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Comparative Study of GSTP1 Gene Polymorphism Indices (IIe105Val) in Pregnant Women with Different Forms of Preeclampsia

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Abstract **Background.** Genetic factors for preeclampsia are being actively studied worldwide, but results are often inconsistent and not confirmed by repeated studies in different populations, highlighting the need for further study of the genetic causes of this pregnancy complication. **Aim.** To study the indicators of GSTP1 gene polymorphism (IIe105Val) in pregnant women with preeclampsia. **Materials and methods.** Genetic studies were conducted and GSTP1 gene polymorphisms (IIe105Val) were studied in 87 pregnant women of the main group and 90 women with physiological pregnancy who participated in our study. In turn, we divided 87 pregnant women of the main group into 2 groups. More precisely, Group I included 47 pregnant women with severe preeclampsia. Group II consisted of 40 pregnant women with moderate preeclampsia. **Results.** In our study, we analyzed the prognostic significance of the studied variants of polymorphism genes for the development of preeclampsia in pregnant women complicated by the preeclampsia group in the ethnic Uzbek population Thus, our study found a positive correlation between interleukin-2 (IL-2) and fetal growth retardation. It also showed that IL-2 is a reliable marker for fetal growth retardation alone. Thus, the GSTP1 gene polymorphism (IIe105Val) in the mutant Val/Val genotype had an AUC of more than 0.71, which proves its important role in the risk of developing preeclampsia. **Conclusions.** Thus, some polymorphisms of the GSTP1 gene (IIe105Val) may be risk factors for the development of preeclampsia and, as an independent genetic marker, may increase the risk of developing preeclampsia in pregnant women.

Keywords GSTP1, Preeclampsia, IIe105Val, Pregnant women, Hypertension in Pregnancy

1. Introduction

Preeclampsia (PE) is a systemic disorder occurring during pregnancy and is a major cause of maternal, fetal and neonatal mortality, particularly in low- and middle-income countries [1,2,3,4,17,18,19,20]. PE is characterized by the development or progression of hypertension after 20 weeks of gestation, accompanied by proteinuria or evidence of end-organ damage such as neurological disorders, pulmonary edema, hematological abnormalities, acute kidney injury, liver injury or uteroplacental dysfunction, as defined by the International Society for the Study of Hypertension in Pregnancy (ISSHP) [5,6,7,8,9,21,22,23,24,25]. The UK National Institute for Health and Care Excellence (NICE) defines PE as hypertension after 20 weeks of gestation with proteinuria or organ dysfunction, including renal failure, liver dysfunction, neurological or hematological complications, and uteroplacental dysfunction [10,11,12,13,14,15,16,26,27,28]. The American College of Obstetricians and Gynecologists (ACOG) does not consider proteinuria a mandatory criterion for the diagnosis of PE, emphasizing the importance of elevated blood pressure in combination with complications such as thrombocytopenia, renal failure, liver dysfunction, pulmonary edema, or cerebral/visual symptoms [Ng, K.W., Chaturvedi, N., 2024].

The genetic aspects of preeclampsia are actively studied worldwide, but the research results are often contradictory and not confirmed in different populations, which indicates the need for further study of the genetic factors of this complication [Abramova M.Yu., Churnosov M.I., 2022]. Studies have shown that polymorphism of the glutathione S-transferase pi-1 (GSTP1) gene, as well as the superoxide dismutase 2 (SOD2) and glutathione S-transferase M1 (GSTM1) genes, can contribute to endothelial dysfunction

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and placental hypoxia, playing a significant role in the pathogenesis of preeclampsia [29,30,31,32,33,34]. In this regard, we decided to investigate the role of the GSTP1 gene polymorphism (IIe105Val) in the Uzbek population.

Objective of the study: To study the indicators of GSTP1 gene polymorphism (IIe105Val) in pregnant women with preeclampsia.

2. Materials and Methods

All patients underwent a full clinical examination in the conditions of the Municipal Maternity Hospital No. 2 of the city of Andijan, Andijan region. The diagnosis of preeclampsia was established on the basis of complaints, anamnesis and additional examination methods, and the severity was assessed according to the WHO classification of hypertensive conditions in pregnancy (ICD-10) and the national clinical protocol. In all cases, preeclampsia was combined with various extragenital diseases.

