Original Article

Comparative Analysis Of Rs1800896 Polymorphism Of IL-10 Gene (G1082A) In Pregnant Women At Risk Of Preeclampsia And Complications Of Preeclampsia

Akhmedov F.K., Negmatullaeva M.N.

Bukhara Medical Institute named after Abu Ali ibn Sino, City of Bukhara, Uzbekistan.
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Abstract

Preeclampsia, characterized by gestational hypertension and proteinuria, is a serious complication affecting from 5% to 8% of all pregnancies worldwide. Despite the fact that this pathology is one of the main causes of maternal and child mortality, the causes of its occurrence have not yet been sufficiently studied. It is known that a decrease in placental perfusion, the development of endothelial dysfunction in the vessels, a decrease in pressure in the uterine spiral arteries cause preeclampsia [1,2,8].

Keywords: Preeclampsia, risk, polymorphism, rs1800896, IL-10 (G1082A), pregnant women.

Introduction

Preeclampsia (PE) is a frequently fatal pathology characterized by hypertension and proteinuria in the 20th week of pregnancy, which affects 5-10% of pregnant women. This problem is especially important in developing countries, where the incidence of hypertensive disorders of pregnancy is higher and maternal mortality rates are 20 times higher than in developed countries [2].

Preeclampsia (PE), the leading cause of perinatal death, complicates up to 8% of all pregnancies in Western countries [6]. It is one of the top 4 causes of maternal death and morbidity worldwide, causing 10 to 15% of maternal deaths [7].

Preeclampsia, characterized by gestational hypertension and proteinuria, is a serious complication affecting 5% to 8% of all pregnancies worldwide. Despite the fact that this pathology is one of the main causes of maternal and child mortality, the causes of its occurrence are still not well understood. It is known that a decrease in placental perfusion, the development of endothelial dysfunction in the vessels, and a decrease in pressure in the uterine spiral arteries cause preeclampsia[1.5].

New data have shown that excessive cytokine-mediated inflammatory responses causing endothelial dysfunction may play an important role in the pathogenesis of preeclampsia. Interleukin-10 (IL-10) is a pro-inflammatory cytokine that leads to potential placental hypoxia and ischemia, which in turn leads to endothelial dysfunction and is important in the pathogenesis of preeclampsia. Therefore, we decided to study the role of the polymorphism of the above cytokines in the Uzbek population[3.4].

The purpose of the study: to study a comparative analysis of the rs1800896 polymorphism of the IL-10 gene (G1082A) in pregnant women at risk of developing preeclampsia and pregnant women complicated by preeclampsia

Materials and research methods.

The study was conducted on the basis of antenatal clinics and the Regional Perinatal Center of Bukhara together with the Department of Obstetrics and Gynecology No. 2 of the Bukhara State Medical Institute. Genetic studies were carried out in 121 pregnant main groups and 110 physiologically pregnant women included in our study, the polymorphism of IL-10 genes (G1082A) was studied. In turn, we divided 121 pregnant women from the main group into 2 groups. In particular, we recruited 71 pregnant women with a history of preeclampsia in the first and second trimesters of pregnancy and at risk of developing it. The second group consisted of 50 pregnant women with clinical manifestations of preeclampsia at the beginning of the third trimester of pregnancy.

Research results.

We studied the frequency distribution of alleles and genotypes of the IL-10 gene polymorphism (G1082A) in the group of pregnant women at risk for preeclampsia complicated by preeclampsia and in the normal course of pregnancy. Homozygous genotype G/G was 12.4%, heterozygous genotype G/A - 38.84%, homozygous mutant form A/A - 48.76% in the main group of pregnant women at risk of preeclampsia and complicated by preeclampsia. In pregnant women of the control group, these genotypes were equal to 57.27%, 37.27%, 5.45%, respectively. The frequency of wild-type G allele and mutant A allele was 31.82% and 68.18% in the main group and 75.91% and 24.09% in the control group, respectively.

The main group of pregnant women included in our study was divided into two groups: group I (n=71) pregnant risk groups for the development of preeclampsia, group II (n=50) pregnant women with complicated preeclampsia. The results of our studies showed that the wild-type polymorphic type or the homozygous genotype of the G/G genotype was 9.86% in pregnant women of group I and 16% in pregnant women of group II, while the frequency of occurrence of the G/G genotype in pregnant women of the studied control group was 57 .27%. Heterozygosity (G/A genotype) was 43.66% and 32% in pregnant women of the 1st and 2nd groups, and in the control group - 37.27%. Compared with the control group, in the group of pregnant women with the risk of preeclampsia and complicated by preeclampsia, a higher frequency of the homozygous mutant A/A genotype was found - 46.48%, 52% and 5.45% in the control group.

