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THE ROLE OF XENOBIOTIC ENZYME GENES OF THE FIRST AND SECOND PHASES IN THE PATHOGENESIS OF FETAL GROWTH RESTRICTION SYNDROME

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РОЛЬ ГЕНОВ ФЕРМЕНТОВ КСЕНОБИОТИКОВ ПЕРВОЙ И ВТОРОЙ ФАЗЫ В ПАТОГЕНЕЗЕ СИНДРОМА ОГРАНИЧЕНИЯ РОСТА ПЛОДА

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ХОМИЛА РИВОЖЛАНИШИНИ ЧЕКЛАШ СИНДРОМИ ПАТОГЕНЕЗИДА БИРИНЧИ ВА ИККИНЧИ ФАЗАЛИ КСЕНОБИОТИК ФЕРМЕНТЛАРИ ГЕНЛАРИНИНГ ЎРНИ

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Цель: *оценка выявляемости аллельных вариантов полиморфизма генов ферментов биотрансформации ксенобиотиков у беременных с синдромом ограничения роста плода.* ***Материал и методы:*** *под наблюдением были беременные с синдромом потери плода (СПП), образцы ДНК больных и здоровых доноров, гены глютатионтрасфераз GSTM1 (1p13.3), GSTT1 (22q11.2) и ген глютатионтрасфераз GSTP1 (IIe 105 Val). У всех беременных проводили общеклинические, лабораторные и функциональные, молекулярно-генетические исследования.* ***Результаты:*** *при анализе ассоциированности межгенных комбинаций нулевых полиморфизмов генов GSTM1 и GSTT1 было выявлено, что шанс развития патологии при наличии данной сочетаний генотипического варианта del/del генов GSTM1 и GSTT1 значимо возрастает: до 7.8 раза больше по сравнению другими генотипами (χ^2=12.4; P=0.0004; OR=7.8; 95% CI 2.146-28.65). Функционально неблагоприятный аллель G гена GSTP1 в 2.7 раза статистически достоверно преобладал в исследованных хромосомах беременных с СПП по сравнению с беременными без СПП (χ^2=4.6; P=0.03; OR=4.5; 95%CI1.061-19.5).* ***Выводы:*** *по вариантам генотипов del/del генов GSTM1 и GSTT1 и аллелей G гена GSTP1 можно определить прогноз риска развития синдрома потери плода, характеризующиеся нарушением процесса детоксикации организма во время беременности.*

Ключевые слова: *гены ферментов детоксикации GSTM1 и GSTT1, GSTP1, синдром ограничения роста плода, прогнозирование.*

Мақсад: *ҳомила ривожланиши чегараланиш синдромида ксенобиотикларнинг биотрансформация ферментлари генларининг аллеллик вариантларини баҳолаш.* ***Материал ва усуллар:*** *ҳомила ривожланиш чегараланиш синдроми билан ифодаланган ҳомиладорлар (ХРЧС), беморлар ва донор соғломлар ДНК намуналари, глютатионтрасфераз GSTM1 (1p13.3), GSTT1 (22q11.2) ва глютатионтрасфераз GSTP1 (IIe 105 Val) генлари. Барча ҳомиладорларда умумий-клиник, лаборатор ва функционал, молекуляр-генетик тадқиқот ишлари олиб борилди.* ***Натижалар:*** *текшириш ишлари шуни кўрсатмоқдаки, ҳомила ривожланишининг чегараланиш синдроми ривожланишининг эҳтимолида GSTM1 ва GSTT1 генларининг бирлашган нол генотипларида 7,8 маротаба юқори аҳамиятга эга бўлди (χ^2=12.4; P=0.0004; OR=7.8; 95% CI 2.146-28.65). Ҳамда GSTP1 генининг номаъқул G аллели эса ҳомила ривожланиш чеклови синдромида ҳомилаликнинг нормал ҳолатига нисбатан 2,7 мартагача ҳаққоний равишда ошиши кузатилди. (χ^2=4.6; P=0.03; OR=4.5; 95%CI1.061-19.5).* ***Хулоса:*** *GSTM1 ва GSTT1 генларининг del / del генотиплари ва GSTP1 генининг G аллели вариантларида ҳомиладорлик пайтида организмнинг детоксикация жараёнининг бузилиши билан тавсифланадиган ҳомила йўқотиш синдроми ривожланиш хавфини аниқлаш мумкин.*