Inclusion criteria:

- Blood pressure ≥130/90 mmHg;
- Diastolic pressure >90 mm Hg;
- Proteinuria >0.033 g/l.

Patients with isolated oedema syndrome were not included, since oedema is not considered as a criterion for assessing the severity of preeclampsia in most countries.

The main group consisted of 87 pregnant women aged 18–40 years, the control group consisted of 90 healthy women with normal pregnancy, comparable in gestational age and intergenetic interval. Genetic studies of the GSTP1 gene polymorphism (IIe105Val) were performed in 87 women of the main group and 90 women of the control group. The main group was divided into two subgroups depending on the severity of preeclampsia: Subgroup I included 47 women with severe preeclampsia, subgroup II — 40 women with moderate preeclampsia.

3. Research Methods

Clinical and laboratory studies included a complete blood count and urine analysis, determination of hematocrit, protein levels in single and daily urine, microalbuminuria, blood enzymes, creatinine, total protein, urea, as well as genetic analysis of the GSTP1 gene polymorphism (IIe105Val).

The data were processed on a Pentium-IV computer using Microsoft Office Excel-2012 with statistical analysis functions. The methods of variation parametric and nonparametric statistics were used, including calculation of the arithmetic mean (M), standard deviation (σ), standard error of the mean (m), relative values (%, frequency). The statistical significance of differences in mean values was determined by the Student's criterion (t) with the calculation of the probability of error (P), taking into account the normality of distribution (kurtosis criterion) and equality of variances (Fisher's F-criterion). The significance level was accepted at $P<0.05$. For qualitative values, the χ^2 (chi-square) criterion was used.

4. Results

The distribution of allele and genotype frequencies of the GSTP1 gene polymorphism (IIe105Val) was studied among pregnant women with moderate and severe preeclampsia, as well as with normal pregnancy. In the main group, which included women with moderate and severe preeclampsia, the homozygous genotype IIe/IIe was 63.22%, the heterozygous genotype IIe/Val was 34.48%, and the homozygous mutant genotype Val/Val was 2.3%.

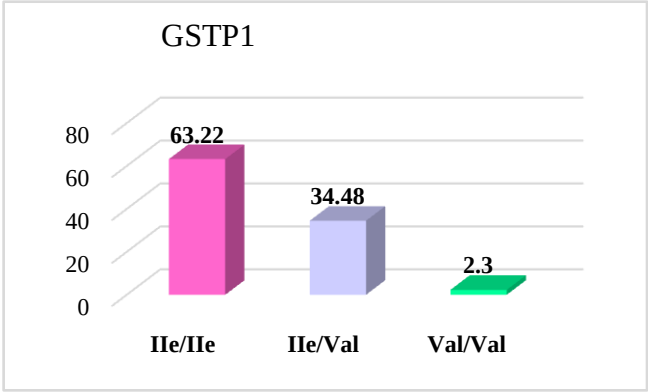

Figure 1. The result of the distribution of GSTP1 genotypes in the main group (n = 87)

The results of the study showed that the frequency of the homozygous wild-type genotype IIe/IIe was 72.34% in subgroup I (severe preeclampsia), 52.5% in subgroup II (moderate preeclampsia), and 78.89% in the control group. The heterozygous genotype IIe/Val was detected in 27.66% of women in subgroup I, 42.5% of women in subgroup II, and 20.0% of women in the control group. The homozygous mutant genotype Val/Val was not found in subgroup I, while in subgroup II it was found in 5.0% and in the control group in 1.11%.

The distribution of genotypes of the GSTP1 gene polymorphism (IIe105Val) was tested for compliance with the Hardy-Weinberg equilibrium. Deviations from the equilibrium were practically absent in the main and control groups (D=0.01 for both groups).

In the main group, for the GSTP1 locus, the observed empirical $H_{obs\ value}$ for the homozygous IIe/IIe genotype was 0.632%, and the theoretical Hexp was 0.647% (χ^2=0.031; p=0.353). For the IIe/Val and Val/Val genotypes, the observed Hobs values were 0.045% and 0.038%, and the theoretical H_{exp} were 0.255% and 0.526%, respectively (χ^2=0.255; p=0.353 and χ^2=0.526; p=0.353), which did not show a statistically significant decrease.

