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EFFECT OF INTERLEUKIN-6- INFLAMMATORY MARKER GENE MUTATION ON THE DEVELOPMENT OF POSTPARTUM HEMORRHAGE

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Abstract:

Postpartum hemorrhage (PPH) is one of the serious complications that occurs in women after childbirth. PPH is defined as excessive bleeding of more than 500 ml after vaginal delivery or more than 1000 ml after cesarean section. PPH is one of the leading causes of maternal mortality worldwide and is thought to be caused by a combination of genetic and environmental factors [1]. This article provides information about genes leading to postpartum hemorrhage

Keywords: endothelial dysfunction, gene, hemodynamic system, interleukin-6 postpartum hemorrhage, uterine atony.

INTRODUCTION. One of the genetic factors that has recently attracted the attention of scientists and researchers is the mutation of the interleukin-6 (IL-6) gene. The IL-6 gene is responsible for the production of a cytokine that plays a role in the inflammatory response. IL-6 is also involved in blood coagulation and angiogenesis, which together are important parts of the mechanism for preventing excessive bleeding after childbirth [2].

Studies have shown that mutations in the IL-6 gene may contribute to the development of PPH. In particular, single nucleotide polymorphisms (SNPs) in the IL-6 gene are associated with an increased risk of PPH. This SNP is located in the promoter region of the IL-6 gene, which is responsible for the regulation of its expression [3].

Moreover, studies in this area show that people with IL-6 SNPs have a reduced ability to produce IL-6 in response to inflammation. This can lead to a weakened inflammatory response and impaired blood clotting, thereby indirectly increasing the risk of PPH. In addition, IL-6 SNP is also associated with decreased IL-6 levels in umbilical cord blood, which may increase the risk of fetal distress during labor [4].

Although the association between IL-6 SNPs and PPH is not yet fully understood or proven, it highlights the potential importance of genetic factors in the development of this condition. Future studies may help clarify the role of the IL-6 gene in PPH and identify other genetic factors that contribute to this serious complication.

Thus, the IL-6 gene mutation may be a genetic factor contributing to the development of postpartum hemorrhage. Further research is needed to understand the specific mechanisms and to identify other genetic factors that may increase the risk of PPH. This knowledge will ultimately lead to improved prevention, diagnosis, and treatment of this serious obstetric complication.

AIM OF THE WORK was an assessment of the influence of the C-174G polymorphism in the IL6 gene with the risk of developing postpartum atonic hemorrhage among women of the Uzbek ethnic group.

MATERIALS AND METHODS. We examined 101 women who were diagnosed with postpartum atonic bleeding of varying severity, who were included in the main group. The diagnosis of atonic PPH was made according to the criteria of the national clinical protocol of the Republic of Uzbekistan "Prevention and tactics of management of postpartum obstetric hemorrhage" approved on March 1, 2021. According to the protocol, the diagnosis of PPH was made when: blood loss ≥ 500 ml during vaginal delivery; for blood loss ≥1000 ml during cesarean section; and also, any clinically significant amount of blood loss (leading to hemodynamic instability) occurring within 12 weeks after birth [5]. Exclusion criteria included women who developed PPH due to retained placenta tissue or membranes, trauma to the birth canal, and a coagulation disorder not associated with bleeding. The control group consisted of 103 women without significant chronic somatic pathology, who had a history of natural childbirth without any complications or obstetric pathology. All women studied were of Uzbek nationality. All patients provided written informed consent to participate in the study.

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All women underwent clinical, laboratory and instrumental studies, which also included standard methods of collecting anamnesis and physical examination.

Genotyping and detection of genetic polymorphisms of the C-174G gene in the IL6 gene were carried out using real-time PCR. Statistical analysis was performed using the OpenEpi v.9.2 application package. The distribution of genotypes was checked for compliance with the Hardy–Weinberg equilibrium using the computer program "GenePop" (http://wbiomed.curtin.edu.au/genepop) and assessed using the χ2 test.

