen S. Plasminogen activator ınhibitor-1 polymorphism in women with pre-eclampsia. Genet Test 2003;7(3):265–8.
23. De Maat MP, Jansen MW, Hille ET, Vos HL, Bloemenkamp KW, Buitendijk S, et al. Preeclampsia and its interaction with common variants in thrombophilia genes. J Thromb Haemost 2004;2(9):1588–93.
24. Morgan JA, Bombell S, McGuire W. Association of plasminogen activator inhibitor-type 1 (-675 4G/5G) polymorphism with pre-eclampsia: Systematic review. PLoS One 2013,8(2):e56907.
25. Ballegeer V, Spitz B, Kieckens L, Moreau H, Van Assche A, Collen D. Predictive value of increased plasma levels of fibronectin in gestational hypertension. Am J Obstet Gynecol 1989;161(2):432–6.
26. Wikström AK, Nash P, Eriksson UJ, Olovsson MH. Evidence of increased oxidative stress and a change in the plasminogen activator inhibitor (PAI)-1 to PAI-2 ratio in early-onset but not late-onset preeclampsia. Am J Obstet Gynecol 2009;201(6):597.e1–8.
27. Udenze IC, Arikawe AP, Makwe CC. Early pregnancy plasminogen activator inhibitor-1 levels in Nigerian women and its relationship with pre-eclampsia. Niger J Clin Pract 2017;20(5):517–22.
28. Muetze S, Eggermann T, Leeners B, Birke C, Kuse S, Ortlepp JR, et al. The 4G/5G polymorphism in the plasminogen activator inhibitor-1 gene is not associated with HELLP syndrome. J Thromb Thrombolysis 2009;27(2):141–5.