In the control group, the frequency of IIe/IIe, IIe/Val and Val/Val genotypes was 0.789/0.79, 0.2/0.198 and 0.011/0.012, respectively (χ^2=0.014; p=0.862), indicating a low probability of systematic errors in the study (Table 1).

Table 1. Distribution indicators of genotypes of the GSTP1 gene polymorphism (IIe105Val) according to the RHV of observed and expected results in the study groups

Main group					
Alleles	Allele frequency				
IIe	0.8				
Val	0.2				
Genotypes	Genotype frequency		χ^2	p	df
	observable	expected			
IIe / IIe	0.632	0.647	0.031		
IIe / Val	0.345	0.314	0.255		
Val / Val	0.023	0.038	0.526		
Total	1	1	0.812	0.353	1

Control group					
Alleles	Allele frequency				
IIe	0.89				
Val	0.11				
Genotypes	Genotype frequency		χ^2	p	df
	observable	expected			
IIe / IIe	0.789	0.79	0		
IIe / Val	0.2	0.198	0.003		
Val / Val	0,011	0,012	0,011		
Total	1	1	0,014	0.862	1

Note: (* H_{exp} - Expected indicator, * H_{obs} - Observed indicator)

The analysis of the data presented in the table shows that in pregnant women of the main group, the observed indicator of the heterozygous genotype of the GSTP1 gene polymorphism (IIe105Val) demonstrated a tendency to increase (statistically insignificant) compared to the expected value (0.34/0.31; D=+0.1). In the control group, the indicators were 0.2/0.2; D=0.01, respectively.

Table 2. Differences between observed and expected indicators of the heterozygous genotype of the GSTP1 gene polymorphism (IIe105Val) in the main and control groups

Groups	Ho	He	D*
Main group	0.34	0.31	0,1
Control group	0.2	0.2	0.01

Note: D = (Ho - He)/He

During the study, the frequency of alleles of the GSTP1 gene was distributed as follows: in the main group, the proportion of the allele IIe accounted for 80.5%, and the mutant allele Val — 19.5%, while in the control group these figures were 88.9% and 11.1%, respectively. For the allele IIe: χ^2=4.9; p=0.11; RR=0.9; 95% CI: 0.57–1.44; OR=0.5; 95% CI: 0.29–0.93. For the mutant allele Val: χ^2=4.9; p=0.11; RR=1.1; 95% CI: 0.54–2.25; OR=1.9; 95% CI: 1.08–3.51. In terms of odds ratio (OR), the mutant Val allele increases the risk of developing preeclampsia in pregnant women participating in the study (OR=1.9; 95% CI: 1.08–3.51). The results obtained for both alleles were statistically significant (χ^2=4.9; p=0.11).

When comparing the IIe / IIe, IIe / Val and Val / Val genotypes of the IIe105Val polymorphism of the GSTP1 gene in the main and control groups, it was found that the wild genotype IIe / IIe was more common in the control group, while the heterozygous IIe / Val genotype and the mutant Val / Val genotype prevailed in the main group. The frequency of the IIe / IIe , IIe / Val and Val / Val genotypes in the main group was 63.2%, 34.5% and 2.3%, respectively, while in the control group it was 78.9%, 20.0% and 1.1%. For the IIe / IIe genotype in the control group: χ^2 = 5.3; p = 0.08; RR = 0.8; 95% CI: 0.45–1.41; OR = 0.5; 95% CI: 0.24–0.89. In the main group, the heterozygous genotype IIe / Val (χ^2=4.7; p=0.7; RR=1.7; 95% CI: 0.97–3.06; OR=2.1; 95% CI: 1.07–4.13) and the mutant genotype Val / Val (χ^2=0.4; p=0.71; RR=2.1; 95% CI: 1.07–4.13; OR=2.1; 95% CI: 0.2–22.34) were more common (Table 3).

