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THE IMPORTANCE OF GENETIC RESEARCH METHODS IN EVALUATION OF THE IMMUNE SYSTEM OF WOMEN WITH ENDOMETRIAL HYPERPLASIA AND ADENOMYOSIS

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Abstract: We observed perimenopausal women with endometrial hyperplasia, in whom embryotropic antibodies in blood serum were determined by the ELIP test in order to assess the body's immunoreactivity. The revealed shifts in immunoreactivity are evidence of the readiness of trigger mechanisms in the implementation of newly formed GE. Probably, the solution to the issues of preventing the recurrence of GE lies in both the correction of the state of the immune system, taking into account the reactivity, and the endocrine-metabolic adaptive-homeostatic reactions in the female body mediated by it.

Key words: embryonic autoantibodies, endometrial hyperplasia, ELIP test.

Endometrial hyperplastic processes (EHP) can occur at any age, but the incidence of this disease increases significantly during the perimenopause period. The peak incidence of mammary gland diseases also occurs at the age of 41-50 years [3,4,7].

Polymorphism of clinical symptoms of hyperplastic processes of the genitals, and often their absence, various interpretations of one or another diagnostic method, the absence of diagnostic approaches in predicting relapses make it difficult to choose a rational method of treating patients with hyperplastic diseases. Among the various factors that determine the development and progression of the hyperplastic process, until recently, hormonal imbalance in the woman's body was mainly considered [6, 12, 15].

Along with the determination of the receptor status of the endometrium in hyperplastic processes, the role of molecular genetic factors in the pathogenesis of uterine mucosal hyperplasia is currently being actively studied. Studies have shown that genetic disorders such as mutations in the BRA, PTEN, TP53 genes, etc., which alter cellular metabolism, contribute to the occurrence and progression of hyperplastic processes [2].

In the literature of recent years, much attention has been paid to studies of the regulation of the ability of cells to reproduce, survive and differentiate. Of particular interest to researchers are matrix metalloproteinases, which affect cells due to their ability to change the intercellular environment [7].

Matrix metalloproteinases (MMPs) are a group of structurally related zinc-dependent endopeptidases that play a key role in tissue remodeling processes [4]. These proteins are known to be expressed in all tissues at all stages of ontogenesis, and their expression is activated under conditions of intense tissue remodeling. Among the MMP family, which includes at least 26 proteins, there are collagenases, gelatinases, stromelysins, and membrane-type MMPs (MT-MMPs). Under physiological conditions, these proteins degrade basement membranes and components of the extracellular matrix, which plays a dynamic role in metabolic processes affecting cell proliferation, differentiation, migration, apoptosis and angiogenesis [3].

Recent studies have convincingly shown that not only increased cell proliferation, but also disturbances in the processes of programmed cell death play an important role in modulating

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proliferative and hyperplastic changes. Understanding the role of hereditary predisposition factors in the development of hyperplastic diseases of the uterus and ovaries will allow us to outline new ways of studying the pathogenesis of diseases and new approaches to treating patients [1,2,11].

Objective of the study: To evaluate the immunoreactivity of the body of women with endometrial hyperplastic processes and adenomyosis by determining embryonic autoantibodies and gene polymorphism in blood serum.

Materials and methods examinations. We analyzed the case histories of 35 patients with endometrial hyperplasia and 20 women with recurrent GE who received inpatient treatment in the gynecology department of the multidisciplinary clinic of Samara State Medical University from January 2022 to December 2022. The control group consisted of 23 potentially healthy women. The women's age ranged from 43 to 51 years, with an average of 46.9±1.6 years. A comprehensive clinical and laboratory examination included examination of the external genitalia, vagina, and cervix in speculums; bimanual examination, ultrasound examination of the pelvic organs and mammary glands, endoscopic examination of the uterine cavity, histological examination of biopsies. digital mammography and determination of embryonic autoantibodies in the blood serum using the ELIP test.

