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Peculiarities of Incidence and Contribution of the Polymorphous Estrogen Receptor Gene ESR1 (rs9340799) in Various Forms of Genital Prolapse

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Abstract We have studied the occurrence and contribution of the polymorphic estrogen receptor gene ESR1 (rs9340799) among women with genital prolapse. Gene evaluation was performed by analyzing DNA samples by standard PCR. Our results of the study allowed us to establish that the mutant A allele and the A/A genotype of the rs9340799 polymorphism in the estrogen receptor gene ESR1 are associated with an increased risk of developing a severe degree of genital prolapse and can be considered as independent genetic markers that have a pathogenetic contribution to the aggravation of the disease, while the main genotype G/G is a protective marker that prevents the transition of the disease into a severe form.

Keywords Genital prolapse, Estrogen receptor, Polymorphism, Gene, ESR1 (rs9340799), Frequency, Allele, Genotype, Carriers

1. Introduction

Genital prolapse (PG) today is a very common gynecological pathology, in which approximately 37% of women, due to the aggravation of their general condition and deterioration in the quality of life, turn to medical institutions for surgical treatment [6,10].

It is known that the normal function of the pelvic floor is maintained due to the full interaction of the bones, muscles, ligaments and fascia of the pelvis, as well as their innervation. [1,4]. Their various defects arising under the influence of certain factors (age, menopause, obesity, genetic status, bad habits, hard physical work, physical inactivity, chronic constipation, connective tissue pathology, a history of operations) undoubtedly serve as the basis for the development of PG in women [3]. Meanwhile, it is not always possible to determine the exact pathogenetic mechanisms of the formation of this complex pathology, which are based on very unclear complex processes. In this regard, the increasing interest of modern researchers is attracted by more subtle mechanisms for the development of PH, which involve the participation of a number of polymorphic genes, the dysregulation of which leads to structural and quantitative changes in the components (collagen, fibronectin, elastin, etc.) of the pelvic floor tissues [7,8,9].

Among the existing scientific data on molecular genetic factors, the literature presents the results of studies aimed at studying the contribution to the development of PG of the polymorphic estrogen receptor gene (ESR1) [2]. However, along with studies proving the participation of the above genetic variants of polymorphisms in the pathogenesis of PG, there are also conflicting data regarding their influence on the development of changes in the structure and content of the constituent tissues of the pelvic floor, which serve as the basis for the development of PG. [5].

Taking into account the existing controversial discussions in this area, it seemed to us very important to study the presence of an associative relationship between the polymorphic ESR1 gene (rs9340799) and the risk of developing various forms of PG.

2. Material and Methods

The study was conducted with the participation of 171 women (median age 25±68 years) living in the Republic of Uzbekistan. Among the entire selected cohort, 84 women (the 1st - the main group of patients) were diagnosed with genital prolapse, verified as a result of a survey in the maternity complex No. 3 and the private clinic "Doctor Shifo Bakht" (Samarkand) from 2018 to 2023. G. The remaining 87 women were healthy (5th healthy control group). The main group of women with genital prolapse, depending on the severity, was divided into three groups: 2nd (n=28) with mild severity, 3rd (n=39) with moderate severity and 4th (n=17) with a history of severe disease severity, of comparable age and sex in the general group of RA patients. Molecular genetic studies were performed on the basis of the laboratory of medical genetics of the Republican Specialized

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Scientific and Practical Medical Center for Hematology (Republic of Uzbekistan, Tashkent). In accordance with the generally accepted method, DNA was isolated from blood leukocytes. At the same time, using the Applied Biosystems 2720 system (USA), an analysis (SNP-PCR) of the ESR1 gene (rs9340799) was carried out using the Litekh test systems (Russia). Mathematical analysis of the results was carried out using the program "Open Epi 2009, Version 9.3".

3. Results and Discussion

Studying the correspondence between the distribution of observed (Ho) genotypic frequencies (G/G, G/A and A/A) of the polymorphic estrogen receptor gene ESR1 (rs9340799) to their expected (He) frequencies according to Hardy-Weinberg equilibrium (HWB) in groups of patients with PH (n=84), we found a slightly deviated RCM ($p<0.05$). This was due to some excess in the observed frequency of the attenuated A/A mutant genotype ($\chi2=5.5$; P=0.003; df=1). Assessing the nature of the distribution of frequencies of alleles and genotypes for the polymorphic gene of the estrogen receptor ESR1 (rs9340799) among control healthy women (n=87), the proportions of the main G and mutant A alleles were determined in 90.2%/157 and 9.8%/17 cases, respectively, with the detection of carriage by all three possible variants of the genotypes G/G, G/A and A/A, respectively, in 82.8%/72; 14.9%/13 and 2.3%/2 cases (Table 1).

