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STUDY OF THE PATHOGENETIC BASIS OF THE DEVELOPMENT OF MENSTRUAL CYCLE DISTURBANCES IN ADOLESCENT GIRLS

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Abstract. The article presents the results of a study conducted to study and substantiate the role of genetic factors in adolescent girls aged 11-17 years with various menstrual disorders. The results show that there is a statistically significant association between the rs726547 polymorphism of the CYP19A1 gene and the occurrence of menstrual disorders in adolescents.

Keywords: gene, menstrual cycle, polymorphism, adolescent girls, allele, heterozygote.

The menstrual cycle is one of the most important indicators of reproductive health. Menstrual dysfunction not only causes infertility, but also increases the risk of various chronic diseases in the future, such as diabetes, breast cancer, and cardiovascular diseases [1,4,10]. In addition, it has been established that the presence of long and irregular menstrual cycles is associated with early death [3]. Dysfunctional menstrual cycles are of great importance because they cause not only physical, but also psychological and economic stress in women, starting in adolescence and continuing for many years into reproductive age [2,11].

The state of reproductive health of adolescents is one of the most discussed topics not only by experts in this field, but also by the general public. Official statistics show negative trends in the reproductive health of girls in most regions of our country. According to the statistics of the last 10 years, the incidence of girls aged 11 to 18 years has increased by 3.4 times. In girls aged 15 to 18 years, the irregularity of the menstrual rhythm is mainly due to metabolic diseases and hyperandrogenic changes, which manifest themselves as delayed menstruation (74.9%), amenorrhea (29.7%). The number of girls at risk of absolute or relative infertility has increased (Ashurova S.A., 2010, Ayupova F.M. 2011). An imbalance in the hypothalamic-pituitary-ovarian (HPO) system in adolescent girls can lead to menstrual irregularities, algodysmenorrhea, and premenstrual stress syndrome.There are a number of studies devoted to the study of the genetic basis of menstrual disorders [5,9].

The genetic causes of menstrual disorders may be associated with individual genes, including both the X chromosome and the Y chromosome, or autosomes [6,9]. However, in many cases there is a combination of genetic and environmental influences on the development of pathology, which suggests that menstrual irregularity is a multifactorial disorder in which both genetic and environmental factors play an important role [8,10].

It is known that CYP19A1 is a cytochrome P450 monooxygenase that catalyzes the conversion of androgens C19, androst-4-ene-3,17-dione (androstenedione), and testosterone into estrogens C18, estrone, and estradiol, respectively [7]. The results of foreign studies show that the function of the nucleotide exchange of the intron (rs 726547) of CYP19A1 affects the activity of aromatase, which leads to the conversion of testosterone into active estrogen [3,5]. This means that the minor allele of the C>T CYP19A1 polymorphism can cause aromatase overexpression, which leads to an increase in estrogen concentration and a decrease in androgen concentration. Aromatase overexpression can rarely cause rare types of dysfunction in women (isosexual precocity,

macromastia, menstrual irregularities, and, as in men, rapid bone growth [8]. In men, this condition can cause symptoms such as heterosexual development, including gynecomastia, hypogonadism, sparse hair, and oligozoospermia [11].

Thus, the study of new and existing candidate genes and their pathophysiological mechanisms that cause menstrual disorders in the Uzbek population will provide us with important information for determining the genetic basis, predicting and preventing it in adolescents.

Purpose of the work: to improve the efficiency of diagnosis and treatment of various menstrual dysfunctions in adolescent girls based on the study of the etiopathogenetic role of genetic markers in the development of this pathology.

Materials and methods: This scientific work was carried out at the Department of Obstetrics and Gynecology No. 2 of the Bukhara State Medical Institute, as well as in the central clinics and maternity hospitals of the Bukhara and Romitan regions, in the regional children's multidisciplinary medical center, in the regional perinatal center, as well as in the Regional screening center "Mother and Child".

The study included a total of 272 adolescent girls. All teenage girls were schoolchildren in the city of Bukhara and the Bukhara region. The urban population was 46.3%, rural - 53.7%. The mean age of menarche was 12.4±1.2 years. 192 adolescent girls aged 11 to 17 years old (main group) and 80 practically healthy adolescent girls of the same age with normal menstrual function (control group) were examined with various types of menstrual irregularities. All adolescent girls were included in the study with the consent of their parents.

According to the nature of menstrual disorders, the girls of the main group were divided into 2 subgroups. Group 1A included 105 girls with hypomenstrual syndrome. Group 1B consisted of 87 adolescent girls with hypermenstrual syndrome.

The mean age was 14.1±0.9 years in the control group, 13.8±0.7 years in group 1A, and 14.6±0.8 years in group 1B.

All adolescent girls underwent a comprehensive examination, including clinical, laboratory, instrumental and statistical research methods. Examination of girls began with a thorough and detailed history taking, which determined the nature of the menstrual function (the age of the onset of menarche, the regularity of the cycle and its violation, the interval of menstruation, the presence of pain during menstruation), previously used methods of treatment and correction of disorders, the duration of their use.