The inclusion criteria for the study were as follows: perimenopausal age, morphologically confirmed diagnosis of endometrial hyperplasia, absence of antibacterial therapy over the past 3 months for an objective assessment of the infectious status, absence of hormonal therapy over the past 3-6 months. Informed consent was a prerequisite for participation in the study.

Exclusion criteria: patients with coagulopathy and iatrogenic bleeding, as well as with malignant diseases of any localization, were not included in the studies.

A comprehensive enzyme immunoassay of blood, the ELIP test, allows one to determine the immunoreactivity of natural embryotropic antibodies interacting with proteins (S 100, nuclear chromatin protein).

Before taking the test, the following preparations were made:

- Blood was donated on an empty stomach in the morning
- It was recommended to refrain from overeating the day before the test.
- For 2 days before the examination, it was forbidden to consume alcoholic and carbonated drinks.
- Psycho-emotional stress was eliminated

Venous blood was examined using the ELISA method.

The condition of the female body can be assessed by determining the serum content of autoantibodies of isotype G, which interact with antigens:

The results of determination of serum immunoreactivity obtained with the help of ELISA are expressed as a percentage of the reaction level of the reference control serum. Physiological knowledge of immunoreactivity in more than 95% of clinically healthy individuals is in the range of values from 15 to 40% classification group K1 (normal group); K2 (group of moderate deviations) - the level of EA within 25 to 65%; K3 (group of moderate deviations) - from 45 to 100%; K4 (pronounced deviations) - from 65 to 150%; K5 (very strong deviations); K6 - exclusive deviations.

If the intensity of the reaction of the studied serum with any of the studied proteins - antigens was 5-40% of the intensity of the reaction of the studied standard serum, it was considered normal. If the intensity of the reaction of the studied serum with any of the proteins was 41% or more of that of the standard serum, the serum was assigned to the group of hyperreactive deviations. If the intensity of the reaction of the studied serum with any of the studied proteins was below 5%, it was assigned to the group of hyporeactive.

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Table 1
Distribution of women depending on the results of the ELIP test

No.	groups	K1	K2 hypo	K2 hyper	K3 hypo	K3 hyper	K4 gopo	K4 hyper	K5 hypo	K5 hyper	K6 hypo	K6 hyper
1	GE n = 35	1	19		5	1	9					
2	Relapse of GE n=20	0	0		4	1	7	1	4	1	2	
3	Control n=23	21	2									
	Total n=78	22	21		9	2	16	1	4	1		2

As can be seen from Table 1, in the control group, in 21 women, the intensity of the reaction of the studied blood serum ranged from 5 to 40%, i.e. 91.3% of women belonged to the qualified group K1 and only two patients belonged to the group K2 (hyperreactivity).

In the group of women with endometrial hyperplasia, the following results of the ELIP test method were revealed: Normore activity was found in one patient, hyperreactivity was diagnosed in 33 of 35 patients, and hyperreactivity was found in one.

In case of relapse of GE, there was no Normore activity in any patient; hyperreactivity was observed in 17 out of 20 patients, and hyperreactivity in 3 cases.

Thus, the results of the ELIP test in women with recurrent GE seem more interesting, where Normore activity was diagnosed only in one case, while in the remaining cases, shifts in immunoreactivity were observed, mainly towards hyperreactivity. The identified shifts in immunoreactivity are evidence of the readiness of trigger mechanisms in the implementation of newly formed GE. Probably, the solution to the issues of preventing recurrence of GE lies in both the correction of the state of the immune system, taking into account reactivity, and the endocrine-metabolic adaptive-homeostatic reactions in the female body mediated by it.

To analyze the distribution of allele frequencies and genotypes of polymorphisms In the study groups, their distribution by the studied polymorphic loci was checked for compliance with the RHC using Fisher's exact test. The sample group included 95 conditionally healthy female donors, which formed the control group. And also 90 patients with GPM, which were distributed into two groups: Group I - patients with GPM, n = 55 and Group II - patients with GPM and DZMZ, n = 35.