In the study, the main group of pregnant women was divided into two subgroups. The first subgroup included women with severe preeclampsia, in whom the IIe allele of the GSTP1 gene was 86.2%, and the Val allele was 13.8%. In the control group, these figures reached 88.9% and 11.1%, respectively. Compared with the first subgroup, the control group showed a slight predominance of the IIe allele (χ^2=0.4; p=0.74; RR=1.1; 95% CI: 0.39–2.38; OR=0.8; 95% CI: 0.37–1.64). The frequency of the mutant Val allele in the first subgroup was slightly higher than in the control (χ^2=0.4; p=0.4; RR=1.0; 95% CI: 0.59–1.82; OR=1.3; 95% CI: 0.61–2.71). These data suggest that the mutant Val allele may increase the risk of preeclampsia, while the IIe allele probably has a protective function. However, the results did not reach statistical significance (χ^2=0.4; p=0.74).

Table 3. Frequency of occurrence of genotypes and alleles of the IIe105Val locus in the GSTP1 gene (probabilistic control model)

Alleles and genotypes	Number of alleles and genotypes examined				χ^2	p	R.R.	95%CI	OR	95%CI
	Main group		Control group							
	n	%	n	%						
IIe	140	80.5	160	88.9	4.9	0.11	0.9	0.57 - 1.44	0.5	0.29 - 0.93
Val	34	19.5	20	11.1	4.9	0.11	1,1	0.54 - 2.25	1.9	1.08 - 3.51
IIe / IIe	55	63.2	71	78.9	5.3	0.08	0.8	0.45 - 1.41	0.5	0.24 - 0.89
IIe / Val	30	34.5	18	20.0	4.7	0.11	1.7	0.97 - 3.06	2.1	1.07 - 4.13
Val / Val	2	2,3	1	1,1	0.4	0.71	2.1	0.42 - 10.21	2.1	0.2 - 22.34

Note: Statistical significance was determined using the χ^2 test. The significance level was set at $p< 0.05$.

In the control group, the frequency of the homozygous IIe/IIe genotype was higher than in the first subgroup (78.9% versus 72.3%; χ^2=0.7; p=0.50; RR=0.9; 95% CI: 0.34–2.45; OR=0.7; 95% CI: 0.31–1.58). The heterozygous IIe/Val genotype was more common in the first subgroup (27.7% versus 20.0% in the control group; χ^2=1.0; p=0.58; RR=1.4; 95% CI: 0.52–3.67; OR=1.5; 95% CI: 0.67–3.47). The homozygous Val/Val genotype was absent in both groups.

5. Discussion

Data analysis showed that heterozygous IIe/Val genotype was associated with an increased risk of preeclampsia (OR=1.5; 95% CI: 0.67–3.47). Comparison of genotype and allele frequencies of the IIe105Val locus of the GSTP1 gene between the second subgroup (n=40) and the control group is presented below. In the second subgroup (pregnant women with mild preeclampsia), the proportion of the IIe allele was 73.8%, and the Val allele was 26.3%, while in the control group it was 88.9% and 11.1%, respectively. The IIe allele was predominant in the control group (χ^2=9.6; p=0.01; RR=0.8; 95% CI: 0.4–1.71; OR=0.4; 95% CI: 0.18–0.68). The frequency of the mutant Val allele was higher in the second subgroup (χ^2=9.6; p=0.01; RR=1.2; 95% CI: 0.64–2.27; OR=2.8; 95% CI: 1.47–5.53).

The homozygous IIe/IIe genotype was more common in the control group (78.9% versus 52.5% in the second subgroup; χ^2=9.3; p=0.01; RR=0.7; 95% CI: 0.25–1.75; OR=0.3; 95% CI: 0.14–0.65). The heterozygous IIe/Val genotype was more common in the second subgroup (42.5% versus 20.0% in the control group; χ^2=7.1; p=0.01; RR=2.1; 95% CI: 0.81–5.58; OR=3.0; 95% CI: 1.33–6.55). The homozygous Val/Val genotype was more often detected in the second subgroup (5.0% versus 1.0% in the control group; χ^2=1.9; p=0.27; RR=4.5; 95% CI: 0.86–23.49; OR=4.7; 95% CI: 0.51–43.16).