Калит сузлар: *детоксикация ферментларининг генлари GSTM1 ва GSTT1, GSTP1, ҳомила ривожланишининг чегараланиш синдроми,аниқлаш.*

Fetal growth restriction syndrome (FGRS) is a clinical syndrome caused by morphological and functional changes in the placenta and penetrant by limit of the growth and development of the fetus, its hypoxia, that arise as a result of the combined reaction of the fetus and placenta to various disorders of the pregnant woman. This syndrome is based on pathological changes in the fetal and / or uterin-placental complexes with a derangement of the compensatory-adaptive mechanisms at the molecular, cellular and tissue levels. In this case, the transport, trophic, endocrine, metabolic, antitoxic functions of the placenta underlying the pathology of the fetus and newborn are disordered [1,3,8-10,15,17].

The most significant risk factors of FGRS development include preeclampsia and a combination of pregnancy with extragenital pathology, accompanied by vascular damage. Various etiological factors, affecting at different stages of the development and functioning of the placenta, are ultimately involved in the general pathogenetic mechanism leading to the development of the fetal growth limit syndrome, one of the main manifestations of which is considered a violation of placental circulation - the main function of the placenta [5,6, 7,8,11,13,15,20,21,23, 24,30,33,34].

For practical health care, the importance of using an advanced pre-coseptual examination algorithm, monitoring of pregnant women in terms of prevention of FGLS, adverse pregnancy and childbirth outcomes is justified.

In this regard, the main direction in the study of the problem of FGLS, is the development of objective methods for prediction, preclinical diagnosis, optimal preven-

tion and treatment, which can significantly reduce the frequency of FGLS, and its complications.

Currently, the most implemented approach to studying the mechanisms of formation of the fetal growth limit syndrome is the identification of disease associations with DNA polymorphisms of candidate genes or their protein products.[25-29,31,32,35]

According to R.L. Bick et al. (2008), there is a clear link between the heterozygous mutation MTHFR and PR, that risk of developing increases by 2 times. Whereas S.C. Guba and R.M. Ridker found a frequency of occurrence of a factor V mutation (Leiden) in 2-3 times.

The prevalence of the MTHFR C677T mutation in various ethnic groups varies significantly from 4% to 65%. Among Asian populations, particularly in Japan, homozygotes were 13.1%, heterozygotes – 47.5%, the same trend was observed in China – 14.0 and 43.8%, in Korea – 7.3% and 66.1%.

The works of H.Ya. Karimov and K.T. Boboev (2008) show the frequency of mutation of a number of genetic markers – the FV factor gene (G1691A), the blood coagulation factor II gene (G20210A) and the methylenetetrahydrophalate reductase gene (MTHFR) (C6771). that the prevalence of mutant alleles among patients in Uzbekistan is for FV Leiden – 12.9%, prothrombin – 4%, MTHFR – 47.8%.

The works N.I. Lyubchich, S.N. Sultanova (2016) revealed a high degree of influence of the joint carriage of FV G1691A + MTHFR C677T genotypes on the risk of premature birth, which confirms the importance of both individual alleles of genes and their combination in the development of thrombophilic complications during pregnancy.

Recently, special attention has been paid to studying the genes of xenobiotic biotransformation enzymes (XBEs), which are candidate genes for the formation of a predisposition to these pathologies, since their protein products interact with the environment, detoxifying or toxicizing foreign chemical compounds that enter the body, including also drugs [7,8,10,12,13-15,18].