Analysis of the correspondence between the expected (H_{exp}) and observed (H_{obs}) frequencies of the distribution of genotypic variants of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) showed compliance with the Hardy-Weinberg equilibrium (HWE, $p > 0.05$). In particular, in patients with AMC, the expected (H_{exp}) and observed (H_{obs}) frequencies genotypes Gln / Gln , Gln / Arg and Arg / Arg of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) were 0.296 and 0.2 ($\chi^2 = 0.004$); 0.497 and 0.46 ($\chi^2 = 0.01$); 0.208 and 0.211 ($\chi 2 = 0.01$), respectively, with an insignificant difference in the results ($p=0.89$).

In the control group, the expected (H_{exp}) and observed (H_{obs}) frequencies of the Gln / Gln , Gln

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/ Arg and Arg / Arg genotypes of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) corresponded to the values of 0.47 and 0.46 ($\chi^2 = 0.01$); 0.43 and 0.44 ($\chi^2 = 0.02$); 0.1 and 0.09 ($\chi^2 = 0.02$), respectively, also with an insignificant difference in the results obtained (p = 0.82) .

The heterozygosity index for observed (H_{obs}) and expected (H_{exp}) parameters in the main group of patients with GMP for the rs17576 polymorphism of the MMP9 gene (Gln279Arg) corresponded to values of 0.49 and 0.50 (D was 0.02) versus 0.44 and 0.43 in the control (D was -0.02) .

In groups I and II of patients with AMC, analysis of expected (H_{exp}) and observed (Hobs) frequencies of the Gln/Gln, Gln/Arg and Arg/Arg genotypes of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) showed the following:

- in group I they had values of 0.37 and 0.42 ($\chi^2 = 0.33$); 0.48 and 0.38 ($\chi^2 = 1.03$); 0.15 and 0.20 ($\chi^2 = 0.80$) with an insignificant difference (p = 0.14);
- in group II H_{exp} and Hobs frequencies of the studied genotypes corresponded to the values of 0.20 and 0.11 ($\chi^2 = 1.2$) ; 0.49 and 0.66 ($\chi 2^{=} 1.9$) ; 0.31 and 0.23 ($\chi^2 = 0.76$) with a difference of p = 0.05.

The heterozygosity index for the observed (H_{obs}) and expected (H_{exp}) parameters in group I for the rs17576 polymorphism of the MMP9 gene (Gln279Arg) was 0.38 and 0.48 versus 0.44 and 0.43 in the control group, while the heterozygosity deviation D was 0.26 and -0.02, respectively, in the studied groups. At the same time, in group II these parameters were 0.66 and 0.49 (D=-0.26) versus 0.44 and 0.43 (D=-0.02) in the control.

Between groups I and II, these indicators were 0.38 and 0.48 versus 0.66 and 0.49 with a heterozygosity deviation (D) equal to 0.26 and -0.26, respectively.

Taking into account the absence of deviations from the Hardy- Weinberg equilibrium in the analysis of the expected (H_{exp}) and observed (Hobs) frequencies of distribution of genotypic variants of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) in the studied groups, we conducted a study of the distribution features of the frequencies of alleles and genotypes of the rs17576 polymorphism of the MMP9 gene (Gln279Arg).

In the control group, the incidence of the Gln allele was 68.4% (n=130), and the Arg allele was 31.6% (n=60). At the same time, the incidence of the homozygous genotype Gln / Gln was 46.3% (n=44), the heterozygous genotype (Gln / Arg) - 44.2% (n=42). It should be noted that, as in relation to the studied polymorphism rs1042522 of the TP53-72 gene (Arg72Pro), in this case the presence of a mutant homozygous genotype (Arg / Arg) was also determined, which was recorded in 9.5% (n=9) of individuals (Table 2).

