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GENE POLYMORPHISM OF BLOOD COAGULATION FACTORS AND ENDOTHELIAL DYSFUNCTION IN EARLY AND LATE PREECLAMPSIA

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Abstract. Gene polymorphism of blood coagulation factors and endothelial dysfunction in early and late preeclampsia. Loskutova T.O., Demchenko T.V., Kryachkova N.V. *The aim of our study was to find out the influence of gene polymorphisms of coagulation factors, endothelial dysfunction and regulators of blood pressure in early (EPE) and late preeclampsia (LPE). The study of genetic polymorphisms of blood coagulation factors and fibrinolysis (1691 G/A factor V Leiden (FVL), 20210 G/A prothrombin, -675 5G/4G PAI-1, 455 G/A fibrinogen β), endothelial dysfunction (192 Q → R paraoxonase 1, 677 C/T MTHFR, arterial pressure regulator (235 M/T angiotensinogen II (AGT II)) using an PCR was performed. A prospective cohort study of 39 women with EPE, 93 with LPE and 44 pregnant women with a physiological pregnancy (C group) was conducted. The average gestational age at the time of delivery in EPE group was lower than in LPE and control group (p<0.001). In group with EPE new-borns had low weight-growth characteristics, low grade by the Apgar scale and foetal distress (38.5% vs. 9.7%, p<0.05). Caesarean section in EPE group was performed by 2.25 times more often than in control group and by 2,13 times than in LPE group (p<0,05). It was detected that the number of 1691 GA FVL heterozygote carriers in the group with EPE was significantly higher than in LPE group (p<0.05, OR=3.65, 95% CI 1.5-8.9) and control group (6.04, 1.7-21.6). The number of 20210 GG homozygotes and 20210 GA heterozygotes in prothrombin gene was probably lower in EPE group compared with the LPE and control group (0.03, 0.002-0.49, and 0.18, 0.06-0.53, respectively). Increase in frequency of 677 TT MTHFR genotype in EPE compared with control group (17.27; 0.9-317) was established. Also, the carriers of 235T allele AGT II gene have an increased risk of EPE and PPE development (2.25, 1.2-4.2), (1.9, 1.1-3.3) respectively. The allele -455A of fibrinogen β gene increases the chances of developing EPE by 4.4 times (2.0-9.5) and LPE by 3.5 times (1.7-7.1). Risk factors that significantly increase the chances of developing early preeclampsia were identified: allele 1691 A of FV Leiden (5.96, 1.5-8.9), allele 20210 A of prothrombin (39.8, 2,3-679), 677T MTHFR (2.5, 1.18-5.3). In was detected that other researched polymorphisms between groups with PE were not significantly different and did not affect on time of preeclampsia development.*

Реферат. Полиморфизм генов факторов свертывания крови и эндотелиальной дисфункции при ранней и поздней преэклампсии беременных. Лоскутова Т.А., Демченко Т.В., Крячкова Н.В. *Целью нашего исследования было выяснить роль генных полиморфизмов факторов коагуляции, эндотелиальной дисфункции и регулятора артериального давления на возникновение ранней (РПЭ) и поздней преэклампсии (ППЭ) беременных. Проводилось определение генетических полиморфизмов факторов свертывания крови и фибринолиза (1691 G/A фактор V Лейден (FVL), 20210 G/A протромбин, -675 5G/4G PAI-1, 455 G/A фибриноген β), эндотелиальной дисфункции (192 Q → R параоксоназа 1, 677 C/T MTHFR), регулятора артериального давления (235 M/T ангиотензиноген II (AGT II)) с использованием ПЦР. Проспективное когортное исследование включало 39 женщин с РПЭ, 93 – с ППЭ и 44 беременных с физиологической беременностью (контрольная группа). Средний гестационный возраст на момент родов в группе РПЭ был ниже, чем в группе ППЭ и в контрольной группе (p<0,001). Также в группе с РПЭ новорожденные имели более низкие массо-ростовые характеристики, более низкую оценку по шкале Апгар, дистресс плода (38,5% против 9,7%, p<0,05). Роды путем кесарева сечения наблюдались в 2,25 раза чаще, чем в контрольной группе, и в 2,13 раза, чем в группе с ППЭ (p<0,05). Было обнаружено, что количество носителей гетерозиготы 1691 GA FVL в группе с РПЭ было значительно выше, чем в*

