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THE ROLE OF THE C-786T POLYMORPHISM OF THE NOS3 GENE IN THE DEVELOPMENT OF HYPERTENSIVE DISORDERS DURING PREGNANCY

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ABSTRACT

C-786T in the NOS3 gene can serve as a diagnostic and prognostic marker for the development of hyperten¬ sion during pregnancy.

Objective. To determine the role of C-786Tpolymor phism in the NOSS gene in the development of hyperten sive conditions during pregnancy.

Material and methods. The subjects were divided into 4 groups: The first group - 43 pregnant women with severe preeclampsia. The second group - 33 pregnant women with mild preeclampsia. The third group - 28 pregnant women with gestational hypertension. The con trol group consisted of 107 apparently healthy pregnant women.

Results. The distribution of alleles and genotypes of the C-786T polymorphism of the NOS3 gene was stud ied in the main group and among patients with severe preeclampsia. Allele C was detected statistically insig nificantly less frequently in severe preeclampsia - in 68.6% of cases (fr= 0.07; p=0.79; RR=1.02; 95% CI: 0.74-1.41; OR=1.08; 95% CI: 0.63-1.86), compared with 70.2%> detection in the main group. The T allele in patients with severe preeclampsia was found in 31.4% of cases f r 0.07; p=0.79; RR=0.98;95%CI:0.46- 2.06; OR=0.93; 95%CI:0.54-1.60), relative to patients the main group, where its detection rate was 29.8%>.

Conclusions. The diagnostic value ojp studying the C-786T polymorphism in the NOSS gene in the devel opment of hypertensive conditions during pregnancy has been proven.

Intraduction. From the standpoint of modern science, hypertensive disorders during pregnancy, particularly preeclampsia, are the result of a close interaction between genetic components and environmental factors; it is possible to confidently state that the disease has a multifactorial origin.

Given the importance of endogenous NO for maintaining normal endothelial function, it is possible that polymorphisms in the gene encoding the enzyme responsible for NO synthesis (endothelial NO synthase; eNOS) may affect the production of

endogenous NO [1,3,7] and contribute to the development of preeclampsia or gestational hypertension.

Three clinically significant polymorphisms in the eNOS gene have been widely studied: a SNP in the promoter region (T-786C), a SNP in exon 7 that leads to an amino acid substitution (Glu298Asp), and a variable number of tandem repeats (VNTR) in intron 4 [2]. Although several previous studies have investigated whether these polymorphisms are associated with preeclampsia, inconclusive results have been obtained.

For example, while one study demonstrated an association between the Asp298 variant (Glu298Asp polymorphism) and PE [6], another study found no association [4]. Moreover, while one study showed a significant association of the C variant (T-786C polymorphism) with PE [11], another study demonstrated no association [6]. These discrepancies may be partly due to evaluating only a single polymorphism rather than combinations of polymorphisms [5,8], and it is generally believed that the analysis of combinations of genetic markers in the region of interest (haplotypes) may be much more informative than testing the effects of genetic markers one by one [5,10]. In the study by Valeria C. Sandrim et al. (2016), the distribution of genetic variants of the three abovementioned eNOS polymorphisms was compared among healthy pregnant women, pregnant women with hypertension, and women with preeclampsia.

Nitric oxide is produced enzymatically by nitric oxide synthase (NOS), which converts L-arginine into L-citrulline and NO in the presence of oxygen.

Furthermore, it has been reported that asymmetric dimethylarginine (ADMA) acts as an endogenous inhibitor of endothelial NOS (eNOS) by competing with the enzyme for L-arginine [9].

Aim of the study. To determine the diagnostic role of the C-786T polymorphism in the NOS3 gene in the development of hypertensive disorders during pregnancy.

