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GENETIC ASPECTS OF PELVIC ORGAN PROLAPSE

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Summary. The article is devoted to the genetic study of predisposition to pelvic organ prolapse. The genetically determined activity of a number of phase II enzymes of the detoxification system is one of the endogenous pathogenetic conditions that contribute to the formation and progression of pelvic organ prolapse.

Key words: pelvic organ prolapse, matrix metalloproteinase-9, matrix metalloproteinase-12.Актуальность.

Relevance. Protecting the health of women, mothers and children is a priority area of scientific research in the Republic of Uzbekistan. Achieving priority is possible by providing quality medical services and improving the quality of life of women of various age groups. Improving the quality of life of women is one of the most important tasks of modern medicine and practical healthcare. Pelvic organ prolapse (POP) has a significant impact on reducing the quality of life of women. This pathology represents one of the important problems of modern gynecology.

PPO is a hidden pandemic, affecting millions of women around the world; its frequency does not tend to decrease and varies from 20 to 78% in the structure of gynecological diseases [1,3,25,26]. The widespread prevalence of pelvic floor insufficiency indicates its medical, as well as socio-economic significance. VET affects the development of psychological disorders and changes in the sexual function of women [2,3,5,23,24,25]. A high (80%) frequency of genital prolapse among women of older age groups has been proven, as well as a tendency towards rejuvenation of this pathology and an increase in its proportion (from 10% to 50%) among women of reproductive age [3,4,18,19,20,21,22]. In recent years, many countries around the world have seen an increase in life expectancy, which is the reason for the increase in the number of perimenopausal women. It is known that during this period certain changes in organs and systems occur in women's bodies. Pelvic organ prolapse (POP) is still a serious problem in modern medicine, despite many studies of risk factors, etiology, pathogenesis, attempts to create diagnostic criteria and several hundred types of operations, including high-tech techniques [1, 2,27]. Pelvic organ prolapse occurs among women of different ages: in 20-39 years old - in 19.7-50.3% of patients, and in the older cohort of 5079-year-olds, somewhat more often (41-77.2%) [3,7,8,9,10,11]. It is believed that the prevalence of POP in the female population over 50 years of age is about 60% [4,12,13,14,15,16,17].

If we turn to proven risk factors for POP, they include age, menopause, obesity, ethnicity, family history, pregnancy and vaginal birth, especially complicated by perineal trauma [3, 5, 6]. It is logical to assume that PTO that has a confirmed stage (according to any classification, from ICD to POP-Q) begins at a young age, and then, slowly progressing, manifests itself after many years, and sometimes decades. That is why modern researchers are paying more and more attention to the failure of the pelvic floor, which we consider the prodrome of POP.

This, at first glance, harmonious picture is disturbed by numerous contraversions about the early manifestation and development of prolapse in young patients or the formation of the disease in

nulliparous women and, on the contrary, the normal topography of the pelvic organs in multiparous and even multiparous women [1,5, 6]. Over the past two decades, this discrepancy has been commonly explained by the syndrome of systemic hereditary connective tissue dysplasia (SCT) [7]. However, despite attempts, convincing morphological and genetic criteria for undifferentiated DST in the vast majority of women suffering from POP have still not been found. Research is scattered and inconclusive [8].

Nevertheless, the search for genetic determinants not so much of PTO itself, but rather the rate of its development, which, on the one hand, would explain these discrepancies, and on the other hand, would help clarify many pathogenetic aspects of the disease, seems to be an extremely important area of perineological research.

The main dynamic load to maintain the pelvic organs in the correct position falls on the muscular layer of the pelvic floor. However, an important role in the process of maintaining normal topographic relationships in the body is indeed played by connective tissue, represented mainly by collagen fibers. Type 1 collagen, being the strongest, is the main collagen of the ligamentous apparatus. Collagen types 3 and 4 are the basis of the extracellular matrix. According to current studies, in women with POP, collagen types 3 and 4 predominate, and the content of collagen type 1 is lower than in women with a normal pelvic floor [2,9]. To maintain collagen fibrils in tissues, normal expression of a number of genes encoding the biosynthesis of collagen chains is required. Changes affecting collagen destruction may worsen or accelerate the clinical course of genital prolapse [1,3].

We believe that a more detailed, comprehensive search for genetic markers of severe stages of POP can become an important part of predicting the disease, identifying risk groups, and choosing tactics for managing patients with the initial stages of POP.

The purpose of the study is to determine the genetic cause of various stages of pelvic organ prolapse in women.

Material and methods. The study was carried out on the basis of the gynecology department of the perinatal center and in the Carmen and Lorastom clinics of the Bukhara region from September 2017 to July 2023. According to the purpose of the study, 66 patients from 25 to 82 years old with a history of 1 to 7 births suffering from various forms of apical prolapse. There were no isolated forms of anterior PTO in the studied cohort. All patients were examined by general clinical methods, with special attention paid to studying the condition of the pelvic floor. All patients were assessed for general and gynecological status using bimanual, manometric (perineometry), sonographic examination and vaginal palpation with determination of perineal muscle strength according to the Oxford scale.

Based on verified clinical data, 3 groups of patients with diagnoses corresponding to ICD-10 were created: 1st group - prolapse of the vaginal walls with the formation of cysto- and/or rectocele; 2nd group - incomplete uterine prolapse; Group 3 - complete uterine prolapse.

Amplification of the MMP12, TIMP and MMP-9 genes was carried out by allele-specific polymerase chain reaction (PCR) using SNP-express reagent kits in accordance with the manufacturer's protocol. Total DNA was isolated from the venous blood of 66 patients.