Table 2.
Distribution frequency of alleles and genotypes of polymorphism rs17576 of the MMP 9 gene (Gln 279 Arg)

Groups	n	Allele frequency				Genotype frequency distribution					
		Gln		Arg		Gln / Gln		Gln / Arg		Arg / Arg	
		n	%	n	%	n	%	n	%	n	%
Main group	90	98	54.4	82	45.6	27	30.0	44	48.9	19	21.1
I - group	55	67	60.9	43	39.1	23	41.8	21	38.2	11	20
II - group	35	31	44.3	39	55.7	4	11.4	23	65.7	8	22.9
Control	95	130	68.4	60	31.6	44	46.3	42	44.2	9	9.5

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Analysis of the distribution of the proportion of alleles and genotypes of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) in the main group showed that the Gln allele was recorded in 54.4% (n = 98), and the Arg allele in 45.6% (n = 82) of cases. Meanwhile, the carriage of the homozygous genotype Gln / Gln was recorded in 30% (n = 27), the heterozygous genotype Gln / Arg in 48.8% (n = 44), and the homozygous mutant genotype Arg / Arg in 21.1% (n = 19) of cases.

At the same time, we found it interesting to conduct a comparative analysis of the distribution of allele and genotype frequencies in groups I and II of patients with AMC. In patients with GPM in group I, the proportion of the allele Gln accounted for 60.9% (n=67), allele Arg – 39.1% (n=43). Homozygous genotype Gln / Gln was determined in 41.8% (n=23) of cases, while heterozygous Gln / Arg and homozygous Arg / Arg genotypes were detected in 38.2% (n=21) and 20% (n=11) of cases.

Some differences in the distribution of allele and genotype frequencies were determined in group II of patients with GMP and DZMZ: the Gln allele was recorded in 44.3% (n=31), and the Arg allele in 55.7% (n=39) of cases. The proportion of carriage of the homozygous Gln / Gln genotype was 11.4% (n=4), heterozygous Gln / Arg genotype 65.7% (n=23), and homozygous Arg / Arg genotype 22.9% (n=8) of cases.

The comparative assessment of the proportion of carriage of alleles and genotypes of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) made it possible to establish that in the main group the proportion of alleles Gln and Arg almost twice significantly exceeds the proportion of such indicators in the control group ($\chi^2 = 7.63$; p = 0.01; O R = 1.8; 95% CI : 1.19 -2.77).

A somewhat different picture was observed with respect to the distribution of the homozygous genotype Gln / Gln ($\chi^2 = 5.202$ p = 0.9; O R = 0.5; 95% CI : 0.27-0.91) and the heterozygous genotype Gln / Arg ($\chi^2 = 0.41$; p = 0.52; O R = 1.2; 95% CI : 0.68-2.15). However, the occurrence of the mutant homozygous genotype Arg / Arg was significantly higher in patients with GMP compared to its proportion in the controls ($\chi^2 = 4.87$; p = 0.03; O R = 2.6; 95% CI : 1.09-6.0).

Thus, the obtained data indicate the presence of statistically significant differences in the distribution of allele frequencies. Arg and the mutant genotype Arg / Arg polymorphism rs17576 of the MMP9 gene (Gln279Arg) between the main group of patients and without indication of menstrual dysfunction, which in turn allows us to identify this allele and genotype as genetic factors predisposing to an increased risk of developing GMP in perimenopausal women (Table 3).

