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Review Article

Markers of Connective Tissue Dysfunction in the Aspect of Surgical Treatment of Pelvic Organ Prolapse

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Abstract

Pelvic organ prolapse (POP) is a serious and relevant urogynecological problem. According to modern data, about 47% of women of working age suffer from this condition [1]. Due to the lack of established criteria for choosing a surgical correction method, recurrence of pelvic organ prolapse and stress urinary incontinence after pelvic floor surgery with native tissue repair vary between 30 - 58% [2] and with mesh implants - 6,9% [3]. Choosing a method of surgical treatment, it is necessary to take into account medical history, clinical, instrumental, genetic, biochemical, morphological and immunohistochemical examinations. Combination of various methods is used to identify pelvic organ prolapse markers in each clinical case. The choice of surgical treatment is made after obtaining results on the state of the pelvic floor.

Keywords: *Markers; Gene Expression; Pelvic Organ Prolapse; Predictors*

Introduction

Pelvic organ prolapse (VET) is a serious and relevant urogynecological problem. According to current data, about 47% of women of working age suffer from this disease [1]. Due to the lack of uniform criteria for choosing the method of surgical correction, recurrence of VET after pelvic floor surgery with own tissues reaches a significant 30 - 58% [2] and with the use of mesh implants (SI) - 6.9% [3].

One of the main causes of VET is generally recognized connective tissue dysplasia (DST) [4]. This pathology means a systemic defect in the fibrous structures and the main substance of the connective tissue (CT), as a result of which there is a violation of the supporting and fixing functions of the ligamentous apparatus. Faced with VET, requiring surgical correction, the doctor raises the question of choosing a treatment method. At the present stage, surgical treatment is the leading method for this pathology. There are more than 300 types of surgical interventions to correct pelvic floor pathology. These include various plastic surgeries using their own tissues [5]. According to some authors, the number of relapses after anterior colporography reaches 31%, after a posterior - 35% [6]. This is due to the progradient course of the DST. With such a pathogenetic mechanism of the formation of VET, of course, there is a need to use synthetic implants. At the same time, when they are used, there is a risk of developing implant-associated complications, namely: erosion of the vaginal mucosa above the mesh, displacement of the synthetic implant, the appearance of pain, dyspareunia, and again, the possibility of relapse and the

occurrence of PTV de novo cannot be ruled out [7]. In this regard, an acute question arises about the choice of tactics for surgical treatment of VET, which will depend on the morphological and functional state of the CT. Various markers can be used to determine it.

Markers that indicate the possibility of developing VET can include: anatomical and physiological data, the state of muscle tone of the pelvic floor, comorbid pathology, various substances that indicate disorganization of connective tissue, the level of expression of certain genes that are determined both in peripheral blood and in tissues, affecting the condition of the pelvic floor and others. They are usually divided according to the method of obtaining the source material for analysis, into invasive and non-invasive.

Non-invasive include general clinical and anatomophysiological data, which are potential predictors of the development of VET. When examining and collecting the patient's history, it is important to pay attention to such aspects as occupational hazards associated with physical exertion, high parity, concomitant connective tissue diseases: heart valve prolapse, osteoarthritis, habitual dislocations, hernias of the anterior abdominal wall, hernia of the esophageal opening of the diaphragm, protrusion of the intervertebral disk, etc [8]. One study showed that striae can be a marker for determining pelvic floor weakness. In patients with the presence of PTO, striae were several times more common than in the control group [9].

Invasive diagnostic methods include a technique that can predict the development of VET by the pressure gradient of the muscles of the pelvic floor on the tactile imaging sensor [10]. In studies, it was shown that in women with VET, the pressure gradient measured by the sensor is 2 - 4 times less than in the control group. In addition, an active dynamic change in muscle tone was measured and described [10]. Based on the data on the state of muscle tone in different areas, biomechanical mapping of the muscles of the pelvic floor can be performed [11], which accordingly gives an idea of the supporting physiological function of the muscle apparatus. An indisputable advantage of this method is its minimally invasiveness and the possibility of screening.

Do not forget about classical methods that allow you to assess the number and severity of defects, the level of pathology of muscular-fascial structures. These include a comprehensive urodynamic study (CUD) [12], proctography [13], vaginotensometry [14]. Markers defined in peripheral blood and urine are of the greatest importance. One of these for VET is oxyproline (hydroxyproline). Oxyproline is one of the main amino acids of collagen, which allows us to consider it a marker that reflects the catabolism of this protein. This predictor is determined both in urine and in peripheral blood and is closely associated with PTO [15,16]. An increase in the blood oxyproline content during VET with a high degree of probability correlates with the results obtained during the immunohistochemical study of tissues and corresponds to the clinical manifestations of pelvic floor failure [15]. However, the level of this marker can increase with other pathologies, such as osteoporosis, collagenoses, autoimmune diseases [15], which makes its diagnostic significance less significant. Deoxypyridinoline (DPID) is another predictor that is detected in the urine and indicates disorganization of CT [16]. Type III procollagen N-terminal propeptide may be a potential marker. In the study of V.V. Pareishvili., *et al*. (2018) it was demonstrated that in women, indices of this marker could determine undifferentiated DST. The study involved pregnant women at gestational age 22 - 36 weeks. The accuracy of the method was 91%, specificity 95%, and sensitivity 88% [17].