Meanwhile, in the 1st main group (n=84) of women with PG compared with healthy ones, the frequency of the main G allele slightly decreased from 90.2% / 157 to 87.5% / 147, and the weakened A allele, on the contrary, increased from 9.8% / 17 to 12.5%/21. Naturally, with allelic frequency compared with healthy, the proportion of the main G/G genotype decreased from 82.8%/72 to 79.8%/67, with an increase in the frequencies of heterozygous (G/A: from 14.9%/13 to 15.5%/13) and mutant (A /A: from 2.3%/2 to 4.7%/4) genotypes. Next, we evaluated the features of the frequency distribution of allelic and genotypic variants of the polymorphism of the estrogen receptor gene ESR1 (rs9340799) among women with PH, depending on the severity of the pathology. Thus, compared with healthy controls in the 2nd group of patients with mild PH severity (n=28), the frequency of the main allele G slightly increased to 91.1%/51 cases with a decrease in the weakened form (A) to 8.9%/5. Accordingly, with these features, the proportion of the main G/G increased to 85.7%/24, with a decrease in the frequency of the heterozygous variant (G/A) to 10.7%/3 and an increase in the proportion of the weakened mutant form of the A/A genotype to 3.6%/1. In parallel, the analysis of the distribution of allelic and genotypic frequencies in the 3rd group of women with PG with moderate severity (n=39) compared with the healthy group showed a similar picture observed in the 2nd group. In particular, an increase in the shares of the main allele G to 92.3%/72 and the G/G genotype to 82.8%/72 was found, while a decrease in the frequency of the weakened A genotype to 7.7%/6 and an increase in the proportion of the heterozygous form of the G/A genotype to 15.4%/ 6 cases. Here it is also important to note the complete absence of cases of carriage of the weakened A/A mutant genotypes among women with moderate severity of PG. Studying the nature of the distribution of frequencies of alleles and genotypes according to the polymorphism of the estrogen receptor gene ESR1 (rs9340799) in the 4th group of patients with severe PH (n=17), compared with healthy women, a marked decrease in the frequencies of the main allele G was found to 70.6%/24 vs. 90.2%/157 and G/G genotype up to 58.8%/10 versus 82.8%/72, respectively. This pattern was accompanied by a pronounced increase in the frequencies of the weakened form of the A allele up to 29.4%/10 vs. 9.8%/17, the heterozygous G/A genotype up to 23.5%/4 vs. 14.9%/13, and the mutant A/A genotype up to 17.7%/3 vs. 2.3% /2 (Table 1).

Comparative studies between the 1st main group of women with PH (n=84) and healthy women (n=87) made it possible to determine the absence of statistically significant differences in the frequencies of alleles and genotypes for polymorphism of the estrogen receptor gene ESR1 (rs9340799). So, in the main group of women, compared with healthy ones, the attenuated allele A, insignificantly increased among women with PH by 1.3 times (12.5% vs. 9.8; $\chi2=0.6$; P=0.5; OR=1.3; the main G/G genotype decreased by less than one (79.8% vs. 14.9; $\chi2<3.84$; P=0.95; OR=1.0; 95%CI: 0.45–2.4), while the frequency of the A/A mutant genotype, although increased by 2.1 times (4.8% versus 2.3; $\chi2=0.8$; P=0.4; OR=2.1; 95%CI: 0.39 – 11.5), but due to the small number of individuals compared, it did not reach a significant level (Table 2).