Molecular genetic studies were carried out by the author at the Department of "Molecular Medicine and Cellular Technologies" in the Republican Specialized Scientific and Practical Medical Center for Hematology of the Ministry of Health of the Republic of Uzbekistan, under the guidance of MD. Boboev K. T.

The study was performed in real time on a thermal cycler system designed to perform universal polymerase chain reaction (PCR) amplification with high resolution analysis (HRM) channels. Producer: GIAGEN (Germany). The material was DNA samples isolated from the venous blood of adolescent girls.

Results and their analysis. In our study, the rs726547 polymorphism of the CYP19A1 gene was studied and genetically analyzed in 110 patients with menstrual disorders. Based on the distribution of alleles, we found that the proportion of the wild-type C allele in the control group was higher than in the main group (87.1% and 73.6%, respectively), while the proportion of the non-wild-type or mutant allele-T allele was more common. in the main group (this figure in the control group was 12.9%, while in the main group this figure was 26.4% (Table 1).

According to the distribution of genotypes, homozygous CC or wild type genotype was detected in 55.5% of patients, heterozygous genotype - CT was found in 36.4% of girls with menstrual irregularity, homozygous CC or short type genotype was found in 8.1% of patients of the main group. In particular, a significant difference in the percentage

of different genotypes was revealed in the control group. In particular, the proportion of homozygous CC genotype was 77.1%, heterozygous CT genotype and homozygous TT genotype - 20.0% and 2.9%, respectively. Thus, we can conclude that the mutant homozygous genotype is more common in the main group, while the determination of the normal homozygous genotype dominates in the control group (Table 2).

The prevalence of genotypes in the studied rs726547 polymorphisms of the CYP19A1 gene was checked by the Hardy-Weinberg index. The empirical ratio of homozygous genotypes in the main group was 0.56/0.54 and 0.08/0.08, respectively, for the observed and theoretically expected levels (Table 1). In the control group, the frequency of these genotypes was 0.77/0.759 and 0.029/0.017, respectively.

It follows that we did not find a comparative difference between the distribution of observed and expected genotypes in both groups, which corresponds to the Hardy-Weinberg law, which corresponds to the absence of a statistically significant deviation (CG2<3.84; P>0.05).

Table 1.

Correlation of polymorphism of the genotype (C>T) of the CYP19A1 gene according to the Hardy-Weinberg law in girls with menstrual irregularity and in healthy adolescent girls (χ2, df = 1)

Main group					
Alleles	Allele frequency				
C	0,736				
T	0,264				
Genotypes	Genotype frequency		χ2	p	df
	observed	expected			
C/C	0,56	0,54			
C/T	0,36	0,39			
T/T	0,08	0,22			
Total	1	1	0,44	0,74	1

Control group					
Alleles	Allele frequency				
C	0,871				
T	0,129				
Genotypes	Genotype frequency		χ2	p	df
	observed	expected			
C/C	0,771	0,76			
C/T	0,20	0,224			
T/T	0,029	0,016			
Total	1	1	1,2	0,54	1

As for the heterozygous genotype, the level of the heterozygous genotype in patients with rs726547 polymorphism in the CYP19A1 gene in the main group was slightly lower than the theoretical level (0.36/0.39; D=-0.077), and the observed level of the heterozygous genotype was also low, as and in the control group. Now, with the results obtained at the end of our study, we can explain the role of the gene in the pathogenesis of menstrual disorders in adolescents.

According to the relative risk (RR), the risk of developing the disease in the main

group for carriers of the wild allele (C) was 0.69 (95% CI: 0.573-0.827), which means that the C allele plays a reliable and important protective role against menstrual irregularity in the Uzbek population (CG2 = 19.5; p<0.001). On the other hand, in our study, the small allele (T) significantly increases the risk of menstrual irregularities (RR=1.45; 95% CI: 1.21-1.756; CH2=19.5; P<0.001) (Table 2). Regarding genotypes, as mentioned above, when comparing the frequency of occurrence of CYP19A1 (C / T) gene polymorphism with the control group, it was found that genotypes with a significant difference in CC are more common in the control group, while the TT mutant genotype prevails in the main group, as mentioned above.

Thus, the result of the relative risk for homozygous wild-type genotype is RR=0.64; 95% CI 0.499-0.820; CG2 = 11.3 p < 0.001, for heterozygous genotype RR=1.44 95% CI 1.122-1.854; CG2=7.1; p = 0.008 and for the homozygous mutant genotype RR = 1.51; 95% CI 1.057-2.149; CH2 = 2.89; p = 0.09. (Table 2)

Table 2.