More promising is the determination of the expression activity of various genes. These include MMP1 MMP3 and MMP9. Studies have shown a correlation between the expression levels of MMP1, MMP3 and PTO [18]. There is conflicting data regarding MMP9. In a recent study performed by Brazilian scientists, it was shown that no statistically significant differences in C-1562T MMP9 polymorphisms between patients from the study group and control were found [19]. The activity of the NAT2 gene can also serve as a marker. The results after surgical treatment of VET were analyzed. The relapse rate in women with a point mutation of the NAT2 gene was more than 2 times higher than in the effective treatment group [20], which indicates the involvement of this gene in the etiopathogenesis of pelvic floor failure. In addition, a connection was established between the rs1800012 polymorphism of the COL1A1 gene and stress urinary incontinence and prolapse [21]. Another study conducted at the Department of Obstetrics and Gynecology RNIMU them. N.I. Pirogov demonstrated the connection of the 9q21 gene with the etiology of PTO [22]. Researchers from China have identified a new gene, WNK1, which can be

involved in the development of prolapse. After studying the data, they believe that this marker can be used for genetic screening and early diagnosis of the so-called pelvic floor weakness [23].

The substrate for the analysis of the activity of all these genes is peripheral blood, which is a relatively readily available substrate for analysis, which makes diagnosis, to a greater extent, simple and quick. For many studies, the substrate was the sacro-uterine ligaments [25-30,34,35] and with rare exceptions, the analysis was carried out in a biopsy specimen of the vaginal wall [31-33]. Often, it is the sacro-uterine ligaments that are involved in the pathogenesis of pelvic floor weakness syndrome, which has led to the identification of disorders associated with the disorganization of connective tissue in these structures [24]. However, this does not mean that only these structures are involved in the pathogenesis of the disease.

Before moving on to the markers themselves, mention should be made of such a concept as oxidative stress. This pathological physiological process is involved in the pathogenesis of VET, contributes to metabolic disorders in the extracellular matrix, and is believed to be associated with MMPs, TIMP, and TGF-β1, albeit perhaps indirectly [25]. In addition, hypoxia and oxidative stress can reduce protein synthesis in the muscles of the pelvic floor, which can contribute to muscle atrophy. Hypoxia-induced factor-1α (HIF-1α) is an activator for a number of genes involved in the cellular response to hypoxia. Many of these genes can be peculiar predictors of prolapse [26]. Some markers identified in the sacro-uterine ligaments were directly related to the process of oxidative stress. These include: 8-OHdG (8-hydroxydesoxyguanosine) and 4-HNE (4-hydroxynonenal) [27], Mitofusin 2 [28]. All of these predictors were determined using PCR. In addition, work was noted on the determination of other markers associated with PTO, the substrate was also the sacro-uterine ligaments, and PCR was also used for identification, these include: GPx1 (type 1 glutathione peroxidase) [29], the level of electron transfer flavoproteins, apolipoprotein AI, actin, transgeline, cofilin-1, cyclophilin A, myosin and galectin-1 [30].

As a biopsy, vaginal tissues can also act, in which various predictors can be determined. In studies, the connection of prolapse with the following markers was proved: IFN-γ, IFNGR1 and IFNGR2 (diagnostic method - PCR) [31], expression of collagen type I and type III, PDGF (platelet growth factor), MMP3 (diagnostic method - IHC) [32], the level of HIF-1α in stromal cells of the vaginal tissue (diagnostic method - IHC) [33]. However, the sacro-uterine ligaments were also determined to determine the level of HIF-1α, where the relationship of this predictor with the etiology of PTO was again proved [34]. In addition, the relationship of certain loci on chromosomes 10q and 17q with PTO was revealed [35]. In this case, the study of the human genome is one of the most accurate methods, which makes it possible to early predict the development of the disease. Its introduction into the diagnosis could help to identify a predisposition to prolapse at an earlier age.

Conclusion

When choosing a method of surgical treatment, the data of examination, medical history, instrumental, genetic, biochemical, morphological and IHC examinations should be taken into account. In each individual clinical case, different techniques can be used to identify PTO markers. After obtaining results on the morphofunctional state of the pelvic floor, a choice arises about the tactics of surgical management of patients. If there are risk factors and predictors of DST are identified, then it is better to think about the use of synthetic implants. In a different situation, when the patient's state of CT is normal and there are no markers described above, it is more advisable to resort to plastic surgery with my own tissues, supplemented by physiotherapy or volume-forming fillers in order to avoid implant-associated complications or relapse. Thus, the determination of markers characterizing CT dysfunction can significantly affect the choice of surgical treatment tactics, on which the method of surgical intervention will depend.

Conflict of Interest

There is no conflict of interest.

Transparency of Financial Activity

The authors have no financial interest in the materials and methods presented.

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