However, they have not yet been sufficiently studied as genetic predisposition factors in fetal growth limit syndrome. According to the literature, these genes are a rather complex object of study due to a number of their specific features. [10,15,16,19,22] These are overlapping substrate specificity, inducibility, and participation in the metabolism of endogenous compounds. But it is precisely these features of XBE that make it possible to assume that they can be genetic markers at all stages of the development of the disease from its initiation to the outcome and, accordingly, will make it possible to identify a predisposition, help in the early diagnosis of the disease, knowing the patient's genotype, make a prognosis of the course of the disease, and choose the most suitable therapy.

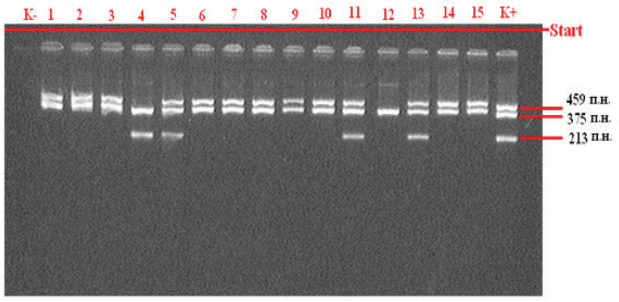
The aim of our research was to study the detectability of allelic variants of gene polymorphism of xenobiotic biotransformation enzymes of pregnant women with fetal growth limit syndrome.

Materials and methods

The object and subject of the study were pregnant women with fetal loss syndrome (FLS), DNA samples from patients and healthy donors, glutathione transferase genes GSTM1 (1p13.3), GSTT1 (22q11.2) and glutathione transferase gene GSTP1 (IIe 105 Val).

The study included 143 pregnant women aged 19 to 34 years, observed at the clinic of Republican Specialized Scientific and Practical Medical Center for Obstetrics and Gynecology, Ministry of Health of the Republic of Uzbekistan (RSSPMCOG MH RUz). All pregnant women underwent general clinical, laboratory and functional studies according to the standard for diagnostics and therapy (2015). Molecular genetic testing of biomaterials (DNA) was carried out on the basis of the Department of Molecular Medicine and Cellular Technology Research Institute of Hematology and Blood Transfusion under the Ministry of Health of the Republic of Uzbekistan. The object and subject of the study were DNA samples of pregnant and healthy donors, glutathione transferase genes of the first phase – GSTM1 (1p13.3), GSTT1 (22q11.2) and the second phase – GSTP1 (IIe 105 Val).

During genetic studies, the population control was used as a comparison group, which was represented by DNA samples (n 72) of conditionally healthy ones from the DNA bank of this department. DNA samples were isolated from peripheral blood lymphocytes in accordance with a modified methodology. The concentration and purity of the extracted DNA was evaluated by measuring the optical density of DNA-containing solutions at a wavelength of 260 and 280 nm against TE on a NanoDrop 2000 spectrophotometer (USA). Genotyping of GSTT1 and GSTM1 polymorphism was carried out by PCR on programmable thermal cyclers CG-1-96 Corbett Research (Australia) and 2720 Applied Biosystems (USA), using test systems of LLC Litekh (Russia), according to the manufacturer's instructions.



Fug. 1. Statistical analysis of the results was carried out using the statistical software package "OpenEpi 2009, Version 2.3".

GSTM1 and GSTT1 gene detection electrophoregram (459 bps - GSTT1 gene, 375 bps - β-globin, 213 bps - GSTM1)

K - Negative control;

K + Positive control;