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группе ППЭ (p<0,05, OR=3,65, 95% CI 1,5-8,9) и в группе контроля (6,04, 1,7-21,6). Количество носителей гомозигот 20210 GG и гетерозигот 20210 GA гена протромбина было значительно ниже в группе с РПЭ по сравнению с ППЭ и контролем (0,03, 0,002-0,49 и 0,18, 0,06-0,53 соответственно). Было также установлено преобладание носителей генотипа 677 TT MTHFR в группе с РПЭ по сравнению с группой контроля (17,27; 0,9-317). Определено, что носители аллеля 235T гена AGT II имеют повышенный риск развития как РПЭ (2,25, 1,2-4,2) так и ППЭ (1,9, 1,1-3,3). Аллель -455A гена фибриногена β увеличивает вероятность развития РПЭ в 4,4 раза (2,0-9,5), а ППЭ в 3,5 раза (1,7-7,1). Таким образом, нами были установлены факторы риска, значительно повышающие шансы на развитие ранней преэклампсии: аллель 1691 A FV Leiden (5,96, 1,5-8,9), аллель 20210 A гена протромбина (39,8, 2,3-679), 677T гена MTHFR (2,5, 1,18-5,3). Доказано, что другие исследуемые полиморфизмы между группами с ПЭ существенно не различались и не имели достоверного влияния на время развития преэклампсии.

Preeclampsia (PE) is a pressing problem of modern obstetrics and occurs in 2-8% of pregnant women, being the leading cause of maternal perinatal mortality. Recent studies show that preeclampsia is the top of the iceberg, as women with preeclampsia are more likely to have cardiovascular disease, more likely to be diagnosed with coronary artery calcification in their third decade and more likely to develop type II diabetes and higher risk of cognitive impairment in the future. The main risk factors are: first pregnancy, obesity, diabetes, antiphospholipid syndrome and systemic lupus erythematosus. Although clinical manifestations of preeclampsia appear in the second half of pregnancy, primary pathogenetic disorders occur in the first trimester of pregnancy during trophoblast invasion and differentiation [4].

Numerous markers have been proposed for the diagnosis of preeclampsia. It has recently been established that preeclampsia can be early (up to 34 weeks) or late (after 34 weeks), based on the gestational age of childbirth [6, 8]. Early preeclampsia is less common (5-20% of all pregnant women with PE), but leads to more adverse pregnancy outcomes. PE thought to be associated with placental abnormalities associated with placental defects, including decreased spiral artery invasion, increased incidence of apoptosis in trophoblast cells, decreased mean area of spiral artery lumen, and higher incidence of placental infarction, decidual arteriopathy and villous hypertonia [4-6,8]. Preeclampsia with early onset is also associated with intrauterine growth retardation (IGR), pathological Doppler parameters in the uterine artery, umbilical artery and adverse neonatal consequences [1, 2, 4, 9]. Late preeclampsia is observed in 80% of cases and is more often characterized by the absence of changes in the placenta, normal Doppler parameters, normal birth weight and more favorable consequences for newborns [1, 2, 9]. There has been collected evidence that hemodynamic characteristics, frequency of placental disorders and biomarkers in these subtypes of preeclampsia are different.

The aim of the work is to study the distribution and influence of polymorphisms of genes of blood coagulation factors, endothelial dysfunction, blood pressure regulator in early and late preeclampsia of pregnant women.

MATERIALS AND METHODS OF RESEARCH

There was conducted a prospective cohort study which included 176 women in the second half of pregnancy. The criterion for involvement in the study is the presence of PE in accordance with the Order of the Ministry of Health of Ukraine N 676 dated 31.12.2004. The group with early preeclampsia (EPE) was formed by 39 patients, with late PE (LPE) – 93 patients. Pregnant women with a physiological course of pregnancy were included in the control group (C) – 44 pregnant women.