The homozygous wild type (allele G) was equal to 31.69% and 32% in pregnant women of the 1st and 2nd groups, while in the control group it was 75.91%. Compared with the control group, in the group of pregnant women with the risk of gestosis and complicated by gestosis, a higher frequency of the homozygous mutant allele A was revealed - 68.31%, 68% and 24.09% in the control group.

The distribution of genotypes for the studied polymorphic loci of the IL-10 gene (G1082A) was checked for compliance with the Hardy-Weinberg equation. The distribution of genotypes of the rs1800896 locus of the IL-10 gene in the studied group of patients and the control group corresponded to the theory for PXB. The G and A allele index in the main group of pregnant women was 0.32 and 0.68, in the control group - 0.76 and 0.24, respectively.

1-table Observed and expected distribution of IL-10 (G1082A) PXB gene polymorphism genotypes in the initial and control groups.

Main group					
alleles	Allele frequency				
G	0,32				
A	0,68				
Genotypes	Genotype frequency		χ^2	p	df
	observable	expected			
G/ G	0,12	0,1	0,62		
G/ A	0,39	0,43	0,58		
A/ A	0,49	0,46	0,13		
Bcero	1	1	1,33	0,243	1

Control group	
alleles	Allele frequency
G	0,76
A	0,24

Genotypes	Genotype frequency		χ2	p	df
	observable	expected			
G/ G	0,57	0,58	0		
G/ A	0,37	0,37	0,01		
A/ A	0,05	0,06	0,02		
Всего	1	1	0,04	0,807	1

The expected and observed rates of this polymorphism G/G, G/A, A/A and genotypes were 0.12/0.10, respectively, in the main group of pregnant women; It was 0.39/0.43 and 0.49/0.46 ($\chi2<3.85$; p=1.33), which means a low probability of systematic errors in the analysis.

When testing the main group of pregnant women who participated in the study for compliance with the Hardy-Weinberg equation, it is seen that the results observed in the homozygous wild-type G/G genotype exceed the expected results. In the main group of women with G/A heterozygote and mutant A/A homozygote, on the contrary, it is seen that the expected results are higher than the observed ones. In the control group, the distribution of these genotypes, respectively, is as follows: G/G - 0.57/0.58, G/A - 0.37/0.37 and A/A -0.05/0.06 ($\chi2<3.85$; p=0.807), (Table 1). Analyzing the data presented in the table, it can be noted that in pregnant women of the main group, the observed indicator for the heterozygous genotype of the IL-10 gene (G1082A) was higher than the expected indicator (0.39 / 0.43, respectively; D = -0.1) is. In pregnant women of the control group, these figures are 0.37/0.37, respectively; and in the control group there were almost no differences between the observed and expected results, D = +0.02.

Table 2 presents a comparative characteristic of the indicators of alleles and genotypes in pregnant women of the main group with those of the control group.

In our study, the frequency of alleles of the IL-10 gene was as follows: in the main group, the proportion of allele G and mutant allele A was 31.8% and 68.2%, while in the control group these figures were 75.9% and 24.1% . % according to the established ratio. For the G allele, respectively ($\chi2=89.9$; p=0.01; RR=0.4; 95% CI: 0.28–0.68; OR=0.1; 95% CI: 0.1–0 ,22). For the mutant allele A, respectively ($\chi2=89.9$; p=0.01; RR=2.4; 95% CI: 1.46–3.89; OR=6.8; 95% CI: 4.55– 10.02). In terms of OR, the mutant A allele increases the risk of preeclampsia in pregnant women included in the study (OR = 6.8; 95% CI: 4.55–10.02). The statistical analysis we obtained for both allelic genes was reliable ($\chi2=89.9$; p=0.01). When comparing the genotypes G/G, G/A, A/A of the IL-10 gene (G1082A) in the main and control groups, it was found that the wild G/G genotype was more common in pregnant women in the control group. group, whereas in the main and control groups, G /A was more common. It was found that heterozygous genotypes had the same frequency of occurrence, and mutant genotypes A/A significantly prevailed in the main group.