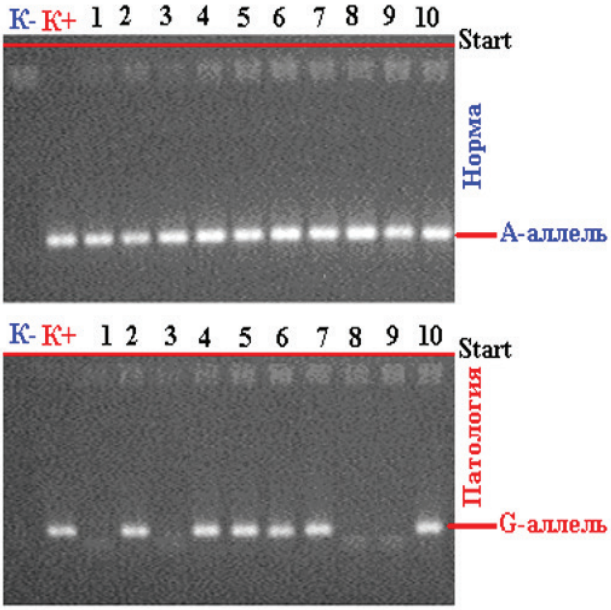
1,3,8,9 – wild genotype A/A;

2,4,5,6,7,10 – heterozygous genotype A/G.

The results of the study

Clinical, laboratory and functional studies have shown that among the 143 pregnant women examined, fetal growth limit syndrome was detected in 105, which amounted to 73.4%. According to the severity degree, I – the degree of severity was diagnosed in 35 (33.3%), II –

the degree – in 48 (45.7%) and III – degree – in 22, which amounted to 20.9%, respectively.



Fug. 2. Electrophoregram for the detection of polymorphism (A / G) of the gene mutation -1 glutathione-S-transferase P1 (rs--):

Information on gene sequences and primer structure was obtained taking into account the original literary source [1] and Gene Bank. The characteristics of the genetic marker and the sequence of synthesized oligoprimers are shown in table 1.

Table 1

The sequence of oligonucleotide primers used for PCR

Gene, localization	Polymorphism	The structure of oligoprimers
GSTM1 (1p13.3)	deletion	F 5-'GAACTCCCTGAAAAGCTAAAGC-3' R 5'-GTTGGGCTCAAATATAGGGTGG -3'
GSTT1 (22q11.2)		F 5'-TTCCTTACTGGTCCTCACATCTC-3' R 5'-TCACCGGATCATGGCCAGCA-3'

Table 2

The sequence of oligonucleotide primers used for PCR

Gene, localiza-tion	Polymorphism	The structure of oligoprimers
GSTP1 (**11 (11.g13)**)	detection	5'-ACCAGGGCTCTATGGCCAA- 5'-TGACCCGAGAAGAACGGGT-3','

Molecular genetic studies of the glutathione transferase genes GSTM1 (1p13.3), GSTT1 (22q11.2) and IIe 105 Val of the GSTP1 xenobiotic enzyme gene in the blood of pregnant women with FGLS revealed the following features of the distribution of alleles and genotypes of GSTM1 and GSTP1 gene polymorphisms (tables 3, 4).

Table 3

Distribution frequency of alleles and genotypes of del / del genes polymorphism of the GSTM1 and GSTT1 in pregnant and control groups

Groups	Genotype Distribution Frequency							
	GSTM1 «+»		GSTM1 (0/0)		GSTT1 «+»		GSTT1 (0/0)	
	*n	%	*n	%	*n	%	*n	%
The main group, n=59	40	67,8	19	32.2	12	20,3	47	79.6
The control group, n=72	46	64.0	26	36.1	54	75.0	18	25.5

n –number of patients examined, * n is the number of alleles studied.

As it can be seen from table 3, in the main group of pregnant women with SPP, functional alleles of GSTM1 "+" were detected in 67.8% of cases (40), while deletion variants (non-functional) of GSTM1 (0/0) were detected in 32.2% (19) cases. Whereas, functional allelic variants of GSTT1 "+" genotypes were detected in 20.3% of cases, and deletion variants in 79.6% (47) cases, respectively.

Table 4

The distribution frequency of alleles and genotypes of polymorphism IIe 105 Val of the GSTP1 gene in groups of patients and control

Group	Allele frequency				Genotype distribution frequency					
	A		G		A\A		A/G		G/G	
	n	%	n	%	n	%	n	%	n	%
The main group, n= 57	74	64.9	40	35.1	21	36,8	32	56,1	4	7,02
The control group, n=72	126	87.5	18	12.5	57	79.2	14	19.4	1	1.4

n –number of patients examined, * n is the number of alleles studied.