There was studied genetic polymorphisms of coagulation factors and fibrinolysis (1691 G → A factor V Leiden (FVL), 20210 G → A prothrombin, 675 5G / 4G type 1 plasminogen activator inhibitor (PAI-1), 455 G → A fibrinogene β), endothelial dysfunction (192 Q → R paraoxonase 1 (PON-1), 677 C → T methylenetetrahydrofolate reductase (MTHFR)), blood pressure regulator (235 M → T angiotensinogen II (AGT II)) by allele-specific polymerase chain reaction (amplifier "MyCycler" manufactured by "Bio-rad", USA) followed by detection by electrophoresis in 3% agarose gel (ultraviolet transilluminator "Vilber Lourmat", France) [7]. A set of reagents "SNP-Express" (RPC "Litex", Russian Federation) was used. DNA from blood leukocytes, which was isolated using the reagent "DNA-express blood" (RPC "Litex", Russian Federation) was used for analysis. The research was conducted on the basis of the clinical-diagnostic laboratory of MI “Dnipropetrovsk Regional Clinical Hospital named after I.I. Mechnikov”.

Statistical processing of study results was performed using licensed computer programs Microsoft Excel 2010 and Graph Pad Prism 5 (license number 35B73650-6899-11DA-6784-00232A9018BE). The main characteristics are presented in the form of the number of observations (n), the arithmetic mean (M), the standard error of the mean (±m), the relative values (abs.,%), the level of statistical significance (p). The normality of the distribution of quantitative variables was assessed

using the Shapiro-Wilk and Kolmogorov-Smirnov criteria. Comparison of statistical characteristics in the groups was performed using parametric and nonparametric criteria: estimation of probability of differences of averages for unrelated samples – by Student's criteria (t), probability of differences of qualitative indicators – by Pearson's Chi-square criterion ($\chi 2$), including Yates corrected), Fisher's exact criterion. The relationship between the factors was assessed by the odds ratio (OR) and its 95% confidence intervals (CI). The discrepancy was considered significant at $p<0.05$ [3].

RESULTS AND DISCUSSION

The characteristics of the surveyed women and the results of pregnancy are presented in Table 1. The average age of women and the distribution by age categories between groups did not differ ($p>0.05$). Analysis of reproductive function showed that the number of women with a history of childbirth in the groups did not differ significantly as well. Women with PE had significantly higher BMI, and the number of patients with BMI>30 kg/m^2 in the group with LPE was significantly higher than in the control ($p<0.05$; OR=3.19; 95% CI 1.13-8.96).

Table 1

Characteristics of women of study groups, M±m

Characteristics	EPE (n=39)	LPE (n=93)	Control (n=44)
Age, years, M±m	28.1±0.9	28.4±0.6	26.7±0.9
Primigravida, n (%)	12 (30.8)	40 (43)	20 (45.5)
First labor, n (%)	23 (59.0)	55 (59.1)	27 (61.4)
BMI, kg/m^2	27.3 ± 0.9*	27.8 ± 0.6*	25.1 ± 0.6
BMI > 30 kg/m^2, n (%)	10 (25.6)	27 (29.0)*	5 (11.4)
Term of labor, weeks	31.4 ± 0.4*,LPE	37.6 ± 0.2*	38.7±0.2
Operative labor, n (%)	26 (66.4) * LPE	29 (31.2)	13 (29.5)
PE of mild degree, n (%)	5 (12.8) LPE	59 (63.4)	-
PE of moderate degree, n (%)	24 (61.6) LPE	28 (30.1)	-
PE of severe degree, n (%)	10 (25.6) LPE	6 (6.5)	-
Fetus distress, n (%)	15 (38.5) LPE	9 (9.7)	-
IGR, n (%)	9 (23.1)	12 (12.9)	-
PDNSP, n (%)	2 (5.1)	-	-
Antenatal fetus death, n (%)	6 (15.4)	-	-
Neonatal weight, kg	1552 ±99.3 *,IIIIE	2916±66.6 *	3439±70.7
Length at birth, cm	41.1±0.8 *,IIIIE	50.4±0.35 *	51.9±0.3
Apgar, 1 min. ≥ 7 , n (%)	7 (17.9) *,IIIIE	52 (55.9)*	36 (81.8)
Apgar, 5 min. ≥ 7 , n (%)	26 (66.7) *,IIIIE	90 (96.8)	44 (100)

Notes: * - the difference is statistically significant compared to group C ($p<0.05$); LPE – the difference is statistically significant compared with the group with late preeclampsia ($p<0.05$); IGR – intrauterine growth retardation; PDNSP - premature detachment of the normally situated placenta; BMI - body mass index.