Comparison of the subgroups revealed that the frequency of the IIe allele was higher in the first subgroup (86.2%) compared to the second (73.8%; χ^2=4.2; p=0.10; RR=1.2; 95% CI: 0.48–2.82; OR=2.2; 95% CI: 1.04–4.73). The Val allele, on the contrary, prevailed in the second subgroup (26.3% versus 13.8%; χ^2=4.2; p=0.10; RR=0.9; 95% CI: 0.45–1.63; OR=1.5; 95% CI: 0.21–0.96). The homozygous IIe/IIe genotype was more common in the first subgroup (72.3% versus 52.8% in the second; χ^2=3.7; p=0.21; RR=1.4; 95% CI: 0.55–3.44; OR=2.4; 95% CI: 0.98–5.72). The heterozygous IIe/Val genotype was more common in the second subgroup (42.5% versus 27.7%; χ^2=2.1; p=0.30; RR=1.7; 95% CI: 0.26–1.61; OR=1.5; 95% CI: 0.21–1.26). The homozygous Val/Val genotype was absent in the first subgroup, but was found in the second.

6. Prognostic Significance

Evaluation of the prognostic value of the IIe105Val polymorphism of the GSTP1 gene showed that the mutant Val allele can increase the risk of preeclampsia. In the main group, AUC was 0.65 (SE=0.89; SP=0.58; OR=1.94; 95% CI: 1.08–3.5; p=0.37). In the first subgroup, AUC=0.62 (SE=0.89; SP=0.64; OR=1.28; 95% CI: 0.61–2.68; p=0.61), in the second — AUC=0.68 (SE=0.89; SP=0.76; OR=2.85; 95% CI: 1.47–5.54; p=0.49). For the mutant Val/Val genotype in the main group, AUC=0.71 (SE=0.72; SP=0.99; OR=2.09; 95% CI: 0.2–22.15; p=0.49), in the first subgroup, AUC=0.72 (SE=0.75; SP=0.99; OR=4.68; 95% CI: 0.51–43.06; p=0.66). The average AUC value (0.65–0.71) indicates a high prognostic value of the mutant Val allele and the Val/Val genotype as markers of preeclampsia risk.

7. Conclusions

The study revealed that in the Uzbek population, the mutant Val allele and the homozygous Val/Val genotype of the GSTP1 gene (IIe105Val) are associated with an increased risk of preeclampsia. The IIe allele and IIe/IIe genotype probably do not play a key role in the development of preeclampsia, but may have a protective effect. Polymorphism of the GSTP1 gene (IIe105Val) can be used as a genetic marker of preeclampsia risk, especially in the case of the mutant Val allele and Val/Val genotype.

Conclusions. Our study revealed that in the Uzbek population of pregnant women with preeclampsia, the mutant homozygous Val/Val genotype of the GSTP1 gene polymorphism (IIe105Val) was more common than in the control group. Statistical data, including OR and AUC, indicate that the mutant Val allele and the Val/Val genotype of the GSTP1 gene are associated with an increased risk of preeclampsia. At the same time, the IIe allele and the homozygous IIe/IIe genotype do not seem to play a significant role in the development of preeclampsia, although the IIe allele may have a protective effect. Nevertheless, preeclampsia was observed in women with the mutant Val allele and the Val/Val genotype. Thus, the GSTP1 gene polymorphism (IIe105Val) may act as a genetic marker that increases the risk of preeclampsia in pregnant women.

REFERENCES

[1] Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. Eur J Obstet Gynaecology Reprod Biol. 2013; 170 (1): 1-7. doi: 10.1016/j.ejogrb.2013.05.005.

[2] Burton GJ, Redman CW, Roberts JM, Moffett A. Pre-eclampsia: pathophysiology and clinical implications. BMJ. 2019; 366: l2381. doi: 10.1136/bmj.l2381.

[3] Steinthorsdottir V, McGinnis R, Williams NO, et al; FINNPEC Consortium; GOPEC Consortium. Genetic predisposition to hypertension is associated with preeclampsia in European and Central Asian women. Nat Commun. 2020; 11 (1): 5976. doi: 10.1038/s41467-020-19733-6.