Table 1. Frequency distribution of variants of alleles and genotypes of the rs9340799 polymorphism in the estrogen receptor gene ESR1 in groups of patients with genital prolapse and healthy people

Group	alleles				Genotypes					
	G		A		G/G		G/A		A/A	
	n	%	n	%	n	%	n	%	n	%
1st - the main group of patients with PG, n=84	147	87.5	21	12.5	67	79.8	13	15.5	4	4.7
2nd group of patients with mild severity of PG, n=28)	51	91.1	5	8.9	24	85.7	3	10.7	1	3.6
3rd group of patients with moderate PG severity, n=39	72	92.3	6	7.7	33	84.6	6	15.4	0	0.0
4th group of patients with severe PG severity, n=17	24	70.6	10	29.4	10	58.8	4	23.5	3	17.7
5th - healthy control group, n=87	157	90.2	17	9.8	72	82.8	13	14.9	2	2.3

Table 2. Evaluation of differences in the distribution of frequencies of variants of alleles and genotypes of the rs9340799 polymorphism in the estrogen receptor gene ESR1 between the main group of patients with genital prolapse and healthy ones

Alleles and genotypes	Surveyed groups				χ^2	P	RR	95%CI	OR	95% CI
	1st main group with PG		Control							
	n	%	n	%						
G	147	87.5	157	90.2	0.6	0.5	1.0	0.53-1.78	0.8	0.39 - 1.49
A	21	12.5	17	9.8	0.6	0.5	1.0	0.5 - 2.13	1.3	0.67 - 2.59
G/G	67	79.8	72	82.8	0.3	0.7	1.0	0.47-1.98	0.8	0.38 - 1.77
G/A	13	15.5	13	14.9	0.0	0.95	1.0	0.46-2.35	1.0	0.45 - 2.4
A/A	4	4.8	2	2.3	0.8	0.4	2.1	0.66-6.55	2.1	0.39 - 11.5

Table 3. Evaluation of differences in the distribution of frequencies of variants of alleles and genotypes of the rs9340799 polymorphism in the estrogen receptor gene ESR1 between groups of patients with mild genital prolapse and healthy

Alleles and genotypes	Surveyed groups				χ^2	P	RR	95%CI	OR	95% CI
	I degree PG		Control							
	n	%	n	%						
G	51	91.1	157	90.2	0.0	0.9	1.0	0.21 - 4.9	1.1	0.39 - 3.14
A	5	8.9	17	9.8	0.0	0.9	1.0	0.62-1.58	0.9	0.32 - 2.58
G/G	24	85.7	72	82.8	0.1	0.8	1.0	0.17 - 6.5	1.3	0.38 - 4.13
G/A	3	10.7	13	14.9	0.3	0.6	0.7	0.09-5.89	0.7	0.18 - 2.58
A/A	1	3.6	2	2.3	0.1	0.8	1.6	0.06-38.2	1.6	0.14 - 17.7

Table 4. Evaluation of differences in the distribution of frequencies of variants of alleles and genotypes of the rs9340799 polymorphism in the estrogen receptor gene ESR1 between groups of patients with moderate genital prolapse and healthy

Alleles and genotypes	Surveyed groups				χ^2	P	RR	95%CI	OR	95% CI
	II degree PG		Control							
	n	%	n	%						
G	72	92.3	157	90.2	0.3	0.6	1.0	0.25-4.15	1.3	0.49 - 3.43
A	6	7.7	17	9.8	0.3	0.6	1.0	0.59-1.62	0.8	0.29 - 2.03
G/G	33	84.6	72	82.8	0.1	0.8	1.0	0.24 - 4.3	1.1	0.41 - 3.22
G/A	6	15.4	13	14.9	0.0	0.95	1.0	0.25-4.22	1.0	0.36 - 2.96

Table 5. Assessment of differences in the distribution of frequencies of variants of alleles and genotypes of the rs9340799 polymorphism in the estrogen receptor gene ESR1 between groups of patients with severe genital prolapse and healthy

Alleles and genotypes	Surveyed groups				χ^2	P	RR	95%CI	OR	95% CI
	III degree PG		Control							
	n	%	n	%						
G	24	70.6	157	90.2	9.7	0.01	0.8	0.23 - 2.62	0.3	0.11 - 0.61
A	10	29.4	17	9.8	9.7	0.01	1.3	0.72 - 2.28	3.8	1.65 - 8.98
G/G	10	58.8	72	82.8	4.9	0.05	0.7	0.14 - 3.71	0.3	0.1 - 0.87
G/A	4	23.5	13	14.9	0.8	0.4	1.6	0.22-11.02	1.8	0.5 - 6.14
A/A	3	17.6	2	2.3	7.3	0.01	7.7	1.41 - 41.8	9.1	1.84-45.12