In the group with EPE compared with LPE a mild degree of PE was in (12.8% vs. 63.4%, $p<0.001$; OR=0.08; 95% CI 0.03-0.24), moderate degree of PE – (61.6% vs. 30.1%, $p<0.001$; OR=3.7; 95% CI 1.7-8.1), severe degree of PE – (25.6% vs. 6.5%, $p=0.003$; OR=5.0; 95% CI 1.67-14.9). The mean gestational age at the time of delivery in the EPE group was less than in the group with LPE and C ($p<0.001$). This is due to the severity of preeclampsia and the development of complications that required preterm delivery. In the group with EPE, newborns were probably more likely to have low weight-for-length characteristics, low score by the Apgar scale (Table 1). Among the complications of pregnancy, fetal distress was probably diagnosed (38.5% vs. 9.7%, $p<0.05$; OR=5.8; 95% CI 2.27-14.97). In pregnant women with LPE by 2.25 times more often, labor by cesarean section occurred than

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in group C (p<0.05) and by 2.13 times more often than in the group with LPE (p<0.05).

Analyzing the genotype distribution of the FVL gene (1691 G → A) (Table 2), it was found that the frequency of "neutral" GG homozygotes in the EPE group is less compared with LPE group (p<0.05, OR=0.25, 95% CI 0.1-0.6) and C group (p<0.05, OR=0.15, 95% CI 0.04-0.5). The number of heterozygotes of 1691 GA FVL in the EPE group is probably greater than in the LPE group (p<0.05, OR=3.65, 95% CI 1.5-8.9) and C group (p<0.05, OR=6.04, 95% CI 1.7-21.6). Carriers of the 1691A FVL allele have an increased risk of developing early preeclampsia (OR=5.96, 95% CI 1.79-19.89). The number of carriers of homozygote 20210 GG and heterozygote 20210 GA of the prothrombin gene was significantly lower in the EPE group compared with the LPE group and C group (p<0.05, OR=0.03, 95% CI 0.002-0. 49 and OR=0.18, 95% CI 0.06-0.53, respectively) (Table 2). Allele 20210 of A prothrombin increases the risk of early preeclampsia (OR=39.8 95% CI 2.3-679). Analysis of allelic and genotypes frequencies of MTHFR 677 C → T showed an increase in the frequency of genotype 677 TT in the group with EPE (Table. 2) compared with C group (OR=17.27, 95% CI 0.9-317). The T allele of the MTHFR gene increases the chances of developing early PE by 2.5 times (95% CI 1.18-5.3).

Table 2

Genotypes frequency in pregnant women of study groups, (%)