A comparative assessment of the distribution of allele and genotype frequencies of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) carried out in Group I of patients with AMC compared to those in the control group allowed us to establish the following facts: in Group I , the allele frequencies

Gln and Arg statistically insignificantly differed from their proportions in the control ($\chi^2 = 1.7$; p = 0.2; O R = 1.4; 95% CI: 0.85-2.27), the frequencies of the Gln / Gln genotypes ($\chi^2 = 0.3$;

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Table 3
Analysis of differences in the distribution of allele and genotype frequencies of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) between groups of patients with GPM and the control group

Alleles and genotypes	Main group, n =90		Control, n =95		χ^2	R	OR	95% CI
	n	%	n	%				
Gln	98	54.4	130	68.4	7.63	0.01	1.8	1.2-2.8
Arg	82	45.6	60	31.6				
Gln / Gln	27	30.0	44	46.3	5.20	0.02	0.5	0.3- 0.91
Gln /Arg	44	48.9	42	44.2	0.41	0.52	1,2	0.7-2.1
Arg/Arg	19	21.1	9	9.5	4.87	0.03	2.6	1.09- 6.0

p = 0.6; O R = 0.86; 95% CI : 0.4 -1.6), Gln / Arg (χ^2 = 0.5; p = 0.5; O R = 0.8; 95% CI : 0.4 -1.54) also did not differ statistically significantly from those in the control. However, it should be noted that the Arg / Arg genotype, although statistically insignificant, still more than twice exceeded the values of the same genotype in the control group (χ^2 = 3.3; p = 0.1; O R = 2.4; 95% CI : 0.9 -6.2) (Table 4).

Table 4
Analysis of differences in the distribution of allele and genotype frequencies of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) between group I and the control group

Alleles and genotypes	I , n=55		Control, n=95		χ^2	R	OR	95% C I
	n	%	n	%				
Gln	67	60.9	130	68.4	1.7	0.2	1.4	0.8-2.3
Arg	43	39.1	60	31.6				
Gln / Gln	23	41.8	44	46.3	0.3	0.6	0.8	0.4- 1.6
Gln /Arg	21	38.2	42	44.2	0.5	0.5	0.8	0.4- 1.5
Arg/Arg	11	20.0	9	9.5	3.3	0,1	2.4	0.9-6.2

A comparative analysis of the distribution of allele and genotype frequencies in a group of patients with relapses of GPM and DZMZ revealed the opposite picture in relation to the above data in I group of patients compared to the control. Namely, in group II the frequency of the Arg allele statistically significantly exceeded its value in the control by 2.7 times (χ^2 = 12.64; p = 0.0004; OR = 2.7; 95% CI: 1.5 -4.8).

In addition, in comparison with the control, there was a significant difference in the frequency of occurrence of the heterozygous genotype Gln /Arg was 2.4 (χ^2 = 4.73; p = 0.03; OR = 2.4; 95% CI: 1.1 -5.4) , and the homozygous genotype Arg / Arg - 2.8 times (χ^2 = 4.03; p = 0.04; OR = 2.8; 95% CI: 1.0 -8.1) (Table 5).

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Table 5
Analysis of differences in the distribution of allele and genotype frequencies of the rs17576 polymorphism of the MMP9 gene (Gln279Arg)

Alleles and genotypes	II, n = 35		Control, n=95		χ^2	R	OR	95% CI
	n	%	n	%				
Gln	31	44.3	130	68.4	12.64	0,0004	2.7	1.5-4.8
Arg	39	55.7	60	31.6				
Gln / Gln	4	11.4	44	46.3	13.37	0,0003	0,1	0.0 5 -0.5
Gln /Arg	23	65.7	42	44.2	4.73	0.03	2.4	1, 1 -5,4
Arg/Arg	8	22.9	9	9.5	4.03	0.04	2.8	1.0-8.1

A comparative analysis conducted between groups I and II of patients with AMC revealed no statistically significant differences in the distribution of allele and genotype frequencies: allele frequency Arg (χ^2 =4.77; p =0.03; O R =0.5; 95% C I: 0.3 -0.9) , frequencies Gln / Arg (χ^2 =6.49; p =0.01; O R =0.3; 95% C I: 0.1 -0.8) and Arg / Arg (χ^2 =0.1; p =0.7; O R =0.8; 95% C I: 0.3 -2.4).