Genotypes G/G, G/A, A/A of the IL-10 gene (G1082A) in pregnant women of the main group were 12.4%, 38.8% and 48.8% compared with the control group, 57.3%, 37 .3% and 5.5%. % respectively. In the control group, the frequency of detection of G/G wild genotype was slightly higher and, accordingly ($\chi2=51.9$; p=0.01; RR=0.2; 95% CI: 0.09-0.54; OR=0, 1, 95% CI: 0.06–0.19). The same ratio of the heterozygous genotype G/A was noted in the main and control groups and, respectively ($\chi2=0.1$; p=0.9; RR=1.0; 95% CI: 0.64-1.71; OR= 1 .1; 95% CI: 0.63 -1.82), it was found that the mutant A/A genotype was superior to the control group and, accordingly ($\chi2=53.4$; p=0.01; RR=8.9; 95% CI: 5.9-13.54; OR=16.5; 95% CI: 7.78-34.97) - ratio (Table 2).

2-TableDifferences between genotypes and alleles of the G1082A locus of the IL-10 gene in the general group of patients of the main and control groups (probabilistic control model).

Alleles and genotypes	Number of examined alleles and genotypes				χ2	p	RR	95%CI	OR	95%CI
	Main group		Control group							
	n	%	n	%						
G	77	31,8	167	75,9	89,9	p = 0,01	0,4	0,28 - 0,62	0,1	0,1 - 0,22
A	165	68,2	53	24,1	89,9	p = 0,01	2,4	1,46 - 3,89	6,8	4,55 - 10,02
G/ G	15	12,4	63	57,3	51,9	p = 0,01	0,2	0,09 - 0,54	0,1	0,06 - 0,19
G/ A	47	38,8	41	37,3	0,1	p = 0,9	1,0	0,64 - 1,71	1,1	0,63 - 1,82
A/ A	59	48,8	6	5,5	53,4	p = 0,01	8,9	5,9 - 13,54	16,5	7,78 - 34,97

When dividing the pregnant women of the main group into two subgroups, in the first subgroup we included pregnant women with a risk of developing preeclampsia, that is, the G allele of the IL-10 gene was 31.7%, the A allele - 68.3. %. In the control group, these figures were 75.9% and 24.1%, respectively. Compared with group I, the proportion of G alleles in the control group, respectively, slightly prevailed; (χ2=69.5; p=0.01; RR=0.4; 95% CI: 0.24-0.73; OR=0.1; 95% CI: 0.09-0.23). And the A allele index was slightly higher in group I compared to the control group, respectively (χ2=69.5; p=0.01; RR=2.4; 95% CI: 1.53–3.74; OR = 6 .8, 95% CI: 4.33–10.66). From the above indicators, it was clear that the mutant allele A, in turn, significantly increases the likelihood of preeclampsia. The wild G allele plays a protective role. The results of our study were statistically significant (χ2=69.5; P=0.01) (Table No. 3).

3-Table Differences between genotypes and alleles of the G1082A locus of the IL-10 gene in group I (n=71) and the control group (probabilistic control model).

Alleles and genotypes	Number of examined alleles and genotypes				χ2	p	RR	95%CI	OR	95%CI
	I-group		Control group							
	n	%	n	%						
G	45	31,7	167	75,9	69,5	p = 0,01	0,4	0,24 - 0,73	0,1	0,09 - 0,23
A	97	68,3	53	24,1	69,5	p = 0,01	2,4	1,53 - 3,74	6,8	4,33 - 10,66
G/ G	7	9,9	63	57,3	40,9	p = 0,01	0,2	0,04 - 0,71	0,1	0,04 - 0,18
G/ A	31	43,7	41	37,3	0,7	p = 0,4	1,2	0,58 - 2,38	1,3	0,71 - 2,39
A/ A	33	46,5	6	5,5	43,0	p = 0,01	8,5	4,7 - 15,44	15,1	6,69 - 33,87

The data presented in table No. 3 show that, compared with group I, the rate of the wild homozygous genotype G/G slightly exceeded the control group (57.3% and 9.9%, respectively; χ2=40.9; p=0.01 ; RR=0.2; 95% CI: 0.04-0.71; OR=0.1; 95% CI: 0.04-0.18). Compared with the control group, the frequency of detection of the heterozygous genotype G/A in group I was slightly higher and amounted to a ratio of 43.7% to 37.3% and, accordingly (χ2=0.7; p=0.4; RR= 1.2 ; 95% CI: 0.58–2.38; OR = 1.3; 95% CI: 0.71–2.39). Compared with the control group, group I showed a significantly higher incidence of the homozygous A/A genotype, which ranged from 46.5% to 5.0% and, respectively (χ2=43.0; p=0.01; RR=8 .5, 95% CI: 4.7–15.44, OR=15.1, 95% CI: 6.69–33.87).

Statistically analyzing the obtained data, it was concluded that the mutant genotype A/A of the G1082A polymorphism in the IL-10 gene in pregnant women of the 1st group with the risk of preeclampsia significantly increases the risk of developing preeclampsia in pregnant women (OR = 15.1; 95% CI: 6.69–33.87; χ2=43.0; P=0.01) (Table 3). The following table (Table 4) shows comparative differences between genotypes and alleles of the IL-10 (G1082A) gene locus in the control group and group II (n=50).