Study groups	Genotype			Alleles	
ANG 235 M→T	MM	MT	TT	M	T
EPE (n=39)	10 (25.6)	18 (46.2)	11 (28.2)*	38 (51.3)	40 (48.7)*
LPE (n=93)	30 (32.3)	38 (40.9)	25 (26.9)*	98 (52.7)	88 (47.3)*
Control group (n=44)	20 (45.5)	20 (45.5)	4 (9.1)	60 (68.2)	28 (31.8)
Prothrombin 20210 G→A	GG	GA	AA	20210G	20210A
EPE (n=39)	28 (71.8)*, LPE	8 (20.5)*, LPE	3 (7.7)	64 (82.1) *,LPE	14 (17.9) *, LPE
LPE (n=93)	87 (93.5)	5 (5.4)	1 (1.1)	179 (96.2)	7 (3.8)
Control group (n=44)	44 (100.0)	0 (0.0)	0 (0.0)	88 (100.0)	0 (0.0)
FVL 1691 G→A	GG	GA	AA	1691G	1691A
EPE (n=39)	25 (64.1)*, LPE	13 (33.3) *, LPE	1 (2.6)	63 (80.8) *, LPE	15 (19.2) *, LPE
LPE (n=93)	82 (88.2)	11 (11.8)	0 (0.0)	175 (94.1)	11 (5.9)
Control group (n=44)	41 (93.2)	3 (6.8)	0 (0.0)	85 (96.6)	3 (3.4)
PAI-1 5G/4G	5G/5G	5G/4G	4G/4G	5G	4G
EPE (n=39)	7 (8.3)*	22 (56.4)	10 (25.6)*	36 (46.2)*	42 (53.8)
LPE (n=93)	22 (23.7)*	52 (55.9)	19 (20.4)*	96 (51.6)*	90 (48.4)
Control group (n=44)	23 (52.3)	17 (38.6)	4 (9.1)	63 (71.6)	25 (28.4)
Fibrinogen β 455 G→A	GG	GA	AA	G	A
EPE (n=39)	13 (33.3)	22 (56.4)	4 (10.3)	48 (61.5)	30 (38.5)*
LPE (n=93)	42 (45.2)	40 (43.0)	11 (11.8)	124 (66.7)	62 (33.3)*
Control (n=44)	34 (77.3)	9 (20.5)	1 (2.3)	77 (87.5)	11 (12.5)
MTHFR 677 C→T	CC	CT	TT	677C	677T
EPE (n=39)	21 (53.8)	12 (30.8)	6 (15.4)*	54 (69.2)*	24 (30.8)*
LPE (n=93)	59 (63.4)	24 (25.8)	10 (10.8)	142 (76.3)	44 (23.7)
Control (n=44)	31 (70.5)	13 (29.5)	0 (0.0)	75 (85.2)	13 (14.8)
PON-1 192 Q→R	QQ	QR	RR	192Q	192R
EPE (n=39)	21 (53.8)	12 (30.8)	6 (15.4)	54 (69.2)	24 (30.8)
LPE (n=93)	47 (50.5)	32 (34.4)	14 (15.1)	126 (67.7)	60 (33.3)
Control (n=44)	29 (65.9)	8 (18.2)	7 (15.9)	66 (75.0)	22 (25.0)

Notes: * – the difference between the values is statistically significant with the corresponding value of the control group (p<0.05); EPE – the difference is statistically significant compared with the group with late preeclampsia (p<0.05).

EPE and LPE are characterized by a smaller number ($p<0.05$) of carriers of the normal homozygote of the PAI-1 5G/5G gene OR=0.2, 95% CI 0.07-0.55 and OR=0.3, 95% CI 0.13-0.6, respectively. The 5G PAI-1 allele has protective properties against the development of EPE ($p<0.05$, OR=0.34, 95% CI 0.18-0.65) and LPE (OR=0.43, 95% CI 0.23-0.73).

Carriers of the 235T allele of the angiotensinogen gene have an increased chance of developing both EPE ($p<0.05$, OR=2.25, 95% CI 1.2-4.2) and LPE ($p<0.05$, OR=1.9, 95% CI 1.1-3.3). The 455A allele of the fibrinogen β gene increases the chances of developing EPE by 4.4 times (2.0-9.5) and LPE – by 3.5 times (1.7-7.1).

Thus, mutations in the FVL, prothrombin and MTHFR genes are more significant for the development of EPE, which coincides with previous studies [1, 2] that proved that these mutations have a significant impact on the development of maternal and fetus complications in pregnant women with PE. This study shows that the existence of mutations in the FVL, prothrombin and MTHFR genes is associated not only with obstetric and perinatal complications that occur in pregnant women with PE, but also with the early onset of PE and, accordingly, more severe course.

CONCLUSIONS

1. Early preeclampsia is characterized by a more severe course, namely: pregnancy is more often complicated by fetal distress, surgical and premature birth, the birth of children with low weight-to-length characteristics and low score by the Apgar scale.
2. Risk factors that increase the chances of developing early preeclampsia were identified: allele 1691 A FV Leiden (OR = 5.96, 95% CI 1.5-8.9), 20210 A prothrombin (OR = 39.8, 95% CI 2.3-679), 677T MTHFR (OR = 2.5, 95% CI 1.18-5.3).
3. Polymorphisms of PAI-1 5G/4G genes, fibrinogen β 455 G → A and angiotensinogen 235 M → T do not differ between groups with preeclampsia.
4. Mutation of paraoxonase-1 192 Q → R has no significant effect on the development of preeclampsia.

Conflict of interest. The authors declare no conflict of interest.

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