Results of genotyping of CYP19A1 gene polymorphism (C>T) in adolescent girls with menstrual irregularity and in healthy people

Alleles and genotypes	Number of studied alleles and genotypes				χ2	P	RR	95%CI	OR	95%CI
	Main group		Control group							
	N	%	N	%						
C	103	80,5	183	87,1	2,7	0,1	0,75	0,543-1,034	0,61	0,335-1,102
T	25	19,5	27	12,9	2,7	0,1	1,34	0,967-1,842	1,64	0,91-2,983
C/C	42	65,6	81	77,1	2,66	0,1	0,71	0,484-1,053	0,56	0,284-1,126
C/T	19	29,7	21	20,0	2,1	0,15	1,36	0,911-2,036	1,69	0,823-3,46
T/T	3	4,7	3	2,9	0,4	0,53	1,34	0,586-3,047	1,67	0,327-8,55

That is, the homozygous wild-type genotype showed a decrease in the protective role by 36%, and the heterozygous genotype played an inductive role in the pathogenesis of menstrual disorders and increased the risk by 44%. The result showed that both indicators were statistically significant. On the other hand, although the homozygous mutant genotype showed a 51% increased risk of menstrual disorders (RR=1.51; 95% CI: 1.057-2.149), this result was not statistically significant (CG2<3.84; p>0.05).

Table 3

Results of genotyping of CYP19A1 gene polymorphism (C>T) in menstrual disorders with hypomenstrual syndrome and in healthy adolescent girls.

Alleles and genotypes	Number of studied alleles and genotypes				χ2	P	RR	95%CI	OR N	95%CI %
	Examined with hypomenstrual syndrome		Control group							
	N	%	N	%						
C	162	73,6	183	87,1	19,5	<0,001	0,69	0,573-0,827	0,41	0,249-0,682
T	58	26,4	27	12,9	19,5	<0,001	1,45	1,210-1,746	2,43	1,467-4,014
C/C	61	55,5	81	77,1	11,3	<0,001	0,64	0,499-0,820	0,37	0,204-0,666
C/T	40	36,4	21	20,0	7,1	0,008	1,44	1,122-1,854	2,28	1,23-4,232
T/T	9	8,1	3	2,9	2,89	0,09	1,51	1,057-2,149	3,03	0,797-11,5

Interestingly, when statistically processing the results of the second subgroup, which included patients with menstrual disorders with hypomenstrual syndrome, we found that the frequency of the T allele was significantly - 2.78 times higher than in the control group (35.9% vs. 12.9% ; minor allele and hypomenstrual type of menstrual irregularity were significant (21.3; P<0.001)).

Table 4

Results of genotyping of CYP19A1 gene polymorphism (C>T) in menstrual disorders with hypermenstrual syndrome and in healthy adolescent girls

Alleles and genotypes	Number of studied alleles and genotypes				χ2	P	RR	95%CI	OR N	95%CI %
	Examined with hypermenstrual syndrome		Control group							
	N	%	N	%						
C	59	64,1	183	87,1	21,3	<0,001	0,44	0,322-0,610	0,26	0,147 - 0,475
T	33	35,9	27	12,9	21,3	<0,001	2,25	1,640-3,103	3,79	2,11-6,82
C/C	19	41,3	81	77,1	18,4	<0,001	0,36	0,222-0,580	0,21	0,1-0,44
C/T	21	45,7	21	20,0	10,5	0,002	2,18	1,38-3,45	3,36	1,58-7,13
T/T	6	13	3	2,9	5,9	0,01	2,37	1,391-4,03	5,1	1,2-21,4

According to the prevalence of genotypes in the first subgroup, the C/T and T/T genotypes significantly prevailed compared with the control group (45.7% and 20.0%; p<0.05; 13 and 2.9%; CG2>3.84 ; p<0.05, respectively). Mutant homozygous form (TT) and heterozygous form (CT) of the CYP19A1 gene played an important role in the development of menstrual disorders with hypermenstrual syndrome, increasing the risk by 2.37 and 2.18 times, respectively. (PP \ y003d 2.37; 95% CI: 1.391 - 4.03 va PP \ y003d 2.18; 95% CI: 1.38 - 3.45) As for the homozygous genotype α / α, it played a strong protective role in our studies, reducing the risk by 2.78 times (RR = 0.36; 95% CI: 0.222-0.580). These results were statistically significant (CG2>3.84; p<0.05) (Table 4).

Thus, the results obtained make it possible to choose a correct and differentiated approach to the diagnosis and treatment of various menstrual disorders.

Conclusions.

Using genetic analysis, it was found that the minor allele (T) of the rs726547 polymorphism was found 2 times more often in group 1B (26.4%) than in the control group (12.9%), which indicates the presence of a statistically significant relationship between menstrual disorders of hypermenstrual type and polymorphism rs726547 in the Uzbek population. An interesting fact is that when dividing the patients into two groups

depending on the type of menstrual disorder (hypomenstrual and hypermenstrual, respectively), we found no statistically significant difference in the frequency of the minor allele in the first subgroup.

Compared with the control group with the homozygous genotype of the non-wild and heterozygous genotype, it was found that the minor allele (T) was found in this group 2.8 times more often (35.9%). The prevalence of CT and TT genotypes was 2.3 times (45.9%) and 4.5 times (13%) higher than in the control group.

In terms of the pathological significance of these polymorphism alleles, the wild-type allele and wild-type homozygous genotype (CC) reduced the risk of menstrual disorders by 56% and 64%, while the minor allele, heterozygous and homozygous wild-type genotypes reduced the risk of this disorder by 2.25 , 2.19 and 2.19, respectively, and were statistically significant ($CG2>3.84$; $p<0.05$).

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