4-table. Differences between genotypes and alleles of the G1082A locus of the IL-10 gene in group II (n=50) and the control group (probabilistic control model).

Alleles and genotypes	Number of examined alleles and genotypes				χ2	p	RR	95%CI	OR	95%CI
	II-group		Control group							
	n	%	n	%						
G	32	32,0	167	75,9	56,4	p = 0,01	0,4	0,21 - 0,84	0,1	0,09 - 0,25
A	68	68,0	53	24,1	56,4	p = 0,01	2,4	1,57 - 3,59	6,7	4,08 - 11
G/ G	8	16,0	63	57,3	23,7	p = 0,01	0,3	0,07 - 1,08	0,1	0,06 - 0,31
G/ A	16	32,0	41	37,3	0,4	p = 0,6	0,9	0,32 - 2,28	0,8	0,39 - 1,61
A/ A	26	52,0	6	5,5	46,5	p = 0,01	9,5	4,38 - 20,76	18,8	8,09 - 43,61

According to our data, the proportion of G allele and mutant A alleles in the IL-10 gene was 32% and 68% in pregnant women of group II, while in the control group these figures were 75.9% and 24.1%, respectively. equal. In

the control group, the share of alleles G and, respectively ($\chi 2$=56.4; p=0.01; RR=0.4; 95% CI: 0.21-0.84; OR=0.1; 95% CI : 0.09-0.25) formed the ratio . In pregnant women of the 2nd group, compared with the control group, the mutant allele prevailed, respectively ($\chi 2$=56.4; p=0.01; RR=2.4; 95% CI: 1.57-3.52; OR=6, 7, 95% CI: 4.08-11).

Compared with group II, the control group was dominated by the homozygous G/G genotype (16.0 and 57.3%, respectively; ($\chi 2$=23.7; p=0.01; RR=0.3; 95% CI: 0, 07–1.08; OR=0.1), 95% CI: 0.06–0.31). In the control group, compared with group 2, the frequency of detection of the heterozygous genotype G/A was slightly higher and amounted to a ratio of 37.3% to 32.0% and, accordingly ($\chi 2$=0.4; p=0.6; RR = 0 .9, 95% CI: 0.32–2.28, OR = 0.8, 95% CI: 0.39–1.61). Compared with the control group, in the 2nd group, the mutant homozygous A/A genotype was more common and amounted to 52.0% to 5.5% and, respectively ($\chi 2$=46.5; p=0.01; RR=9, 5% CI: 4.38-20.76; OR=18.8; 95% CI 8.09-43.61).

Statistically significant parameters such as sensitivity (SE) and specificity (SP) as independent markers were studied by evaluating the predictive performance (AUC) of the G1082A polymorphism in the IL-10 gene. The efficiency of predicting the mutant allele A of the IL-10 gene in patients of the main group was AUC=0.72 (SE=0.76; SP=0.68; OR=6.75; 95% CI=4.55-10.02; p=0.24). In pregnant women of the 1st group, this figure is AUC=0.72; SE=0.72; SP=0.68; OR=6.79; 95% CI=4.33-10.65; p=0.35, and in pregnant women of the 2nd group, this figure is AUC=0.72; SE=0.76; SP=0.68; OR=6.70; 95% CI=4.08-11.01; p=0.44. The mutant allele A of the studied IL-10 gene may be a risk factor for the development of preeclampsia, AUS (Area Under ARGL Nurve) in the main group was AUS=0.72, in group I AUS=0.72, AUS=0.72. in group II. Thus, since the average AUC is 0.72, the prediction of the development of preeclampsia with the mutant allele A of the IL-10 gene has a high predictive efficiency.

Conclusions:

The conducted studies and a number of meta-analyses showed that the IL10 (G1082A) gene polymorphism, like our study, played an important role in the development of preeclampsia, which was proved by statistical analysis.

The results of our study showed that in the Uzbek population, we observed that the mutant homozygous genotype of the rs1800896 polymorphism of the IL-10 gene (G1082A) was more common in patients with preeclampsia than in the control group. According to OR and AUC in our statistical studies, the mutant allele A of the IL-10 gene and mutant homozygous A/A genotypes increase the likelihood of preeclampsia in the Uzbek population.

Thus, IL-10 gene polymorphisms (rs1800896) are a risk factor for preeclampsia and an independent genetic marker that increases the risk of preeclampsia in pregnant women.

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