However, there were significant differences between groups I and II registered in relation to the proportion of carriage of the Gln / Gln genotype , which was 5.6 times more common in patients with GPM in group I (χ^2 = 9.41; p = 0.002; O R = 5.6; 95% CI : 1.7-18.0) (Table 6).

Table 6
Analysis of differences in the distribution of allele and genotype frequencies of the rs17576 polymorphism of the MMP9 gene (Gln279Arg) between groups I and II

Alleles and genotypes	I , n = 55		II , n =35		χ^2	R	OR	95% CI
	n	%	n	%				
Gln	67	60.9	31	44.3	4.77	0.03	0.5	0, 3 -0,9
Arg	43	39.1	39	55.7				
Gln / Gln	23	41.8	4	11.4	9.41	0.002	5.6	1.7- 1 8 ,0
Gln /Arg	21	38.2	23	65.7	6.49	0.01	0.3	0.1- 0.8
Arg/ A rg	11	20.0	8	22.9	0.10	0.7	0.8	0.3-2.4

Thus, the obtained data indicate that when studying the results of the distribution of allele and genotype frequencies of the rs17576 polymorphism of the MMP9 gene (Gln279Arg), statistically significant differences were established in comparison with the values in conditionally healthy donors. In particular, in the main group of patients with GMP, an increase in the allele frequency was established Arg almost twice and homozygous genotype Arg / Arg 2.6 times due to their levels in group II patients. These facts prove the role of the allele Arg and homozygous genotype Arg / Arg of polymorphism rs17576 of gene MMP9 (Gln279Arg) in the risk of developing GMP in perimenopausal women.

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Table 7
Indicators of diagnostic and prognostic efficiency of polymorphism rs17576 of gene MMP9 (Gln279Arg) in the risk of development of GMP and DZMZ

Study groups	Genotypes	Prognostic indicators					
		Se (sensitivity) % (95% A UC)	Sp (specificity) % (95% A UC)	AU C	OR (95% A UC)	χ^2	P
Main group, (n= 90)	Gln / Arg	48.89 (3 8 . 2 – 59 . 7)	55.79 (45.2 – 6 6 .0)	52.3	1 .2 (0 .6 8 – 2.15)	0 .41	0.5 2
	Arg|Arg	63 .89 (58 . 2 –66. 7)	55.79 (45.2 – 6 6 .0)	60 , 3	2 .4 (1.08 – 5.42)	2.8	0.05
I, (n=55)	Gln / Arg	38.18 (25.4 – 52.3)	55.79 (45.2 – 6 6 .0)	47.0	0.8 (0.4 –1.54)	0 .5	0.5
	Arg\Arg	52.8 (29.6-55.7)	55.79 (45.2 – 6 6 .0)	60.0	2 .2 (1.08 – 5.42)	2,2	0.05
II, (n=35)	Gln / Arg	65.71 (47.8–80.9)	55.79 (45.2 – 66.0)	60.8	2.4 (1.08 – 5.42)	4.73	0.0 3
	Arg\Arg	68.7(48.9-85.6)	55.79 (45.2 – 6 6 .0)	62.0	2.6(1.2-6.02)	5.02	0.02

Thus, the determination of AU C of the rs1042522 polymorphisms of the TP53-72 gene (Arg72Pro) and rs17576 of the MMP9 gene (Gln279Arg) in the risk of developing GMP in perimenopausal women in the main group of patients in relation to the rs1042522 polymorphism of the TP53-72 gene (Arg72Pro) amounted to values \ u200b \ u200bless than 0.5 , which indicates the absence of their prognostic value in the risk of developing GMP in perimenopausal women, while AU C for the rs17576 polymorphism of the MMP9 gene (Gln279Arg) amounted to values \u200b\u200bmore than 60.0, which proves its significant role in the risk of developing hyperplastic processes of the genitals and mammary glands in perimenopausal women.

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