Thus, comparing the significance of differences in the distribution of the polymorphic locus of the estrogen receptor gene ESR1 (rs9340799) between the main 1st group of patients with PH and healthy women, its association with the risk of genital prolapse ($\chi2<3.84$; $P>0.05$) was not revealed. Assessing the degree of differences in the carriage of the frequencies of allelic and genotypic variants of the polymorphic estrogen receptor gene ESR1 (rs9340799) in the 2nd group of patients with mild PH (n=28) compared to those in the healthy group, as well as in the main group, practically no statistically significant values were found. In the group of patients, the frequency of allele A decreased to 8.9% versus 9.8 among healthy people, the difference was less than one ($\chi2<3.84$; P=0.9; OR=0.9; 95% CI: 0.32 - 2.58). In terms of genotype differences, among which in the 2nd group of women with PH, the main G/G variant increased by 1.3 times (85.7% versus 82.8; $\chi2=0.1$; P=0.8; OR=1.3;), the heterozygous variant G/A decreased by less than one (10.7% vs. 14.9%; $\chi2=0.3$; P=0.6; OR=0.7; 95% CI: 0.18 -2.58), while the mutant variant A/A increased 1.6

times (3.6% vs. 2.3%; $\chi2=0.1$; P=0.8; OR=1.6; 95% CI: 0.14-17.7) a statistically significant character was also not found (Table 3).

Thus, a comparative assessment of differences in the carriage of allelic ($\chi2<3.84$; P>0.05) and genotypic ($\chi2<3.84$; P>0.05) variants of the polymorphic gene of the estrogen receptor ESR1 (rs9340799) in the 2nd group of patients with mild PH and among women of the healthy group showed the absence of their statistical significance, which does not allow us to determine the studied gene as an independent genetic marker capable of increasing the risk of developing mild PG.

Assessing the degree of significance of differences in the frequencies of alleles and genotypes of the polymorphic gene of the estrogen receptor ESR1 (rs9340799) in the 3rd group of patients with PH with moderate severity (n=39) compared with healthy women (n=87), again no statistically significant character was revealed. differences in allele and genotype frequencies (Table 4).

The evidence of the absence of statistically significant differences is the decrease in the frequency of the weakened A allele by less than one (7.7% vs. 9.8%; $\chi2=0.3$; P=0.6; OR=0.8; 95% CI: 0.29-2.03), an increase in the frequency of the main G/G genotype in 1.1 (84.6% vs. 82.8%; $\chi2=0.1$; P=0.8; OR=1.1; 95%CI: 0.41-3.22) and G/A per unit (15.4% vs. 14.9%; $\chi2<3.84$; P=0.95; OR=1.0; 95%CI: 0.36-2.96). The absence of statistically significant differences in the distribution of alleles ($\chi2<3.84$; P>0.05) and genotypes ($\chi2<3.84$; P>0.05) of the polymorphic gene of the estrogen receptor ESR1 (rs9340799) in the 3rd group of patients with moderate PG severity compared with healthy indicates the absence of their independent contribution to the formation of genital prolapse of moderate severity. A completely different picture was obtained by a comparative analysis of alleles and genotypes of the polymorphic gene of the estrogen receptor ESR1 (rs9340799) between groups of women with severe PG (n=17) and healthy (n=87) (Table 5).