Materials and methods. We conducted a study of 104 pregnant women admitted for inpatient treatment in the second–third trimester, who were divided into three groups. The first group consisted of 43 pregnant women with severe preeclampsia, the second group — 33 pregnant women with mild preeclampsia, and the third group — 28 women with gestational hypertension. The control group consisted of 107 pregnant women with a physiological course of pregnancy. Women in the first, second, and third groups together constituted the main group — 104 pregnant women. The age of the examined women ranged from 19 to 41 years. The mean age of pregnant women in the first group was 29.45±0.79 years, in the second — 26.45±0.79, in the third — 27.45±0.79, and in the control group — 28.18±0.69 years.

The study was conducted at the Department of Obstetrics and Gynecology of the Tashkent Pediatric Medical Institute, Maternity Complex No. 6, and Clinical Hospital No. 4 in Tashkent. Genetic studies were performed at the Department of Molecular Genetics of the Republican Center of Hematology. DNA extraction from blood and PCR analysis were carried out using reagent kits and test systems produced by “Ampli Prime Ribo-prep” (NEXT Bio LLC, Russia).

The concentration of nucleic acid preparations obtained from the samples was determined spectrophotometrically using a NanoDrop-2000 instrument (NanoDrop Technologies, USA).

Results. The distribution of alleles and genotypes of the C-786T polymorphism of the NOS3 gene was studied in the main group and among patients with severe preeclampsia.

The C allele was identified statistically insignificantly less frequently in severe preeclampsia — in 68.6% of cases (f = 0.07; p = 0.79; RR = 1.02; 95% CI: 0.74–1.41; OR = 1.08; 95% CI: 0.63–1.86) compared with 70.2% detected in the main group (Table 1).

The T allele in patients with severe preeclampsia was found in 31.4% of cases (f = 0.07; p = 0.79; RR = 0.98; 95% CI: 0.46–2.06; OR = 0.93; 95% CI: 0.54–1.60), i.e., statistically insignificantly more frequently compared to the main group, where its detection frequency was 29.8%.

The homozygous C/C genotype of the C-786T polymorphism of the NOS3 gene was insignificantly less frequently detected in severe preeclampsia — in 48.8% of cases (χ^2 = 0.12; p = 0.74; RR = 1.06; 95% CI: 0.71–1.60; OR = 1.13; 95% CI: 0.56–2.30) compared with the main group, where it was identified in 51.9% of cases.

The heterozygous C/T genotype, with an almost uniform distribution, was insignificantly more frequently detected — in 39.5% of cases in the group of patients with severe preeclampsia (f = 0.12; p = 0.74; RR = 0.92; 95% CI: 0.60–1.42; OR = 0.88; 95% CI: 0.43–1.82) compared with the main group of patients (Table 1).

Table 1

Differences in Allelic and Genotypic Frequencies of the C-786T Polymorphism in the NOS3 Gene in the Main Group and the Group of Patients with Severe Preeclampsia

Alleles and Genotypes	Number of Examined Alleles and Genotypes				X^2	P	RR	95% CI	OR	95% CI
	Main Group		Severe Preeclampsia							
	n	%	n	%						
C	146	70.2	59	68.6	0.07	0.79	1.02	0.74-1.41	1.08	0.63-1.86
T	62	29.8	27	31.4	0.07	0.79	0.98	0.46-2.06	0.93	0.54-1.60
C/C	54	51.9	21	48.8	0.12	0.74	1.06	0.71-1.60	1.13	0.56-2.30
C/T	38	36.5	17	39.5	0.12	0.74	0.92	0.60-1.42	0.88	0.43-1.82
T/T	12	11.5	5	11.6	0	1.00	0.99	0.52-1.88	0.99	0-0

The heterozygous T/T genotype was present in almost equal proportions both among patients in the main group and among those with severe preeclampsia (f = 0; p = 1.00; RR = 0.99; 95% CI: 0.52–1.88; OR = 0.99; 95% CI: 0–0).