RESULTS. For the C-174G polymorphism in the IL6 gene, it was revealed that in the group of patients the observed, i.e. the actual frequency of genotypes C/C and G/G is not statistically significantly the same compared to the theoretical one (0.04% and 0.65%, versus 0.04 and 0.65, respectively, $\chi2<3.8$; $p>0.05$), and the observed frequency of heterozygotes (G/ T) is not significantly the same than expected (0.31% and 0.31%, respectively, $\chi2<3.8$; $p>0.05$).

These data allow us to say that there are no deviations from the RCV for this polymorphism (Tables 1,2).

Table 1. Expected and observed frequencies of distribution of genotypes of the locus for RCV (C-174G polymorphism in the IL6 gene) in the main group

Main group					
Alleles	Frequency of alleles				
C	0,19				
G	0,81				
Genotypes	Frequency of genotypes		χ2	p	df
	Observed	Expected			
C/C	0,04	0,04	0,01		
C/G	0,31	0,31	0,01		
G/G	0,65	0,65	0		
Total	1	1	0,02	0,842	1

Table 2. Expected and observed frequencies of distribution of genotypes of the locus for RCV (C-174G polymorphism in the IL6 gene) in the control group

Control group					
Alleles	Frequency of alleles				
C	0,18				
G	0,82				
Genotypes	Frequency of genotypes		χ2	p	df
	Observed	Expected			
C/C	0,05	0,03	0,64		
C/G	0,27	0,3	0,29		
G/G	0,68	0,67	0,03		
Total	1	1	0,96	0,315	1

For the C-174G polymorphism in the IL6 gene, the D value in the control group, as well as in the main sample, turned out to be negative, that is, <0. In the control group, the Hexp value is close to 0.5, which suggests a possible high level of heterozygosity of the C-174G polymorphism in the IL6 gene in our population. The relatively high frequency of Hexp=0.31 in the main group of patients is probably a consequence of the high

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fitness of the heterozygous C/G genotype of the C-174G polymorphism in our region (Table 3)

Table 3. Difference between the expected and observed frequencies of heterozygosity of the C-174G polymorphism in the IL6 gene in the study and control groups.

Groups	Ho	He	D*
Main group	0,31	0,31	-0,01
Control group	0,27	0,3	-0,1

The contribution of the C-174G polymorphism in the IL6 gene to the increased risk of developing atonic postpartum hemorrhage (PPH) is insignificant. No statistically significant differences in the distribution of allele and genotype frequencies for this polymorphism were found between the groups of patients with PPH and controls. An independent negative effect of this genetic marker in relation to the development of PPH was not found. At the same time, in the group of patients there was a tendency towards an increase in the frequency of the unfavorable genotype C/G compared to the control group (30.7% and 27.2%, respectively). However, during statistical processing of the data, no significant differences were found, which may be due to the small size of the studied sample or the low frequency of occurrence of this genotype in the population ($\chi2=0.3$; P=0.6; OR=1.2; 95% CI 0.65 - 2.17) (Table 4)

Table 4. Differences in the frequency of allelic and genotypic variants of the C-174G polymorphism in the IL6 gene in patient groups

Alleles and genotypes	Number of observed alleles and genotypes				χ2	p	OR	95% CI
	Main group		Control group					
	n	%	n	%				
C	39	19,3	38	18,4	0,0	p = 0,9	1,1	0,64 - 1,74
G	163	80,7	168	81,6	0,0	p = 0,9	0,9	0,58 - 1,55
C/C	4	4,0	5	4,9	0,1	p = 0,8	0,8	0,21 - 3,09
C/G	31	30,7	28	27,2	0,3	p = 0,6	1,2	0,65 - 2,17
G/G	66	65,3	70	68,0	0,2	p = 0,7	0,9	0,5 - 1,59

CONCLUSION. The C-174G gene polymorphism in the IL6 gene is not associated with the risk of developing atonic PPH in pregnant women of Uzbek nationality. This marker did not show diagnostic or informative value in our study. However, more numerous further studies and searches for polymorphisms of other genes responsible for the development of arterial hypertension in pregnant women are needed.

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