As the comparative analysis of the distribution frequencies of the alleles and genotypes of the IIe 105 Val polymorphism of the GSTP1 xenobiotic enzyme gene among 114 DNA samples in 57 pregnant women revealed the presence of the normal A allele and 64.1% of the G allele in 35.1% of cases. Whereas, in the control group, the frequency of occurrence of the mutant allele IIe 105 Val of the GSTP1 xenobiotic enzyme gene was 12.5%, which was 2.8 times lower in comparison to the main group (P<0.05).

For a detailed assessment of the prognostic criterion for the significance of the polymorphism of the gen-

otypes of xenobiotic enzymes GSTM1, GSTT1 and GSTP1 in the development of fetal loss syndrome in pregnant women, we analyzed the results of analyzes depending on the presence of fetal loss syndrome (FGLS) and without (table 5).

Table 5

Frequency distribution of combined genotypes of deletion polymorphisms of the GSTM1 and GSTT1, GSTP1 genes in groups of pregnant women with and without fetal loss syndrome (FGLS)

Groups	Genotype Distribution Frequency							
	GSTM1 0/0 + GSTT1 0/0		GSTM1 0/0 + GSTT1 «+»		GSTT1 0/0 + GSTM1 «+»		GSTM1 «+» + GSTT1 «+»	
	n	%	n	%	n	%	n	%
I group pregnant with FLS, n=39	11	28,2*	3	7,7	21	53,8	4	10,3
II group pregnant without FLS, n=20	4	20,0	1	5,0	11	55,0	4	20,0

n – number of patients examined; * – reliability in relation to indicators of II – group (P<0.05).

As it follows from the table 5, pregnant women with FGLS, combined functionally defective genotypes GSTM10 / 0 + GSTT10 / 0 were found in 28.2% of cases (11 pregnant women with FLS) than in the II control group individuals (20.0%), which is 1.4 times higher than in this group.

Table 6

Distribution frequency of alleles and genotypes of IIe 105Val polymorphism of the GSTP1 gene in pregnant groups with and without fetal loss syndrome (FLS)

Groups	Genotype Distribution Frequency					
	A/A		A/G		G/G	
	n	%	n	%	n	%
I – group pregnant with FGLS, n=46	13	28,3*	29	63,04*	4	17,4*
II – group pregnant without FGLS, n=11	8	72,7	3	27.3		

n – number of patients examined, * – reliability in relation to indicators of II – group (P<0.05).

As it follows from the table, in the group of pregnant women with FGLS "functionally unfavorable" A/G genotypes of the GSTP1 gene was found in 63.04% (29) versus 27.3% (3) of pregnant women without FLS, which was 2.3 times higher than the indicators of this groups (P<0.05). It should be noted that unfavorable homozygous genotypes were detected only in the I – group of pregnant women with FLS, which amounted to 17.4%.

Table 7

Predictive efficacy of the studied genetic markers

Genetic marker	SE	SP	AUC	OR (95%CI)	*p
del/del genes GSTM1	0.32	0.64	0.48	0.8; 0.4-1.74	0.6
del/del genes GSTT1	0.80	0.75	0.77	11.7; 5.132- 26.9	<0.05
GSTM1+GSTT1	0.86	0.43	0.65	7.8; 2.146- 28.65	0.0004

As it follows from table 7, the indicators of the level of specificity and sensitivity of the del/+polymorphism of the GSTT1 gene were SE=0.8 and SP=0.75, respectively, at significantly high values (OR=11.7; 95% CI 5.132-26.9). At the same time, the calculated AUC indicator demonstrates a high level of effectiveness for predicting the development of the disease, which indicates the possible independent effect of this polymorphism on the risk of pathology development.