[4] Bartsch E, Medcalf KE, Park AL, Ray JG; High Risk of Pre-eclampsia Identification Group. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ. 2016; 353: i1753. doi: 10.1136/bmj.i1753.

[5] Wu P. Haththotuwa R, Kwok CS, et al. Preeclampsia and future cardiovascular health. Circ Cardiovasc Qual Outcomes. 2017; 10 (2): 1-9. doi: 10.1161/CIRCOUTCOMES.116.003497.

[6] Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. Eur J Epidemiol. 2013; 28 (1): 1-19. doi: 10.1007/s10654-013-9762-6.

[7] Zhou W, Nielsen JB, Fritsche LG, et al. Efficiently controlling for case-control imbalance and sample relatedness in large-scale genetic association studies. Nat Genet. 2018; 50 (9): 1335-1341. doi: 10.1038/s41588-018-0184-y.

[8] Bulik-Sullivan BK, Loh PR, Finucane HK, et al; Schizophrenia Working Group of the Psychiatric Genomics Consortium. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet. 2015; 47 (3): 291-295. doi: 10.1038/ng.3211.

[9] Bulik -Sullivan B, Finucane HK, Anttila V, et al; ReproGen Consortium; Psychiatric Genomics Consortium; Genetic Consortium for Anorexia Nervosa of the Wellcome Trust Case Control Consortium 3. An atlas of genetic correlations across human diseases and traits. Nat Genet. 2015; 47 (11): 1236-1241. doi: 10.1038/ng.3406.

[10] Zhao L, Bracken MB, DeWan AT. Genome-wide association study of pre-eclampsia detects novel maternal single nucleotide polymorphisms and copy-number variants in subsets of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study cohort. Ann Hum Genet. 2013; 77 (4): 277-287. doi: 10.1111/ahg.12021.

[11] Boeldt DS, Bird IM. Vascular adaptation in pregnancy and endothelial dysfunction in preeclampsia. J Endocrinol. 2017; 232 (1): R27-R44. doi: 10.1530/JOE-16-0340.

[12] Goulopoulou S. Maternal vascular physiology in preeclampsia. Hypertension. 2017; 70 (6): 1066-1073. doi: 10.1161/HYPERTENSIONAHA.117.08821.

[13] Daehn I.S., Duffield JS. The glomerular filtration barrier: a structural target for novel kidney therapies. Nat Rev Drug Discov. 2021; 20 (10): 770-788. doi: 10.1038/s41573-021-00242-0.

[14] Domigan C.K., Warren C.M., Antanesian V., et al. Autocrine VEGF maintains endothelial survival through regulation of metabolism and autophagy. J Cell Sci. 2015; 128 (12): 2236-2248. doi: 10.1242/jcs.163774.

[15] McGinnis R., Steinthorsdottir V., Williams N.O., et al; FINNPEC Consortium; GOPEC Consortium. Variants in the fetal genome near FLT1 are associated with risk of preeclampsia. Nat Genet. 2017; 49 (8): 1255-1260. doi: 10.1038/ng.3895.

[16] Reinhard N.R., Van Der Niet S., Chertkova A., et al. Identification of guanine nucleotide exchange factors that increase Cdc42 activity in primary human endothelial cells. Small GTPases. 2021; 12 (3): 226-240. doi: 10.1080/21541248.2019.1658509.

[17] Yang X, Yang W, McVey DG, et al. FURIN expression in vascular endothelial cells is modulated by a coronary artery disease-associated genetic variant and influences monocyte transendothelial migration. J Am Heart Assoc. 2020; 9 (4): e014333. doi: 10.1161/JAHA.119.014333.

[18] Ashraf S, Kudo H, Rao J, et al. Mutations in six nephrosis genes delineate a pathogenic pathway amenable to treatment. Nat Commun. 2018; 9 (1): 1960. doi: 10.1038/s41467-018-04193-w.

[19] Uchio -Yamada K, Yasuda K, Monobe Y, Akagi KI, Suzuki O, Manabe N. Tensin2 is important for podocyte -glomerular basement membrane interaction and integrity of the glomerular filtration barrier. Am J Physiol Renal Physiol. 2020; 318 (6): F1520-F1530. doi: 10.1152/ajprenal.00055.2020.