Results. We studied the polymorphism of genes considered the most likely markers of PTO, namely the matrix metalloproteinase genes (MMP9 and MMP12). MMP9 is a protease that is associated with the degradation of collagen and elastin in the extracellular matrix. An increased concentration of MMP9 leads to disruption of elastogenesis and disrupts the development of normal elastic fibers [1,2]. In each group of patients, the ratio of the homozygous normal type of the MMP9 gene AA prevailed over the mutant GG. Noteworthy is the statistically insignificant but actual 2-fold increase in the number of patients with the homozygous mutant MMP9 genotype in the group with complete uterine

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prolapse in comparison with the incomplete variant of apical prolapse. When comparing the frequency of occurrence of recessive homozygotes between women from groups 3 and 1, this difference is even more pronounced, but is still not statistically significant in a small sample. This allows us to conclude that the recessive variant of the MMP9 gene polymorphism is not associated with the development of POP in patients, but may contribute to a more severe clinical course of prolapse. Undoubtedly, to clarify these circumstances, a larger sample of patients is required.

MMP12 is a macrophage metalloproteinase capable of hydrolyzing various proteins, including elastin and type 4 collagen. Increased expression of MMP12 leads to impaired elastic fiber strength [1,3]. When analyzing the polymorphism of the MMP12 gene, attention is drawn to the absence of homozygous mutant genes (GG) in the studied sample of patients with POP, but also to the predominance of the homozygous normal type of polymorphism (AA) in the 1st and 3rd groups of patients. The heterozygous genotype (AG) of the MMP12 gene was found 2 times more often in the group of patients with incomplete uterine prolapse than with a more severe form of prolapse. This allows us to conclude that carriage of the recessive allele G may play some protective role, slowing down the development of degradation of connective tissue structures during prolapse. Of course, with an increase in sample size, these results can be adjusted.

Thus, the total vector of forces influencing the human pelvic organs and contributing to their decline consists of a relatively constant force of gravity and an amplitude-changing force of intra-abdominal pressure. It is possible to resist the pushing of the pelvic organs through the lower aperture of the small pelvis only through the combined and interconnected action of several anatomical devices. The pelvic organs are held in the correct position by complementary structures: suspensory, fixing ligaments, the fascial apparatus of the pelvis and the musculofascial complex of the pelvic floor. Together, normally, they successfully resist buoyant forces, and a pelvic floor hernia does not form. If any of the listed devices is disrupted, others can compensate for this deficiency for some time, but with decompensatory degradation of the retaining structures, prolapse is inevitable. The duration of this subcompensatory stage, essentially the prodrome of POP, is largely determined by the structural, protein characteristics of the tissues and the biochemical characteristics of the restoration and degradation of these structures. This means that the search for genetic determinants not only of prolapse itself, but of the speed of its development, the duration of the prodromal stage of the disease is not only possible, but also necessary. Moreover, this is the only way to get closer to reliable prediction, high-quality prevention and effective timely treatment of POP in the full range of measures - from physiotherapeutic to surgical interventions. The gene polymorphisms we studied were not chosen by chance: they reflect the structural and functional characteristics of the muscular (ACTN3) and connective tissue (MMP9, MMP12) compartments of the pelvic floor, as well as some compensatory mechanisms in response to ischemia. The predominance of the normal variant of polymorphism when studying these genes in our study indicates the absence of obvious genetic determinants of the development of PTO. This is not surprising; POP is not a hereditary disease, but it may have a hereditary component in nulliparous women [1,6].

However, attention is drawn to the fact that the proportion of the mutant allele of the MMP9 gene increases in patients with severe forms of POP, and, conversely, the absence of recessive homozygotes GG of the MMP12 gene in the studied sample. These coding features of metalloproteinases involved in connective tissue remodeling probably influence not only the risk of prolapse itself (the risk should decrease when carrying the GG gene MMP12), but also the risk of developing its severe forms (the risk of severe forms should increase when carrying the GG gene MMP9 gene).

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Despite the optimistic data regarding the search for genetic determinants of both POP itself and its severe stages, it should still be noted that there are no statistically significant differences between the studied groups. There may be several reasons for this. First, there is a small sample of women with POP. Secondly, diagnoses coded in the ICD as different nosological units are actually stages of the same process. This means that for further research it is necessary not only to expand the scope of the studies conducted, but also to use comparison groups in women who have a comparable history, but do not suffer from pelvic organ decline and NTD.

In the PTO group compared to the control group, the phenotype was significantly more common slow acetylation. Thus, the frequency of "medof acetylators was almost 2 times higher than that in a population sample. Absence significant difference in the frequencies of "fast" and "slow acetylators" between subgroups VET, as well as the tendency we noted towards prepossession of "slow acetylators" in POP. Stage I obviously suggests the significance of genetic "slow" N-acetylation type for early them stages of the disease formation process. There is evidence in the literature about the role N-acetyltransferase 2 in the development of gynecological skaya pathology. The high activity of this enzyme it is associated with uterine fibroids, adhesive disease new, the development of urogenital disorders [3, 10, 13]. The results of this study suggest ut that the constitutionally determined ac. The activity of the NAT2 enzyme may also be important in pathogenesis of PTO.

Also, analysis of the combination of genotypes revealed most often a combination of "slow" genetype NAT2 with double "null" genotype gene new GST T1 and GST M1 for severe stages of POP compared with that in patients with PTO initialny stages.

Conclusion. We believe that a closer look at the genetic predisposition to POP and its severe forms will help stratify women into risk groups and contribute to the concept of prognosis for this disease. This means that it will be possible to solve the problems of developing preventive measures, reducing the need for large volumes of surgical intervention and reducing the number of relapses of POP.

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