The SE and SP indices of the combined variant of the del / + polymorphisms of the GSTM1 + GSTT1 genes deviate towards sensitivity and are equal to 0.86 and 0.43, respectively, and the efficiency rating is 0.65. These indicators also show a rather significant level of prognostic value of combinations of unfavorable genotypes as a genetic marker for predicting the development of fetal loss syndrome.

Then, studies of the expected and observed heterozygous frequencies of the IIe 105 Val polymorphism of the GSTP1 gene in pregnant women with FLS and without revealed distinctive features (table 8).

As it follows from the table, the observed, i.e. the actual distribution of GSTP1 gene A/G combinations is significantly higher than expected (63.04 versus 48.09, respectively). The relative deviation D of the observed heterozygosity from that expected in the main group of patients was positive, i.e., D = + 0.31). Whereas in the group of pregnant women without FGLS, the distribution of A/G combinations of the GSTP1 gene in the expected group turned out to be higher (23.55 versus 19.44, respectively). The deviation D of the observed heterozygosity from the expected one turned out to be negative, i.e. D = -0.17.

Table 8

The difference between the expected and observed frequencies of heterozygosity of the IIe 105 Val polymorphism of the GSTP1 gene

Groups	Observed heterozygosity (H_{obs})	Expected heterozygosity (H_{exp})	D*
Pregnant with FLS	63,04	48,09	+0,31
Pregnant women without FLS	19,44	23,55	-0.17

Pregnant women with FGLS, the frequency of the observed heterozygosity of the Iie 105 Val polymorphism of the GSTP1 gene was 63.04%, which was 3.2 times higher than that of pregnant women without FGLS, and the frequency of the expected heterozygosity was 48.09%, which was 2.4 times higher indicators of pregnant women without FGLS (P<0.05).

An analysis of the results shows that the distribution of all genotypes of the IIe 105 Val polymorphism of the GSTP1 gene in the group of pregnant women and the control corresponds to PXB, indicating the absence of the influence of systematic or random factors that can change the genetic structure of populations. A study of the genetic structure of this marker revealed a relatively high level of expected heterozygosity in the main group of patients in relation to the control group (63.04% and 19.4%, respectively.). In both groups, the indicator D is to the left of 0, that means it is negative (D<0). The revealed fact indicates higher frequencies of the expected heterozygotes, and not actually calculated heterozygotes.

Thus, an analysis of the association of intergenic combinations of zero polymorphisms of the GSTM1 and GSTT1 genes revealed that in the group of pregnant women with fetal loss syndrome, combinations of the homozygous del/del genotype responsible for a lower level of protein product synthesis are significantly more common. The chance of developing pathology in the presence of this combination of the genotypic variant of del/del genes GSTM1 and GSTT1 significantly increases: up to 7.8 times more compared to other genotypes (χ2=12.4; P=0.0004; OR=7.8; 95% CI 2.146-28.65). Whereas, the functionally unfavorable G allele of the GSTP1 gene 2.7 times statistically significantly prevailed in the studied chromosomes of pregnant women with FLS compared with pregnant women without FLS (χ2=4.6; P=0.03; OR=4.5; 95% CI1.061-19.5).

Analysis of the results of molecular genetic studies shows that female individuals of the Uzbek population with combined zero genotypes of the xenobiotic enzymes GSTM1 and GSTT1, as well as hetero / homozygous genotypes of the IIe 105 Val GSTP1 polymorphism, have a tendency to risk fetal loss syndrome (χ2=12.4; P=0.0004; OR=7.8; 95% CI 2.146-28.65).

Thus, the combined null genotypes GSTM10/0+ GSTT10/0 of the xenobiotic enzyme genes GSTM1 and GSTT1, as well as hetero (G/A) / homozygous (G/G) genotypes of the IIe 105 Val polymorphism of the GSTP1 gene, are significant markers of an increased risk of loss syndrome fetus in Uzbekistan (P <0.05). Allele A and the functionally favorable genotype A/A IIe 105 Val of the GSTP1 gene are significant protective markers for the development of pathology (χ2=18.6; P<0.05; OR=3.9; 95% CI 2.023-7.07).