[20] Yu S, Choi WI, Choi YJ, Kim HY, Hildebrandt F, Gee HY. PLCE1 regulates the migration, proliferation, and differentiation of podocytes. Exp Mol Med. 2020; 52 (4): 594-603. doi: 10.1038/s12276-020-0410-4.

[21] Feng D, Kumar M, Muntel J, et al. Phosphorylation of ACTN4 leads to podocyte vulnerability and proteinuric glomerulosclerosis. J Am Soc Nephrol. 2020; 31 (7): 1479-1495. doi: 10.1681/ASN.2019101032.

[22] Kattah A. Preeclampsia and kidney disease: deciphering cause and effect. Curr Hypertens Rep. 2020; 22 (11): 91. doi: 10.1007/s11906-020-01099-1.

[23] Hasna J, Abi Nahed R, Sergent F, Alfaidy N, Bouron A. The deletion of TRPC6 channels perturbs iron and zinc homeostasis and pregnancy outcome in mice. Cell Physiol Biochem. 2019; 52 (3): 455-467. doi: 10.33594/000000033.

[24] Garrido - Gomez T, Castillo-Marco N, Clemente- Ciscar M, et al. Disrupted PGR-B and ESR1 signaling underlies defective decidualization linked to severe preeclampsia. Elife. 2021; 10:1 -20. doi: 10.7554/eLife.70753.

[25] Peng W, Liu Y, Qi H, Li Q. Alpha-actinin-4 is essential for maintaining normal trophoblast proliferation and differentiation during early pregnancy. Reprod Biol Endocrinol. 2021; 19 (1): 48. doi: 10.1186/s12958-021-00733-0.

[26] Buhimschi IA, Nayeri UA, Zhao G, et al. Protein misfolding, congophilia, oligomerization, and defective amyloid processing in preeclampsia. Sci Transl Med. 2014; 6 (245): 245ra92. doi: 10.1126/scitranslmed.3008808.

[27] Tong M, Cheng SB, Chen Q, et al. Aggregated transthyretin is specifically packaged into placental nano -vesicles in preeclampsia. Sci Rep. 2017; 7(1): 6694. doi: 10.1038/s41598-017-07017-x.

[28] Kalkunte SS, Neubeck S, Norris WE, et al. Transthyretin is dysregulated in preeclampsia, and its native form prevents the onset of disease in a preclinical mouse model. Am J Pathol. 2013; 183 (5): 1425-1436. doi: 10.1016/j.ajpath.2013.07.022.

[29] Millen KR, Buhimschi CS, Zhao G, Rood KM, Tabbah S, Buhimschi IA. Serum and urine thioflavin -T-enhanced fluorescence in severe preeclampsia. Hypertens. 2018; 71 (6): 1185-1192. doi: 10.1161/HYPERTENSIONAHA.118.11034.

[30] Lokki A.I., Heikkinen-Eloranta J.K., Laivuori H. The immunogenetic conundrum of preeclampsia. Front Immunol. 2018; 9: 2630. doi: 10.3389/fimmu.2018.02630.

[31] Lokki A.I., Heikkinen-Eloranta J. Pregnancy induced TMA in severe preeclampsia results from complement-mediated thromboinflammation. Hum Immunol. 2021; 82 (5): 371-378.

doi: 10.1016/j.humimm.2021.03.006.

[32] Martin A.R., Karczewski K.J., Kerminen S., et al. Haplotype sharing provides insights into fine-scale population history and disease in Finland. Am J Hum Genet. 2018; 102 (5): 760-775. doi: 10.1016/j.ajhg.2018.03.003.

[33] Tyrmi J.S., Arffman R.K., Pujol-Gualdo N., et al; FinnGen Consortium, Estonian Biobank Research Team. Leveraging Northern European population history: novel low-frequency variants for polycystic ovary syndrome. Hum Reprod. 2022; 37 (2): 352-365. doi: 10.1093/humrep/deab250.

[34] Sund R. Quality of the Finnish Hospital Discharge Register: a systematic review. Scand J. Public Health. 2012; 40(6): 505-515. doi: 10.1177/1403494812456637.