The frequencies of detection of alleles and genotypes of the C-786T polymorphism of the NOS3 gene were studied among patients in the main group and those with mild preeclampsia. The C allele was detected insignificantly less frequently in the main group — in 70.2% (χ^2 = 0.76; p = 0.40; RR = 0.93; 95% CI: 0.71–1.22; OR = 0.75; 95% CI: 0.40–1.42) compared to patients with mild preeclampsia (Table 2).

The T allele was detected insignificantly more frequently among patients in the main group — in 29.8% (f = 0.76; p = 0.40; RR = 1.08; 95% CI: 0.41–2.86; OR = 1.33; 95% CI: 0.70–2.51), which was insignificantly higher than in the group of patients with severe preeclampsia.

Table 2

Differences in Allelic and Genotypic Frequencies of the C-786T Polymorphism in the NOS3 Gene in the Main Group and the Group of Patients with Mild Preeclampsia

Alleles and Genotypes	Number of Examined Alleles and Genotypes				X^2	P	RR	95% CI	OR	95% CI
	Main Group		Mild Preeclampsia							
	n	%	n	%						
C	146	70.2	50	75.8	0.76	0.40	0.93	0.71-1.22	0.75	0.40-1.42
T	62	29.8	16	24.2	0.76	0.40	1.08	0.41-2.86	1.33	0.70-2.51
C/C	54	51.9	20	60.6	0.76	0.40	0.86	0.59-1.24	0.70	0.32-1.56
C/T	38	36.5	10	30.3	0.43	0.52	1.21	0.83-1.75	1.32	0.57-3.07
T/T	12	11.5	3	9.1	0.15	0.70	1.27	0.74-2.17	1.30	0.35-4.91

The homozygous C/C genotype of the C-786T polymorphism of the NOS3 gene was detected insignificantly less frequently — in 51.9% of cases in the main group compared to 60.6% (f = 0.76; p = 0.40; RR = 0.86; 95% CI: 0.59–1.24; OR = 0.70; 95% CI: 0.32–1.56) in the group of patients with mild preeclampsia.

The heterozygous C/T genotype was detected among patients in the main group in 36.5% of cases (f = 0.43; p = 0.52; RR = 1.21; 95% CI: 0.83–1.75; OR = 1.32; 95% CI: 0.57–3.07), which was insignificantly less frequent than among patients with mild preeclampsia, where it was detected in 30.3% of cases.

A statistically insignificant predominance of the T/T genotype in the main group — 11.5% (f = 0.15; p = 0.70; RR = 1.27; 95% CI: 0.74–2.17; OR = 1.30; 95% CI: 0.35–4.91) was established compared to 9.1% among patients with mild preeclampsia.

A comparison of allele and genotype frequencies of the C-786T polymorphism of the NOS3 gene was carried out between the main group and the group of patients with gestational hypertension. The C allele was identified insignificantly more frequently — in 70.2% of cases in the main group (f = 0.35; p = 0.57; RR = 1.06; 95% CI: 0.81–1.4; OR = 1.21; 95% CI: 0.65–2.26) compared to the gestational hypertension group, where it was detected in 66.1% of cases (Table 3).

The T allele was detected insignificantly less frequently — in 29.8% of cases in the main group (χ^2 = 0.35; p = 0.57; RR = 0.94; 95% CI: 0.36–2.45; OR = 0.83; 95% CI: 0.44–1.55) compared to patients with gestational hypertension, where it was detected insignificantly more frequently — in 33.9% of cases.

The C/C genotype of the C-786T polymorphism of the NOS3 gene was detected statistically insignificantly more often — in 51.9% of patients in the main group (χ^2 = 0.27; p = 0.62; RR = 1.12; 95% CI: 0.79–1.58; OR = 1.25; 95% CI: 0.54–2.87) compared to 46.4% in the gestational hypertension group.

The heterozygous C/T genotype was detected insignificantly less often in the main group — in 36.5% (χ^2 = 0.07; p = 0.79; RR = 0.93; 95% CI: 0.65–1.34; OR = 0.89; 95% CI: 0.38–2.10) compared to 39.3% of cases in the gestational hypertension group.