The results obtained indicate that the variants of polymorphisms of the GSTM10/0 + GSTT10/0 genotypes of the GSTM1 and GSTT1 genes, as well as the G/A IIe 105 Val genotypes of the GSTP1 gene, are significant prognostic criteria for the risk of fetal growth limit syndrome, which are caused by disorders of the detoxification process in the body in women during pregnancy.

Conclusion

An analysis of the association of intergenic combinations of zero polymorphisms of the GSTM1 and GSTT1 genes revealed that in the main group of patients, combinations of the homozygous del/del genotype responsible for a lower level of protein product synthesis are significantly more common. The chance of developing pathology in the presence of this combination of the genotypic variant of del/del genes GSTM1 and GSTT1 significantly increases: up to 7.8 times more compared to other genotypes (χ2=12.4; P=0.0004; OR=7.8; 95% CI 2.146-28.65). There was a slight increase in the frequency of combinations of the heterozygous genotype 0/0 / "+" of these genes in the patient group compared to the control group (60.9% and 52.7%, respectively; χ2=0.1; P=0.3; OR=1.4; 95% CI 0.697-2.82).

When analyzing the frequency distribution of alleles and genotypes of this polymorphism in the group of pregnant with FLS, significant differences were found compared with the control group. The functionally unfavorable GST allele of the GSTP1 gene 2.7 times statistically significantly prevailed in the studied chromosomes of pregnant women with FLS compared with pregnant women without FLS (χ2=4.6; P=0.03; OR=4.5; 95% CI1.061-19.5).

Thus, the G allele and hetero / homozygous genotypes of the IIe 105 Val polymorphism of the GSTP1 gene are significant markers of an increased risk of developing fetal loss syndrome in Uzbekistan (p<0.05). Allele A and the functionally favorable A/A genotype are significant protective markers for the development of pathology (χ2=18.6; P<0.05; OR=3.9; 95% CI 2.023-7.07).

Based on the variants of the del/del genotypes of the GSTM1 and GSTT1 genes and G alleles of the GSTP1 gene, one can determine the prognosis of the risk of developing fetal loss syndrome, characterized by a violation of the detoxification process of the body during pregnancy.

The data obtained allows us to predict the risk of developing fetal loss syndrome, taking into account the assessment of the nature of the detoxification of the body during pregnancy and can be recommended for widespread use of the diagnostic method in obstetric practice.

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THE ROLE OF XENOBIOTIC ENZYME GENES OF THE FIRST AND SECOND PHASES IN THE PATHOGENESIS OF FETAL GROWTH RESTRICTION SYNDROME

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Objective: *Was to assess the detectability of allelic variants of gene polymorphism of xenobiotic biotransformation enzymes in pregnant women with fetal growth restriction syndrome.* ***Material and method:*** *were pregnant women with fetal loss syndrome (SPF), DNA samples from patients and healthy donors, glutathione transferase genes GSTM1 (1p13.3), GSTT1 (22q11.2) and glutathione transferase gene GSTP1 (IIe 105 Val). All pregnant women underwent general clinical, laboratory and functional, molecular genetic studies.* ***Results:*** *An analysis of the association of intergenic combinations of zero polymorphisms of the GSTM1 and GSTT1 genes revealed that the chance of developing pathology in the presence of this combination of the genotypic variant del / del of the GSTM1 and GSTT1 genes significantly increases: up to 7.8 times more compared to other genotypes (χ^2=12.4; P=0.0004; OR=7.8; 95% CI 2.146-28.65). The functionally unfavorable G allele of the GSTP1 gene 2.7 times statistically significantly prevailed in the studied chromosomes of pregnant women with fetal growth restriction syndrome compared with pregnant women without fetal growth restriction syndrome (χ^2=4.6; P=0.03; OR=4.5; 95%CI1.061-19.5).*

Key words: detoxification enzyme genes GSTM1 and GSTT1, GSTP1, fetal growth restriction syndrome, prediction.