A high degree of statistical significance of differences was found in the frequencies of weakened variants of the allele (A) and genotype (A/A), which in the 4th group of women increased by 3.8 (29.4% vs. 9.8%; $\chi2=9.7$; P=0.01; OR=3.8; 95% CI: 1.65-8.98) and 9.1 times (17.6% vs. 2.3%; $\chi2=7.3$; P=0.01; OR=9.1; 95% CI: 1.84-45.12), respectively. Meanwhile, the differences in the frequencies of the main G/G (58.8% vs. =0.8; P=0.4; OR=1.8; 95%CI: 0.5-6.14) genotypes did not reach a statistically significant level. Thus, a statistical analysis of differences in the carriage of alleles and genotypes of the estrogen receptor gene polymorphism ESR1 (rs9340799) between groups of patients with severe genital prolapse and healthy controls revealed the presence of statistically significant differences in the frequencies of the attenuated A allele and the A/A genotype, which increase the probable the risk of developing a severe degree of PH by 3.8 ($\chi2=9.7$; P=0.01) and 9.1 ($\chi2=7.3$; P=0.01) times, respectively. Therefore, polymorphism of the estrogen receptor gene ESR1 (rs9340799) can be considered as an independent genetic marker contributing to the development of a severe form of genital prolapse. Next, we performed a statistical analysis of the established differences in the frequencies of allelic and genotypic variants of the polymorphism of the estrogen receptor gene ESR1 (rs9340799) between women with mild, moderate and severe PG. In the course of assessing the significance of differences in the frequencies of alleles and genotypes of the polymorphism of the estrogen receptor gene ESR1 (rs9340799) in groups of women with mild and moderate PH, we could not establish their statistically significant nature either for alleles (for the A allele - 8.9% versus 7.7%; $\chi2=0.1$; P=0.8; OR=1.2; 95%CI: 0.34-4.06) neither for genotypic variants (for G/G genotype – 85.7% versus 84.6%; $\chi2<3.84$; P=0.95; OR=1.1; 95 %CI: 0.28-4.29; for the G/A genotype, 10.7% versus 15.4%; $\chi2=0.3$; P=0.6; OR=0.7; 95%CI: 0.15-2.88). However, such an analysis between women with mild and severe PH severity made it possible to establish very significant differences in the distribution of the mutant allele A, in the presence of which the risk of developing a severe PH degree increased by 4.3 times (8.9% vs. 29.4%; $\chi2=6.4$; P=0.03 OR=4.3, 95% CI: 1.38-13.05 In addition, among carriers of the main G/G genotype, due to its protective effect, the risk of developing a severe form of PH was statistically significantly reduced by 4.2 times (85.7% vs. 58.8%; $\chi2=4.1$; P=0.05; OR=4.2; 95%CI: 1.05-16.73). Along with these features, among carriers of heterozygous G/A (10.7% vs. 23.5%; $\chi2=1.3$; P=0.3; OR=0.4; 95% CI: 0.08-1.94) and attenuated mutant A/A genotypes, no statistically significant differences were observed (3.6% versus 17.6%; $\chi2=2.6$; P=0.2; OR=0.2; 95% CI: 0.02-1.47) due to the low number of carriers of these genotypes in the studied groups. A similar picture was observed when comparing the differences in the frequencies of alleles and genotypes of the polymorphism of the estrogen receptor gene ESR1 (rs9340799) between women with moderate and severe severity. Thus, it was found that the mutant allele A can statistically significantly increase the risk of developing a severe degree of PH by 5.0 times (7.7% vs. 29.4%; $\chi2=9.1$; P=0.01; OR=5.0; genotype G/G can statistically significantly reduce the risk of developing severe PH by 3.9 times (84.6% versus 58.8%; $\chi2=4.4$; P=0.05; OR=3.9; 95% CI: 1.1-13.53). At the same time, in relation to heterozygous G/A genotypes (10.7% vs. 23.5%; $\chi2=1.3$; P=0.3; OR=0.4; 95% CI: 0.08-1.94), no statistically significant differences were found between the studied groups of women with middle and severe degrees of severity of PG.

4. Conclusions

A multilateral analysis to study the characteristics of the distribution and the level of differences in the distribution of allele frequencies and genotypes of the rs9340799 polymorphism in the estrogen receptor gene ESR1 among women with various forms of genital prolapse with pelvic floor insufficiency and healthy women made it possible to

establish the presence of a statistically significant increase in the risk of developing a severe form of the disease among carriers weakened mutant allele A and genotype A/A. In particular, compared with healthy women among carriers of the A allele and A/A genotype, the risk of developing a severe form of PH is statistically significantly increased by 3.8 ($\chi2$=9.7; P=0.01) and 9.1 ($\chi2$=7.3; P=0.01) times, respectively, whereas, compared with women with mild and moderate PH severity, in carriers of the A allele, the risk of developing a severe degree is statistically significantly increased by 4.3 ($\chi2$=6.4; P=0.03) and 5.0 ($\chi2$=9.1; P=0.01) times, respectively, despite the fact that among carriers of the main G/G genotype, on the contrary, due to its protective effect, the risk of transition to a severe degree with mild and moderate severity is statistically significantly reduced by 4.2 times ($\chi2$=4.1; P=0.05) and 3.9 (84.6% vs. 58.8%; $\chi2$=4.4; P=0.05). Therefore, it can be concluded from this that the mutant allele A and the A/A genotype of the rs9340799 polymorphism in the estrogen receptor ESR1 gene are associated with an increased risk of developing a severe degree of genital prolapse and can be considered as independent genetic markers that have a pathogenetic contribution to the aggravation of the disease, while the main genotype G/G is a protective marker that prevents the transition of the disease into a severe form.

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