The homozygous T/T genotype was also insignificantly less frequent — in 11.5% of cases in the main group (χ^2 = 0.16; p = 0.70; RR = 0.81; 95% CI: 0.45–1.45; OR = 0.78; 95% CI: 0.23–2.64) compared to 14.3% among patients with gestational hypertension.

The distribution of alleles and genotypes of the C-786T polymorphism of the NOS3 gene was studied in the main and control groups to identify statistically significant differences. The C allele was detected less frequently in the main group — 70.2% (χ^2 = 5.33; p = 0.02; RR = 0.88; 95% CI: 0.59–1.30; OR = 0.59; 95% CI: 0.38–0.92) (Table 4) compared to the control group, where it was identified significantly more often — in 79.9% of cases, indicating its protective properties.

The T allele was statistically significantly more frequent — in 29.8% of cases in the main group (χ^2 = 5.33; p = 0.02; RR = 1.14; 95% CI: 0.70–1.86; OR = 1.69; 95% CI: 1.08–2.64) compared to 20.1% in the control group, suggesting its negative influence regarding the pathology under study.

The C/C genotype of the C-786T polymorphism of the NOS3 gene was statistically significantly less frequent — in 51.9% of cases in the main group (χ^2 = 4.55; p = 0.04; RR = 0.78; 95% CI: 0.46–1.33; OR = 0.55; 95% CI: 0.32–0.95) compared to 66.4% in the control group, indicating its protective effect.

A trend toward predominance of the heterozygous C/T genotype in the main group was found, where it was detected in 36.5% of cases (χ^2 = 2.17; p = 0.15; RR = 1.35; 95% CI: 0.79–2.31; OR = 1.55; 95% CI: 0.87–2.77), compared to 27.1% in the control group.

Thus, the results of our study allow us to conclude that unfavorable genotypic variants of the C-786T polymorphism of the NOS3 gene (associated with endothelial

vascular dysfunction) have a significant contribution to the mechanism of development of hypertensive disorders during pregnancy.

Table 3.

Differences in Allelic and Genotypic Frequencies of the C-786T Polymorphism in the NOS3 Gene in the Main Group and the Group of Patients with Gestational Hypertension

Alleles and Genotypes	Number of Examined Alleles and Genotypes				X^2	P	RR	95% CI	OR	95% CI
	Main Group		Gestational Hypertension							
	n	%	n	%						
C	146	70.2	37	66.1	0.35	0.57	1.06	0.81-1.40	1.21	0.65-2.26
T	62	29.8	19	33.9	0.35	0.57	0.94	0.36-2.45	0.83	0.44-1.55
C/C	54	51.9	13	46.4	0.27	0.62	1.12	0.79-1.58	1.25	0.54-2.87
C/T	38	36.5	11	39.3	0.07	0.79	0.93	0.65-1.34	0.89	0.38-2.10
T/T	12	11.5	4	14.3	0.16	0.70	0.81	0.45-1.45	0.78	0.23-2.64

Table 4.

Differences in Allelic and Genotypic Frequencies of the C-786T Polymorphism in the NOS3 Gene in the Main and Control Groups

Alleles and Genotypes	Number of Examined Alleles and Genotypes				X^2	P	RR	95% CI	OR	95% CI
	Main Group		Control							
	n	%	n	%						
C	146	70.2	171	79.9*	5.33	0.02	0.88	0.59-1.30	0.59	0.38-0.92
T	62	29.8	43	20.1*	5.33	0.02	1.14	0.70-1.86	1.69	1.08-2.64
C/C	54	51.9	71	66.4*	4.55	0.04	0.78	0.46-1.33	0.55	0.32-0.95
C/T	38	36.5	29	27.1	2.17	0.15	1.35	0.79-2.31	1.55	0.87-2.77
T/T	12	11.5	7	6.5	1.61	0.21	1.76	0.85-3.67	1.86	0.71-4.88

*Note: * - $p < 0.05$, significant differences compared to the main group.*

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