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THE IMPORTANCE OF CONNECTIVE TISSUE DYSPLASIA IN PATHOLOGICAL CONDITIONS IN OBSTETRICS AND GYNAECOLOGY

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Abstract

A review of the literature on the problem of connective tissue dysplasia in obstetrics and gynecology is presented. Questions of terminology, classification, clinical manifestations are covered. Currently, many experts note a change in the classical clinical course of significant number of somatic diseases, an increase in the frequency of allergic and autoimmune diseases. Since the 90s years of the last century, one of the main causes of the above-mentioned conditions began to be considered connective tissue dysplasia. Connective tissue dysplasia is an anomaly in the development of the human body, which lies at the basis of the formation of a significant number of somatic diseases, with diverse symptoms and the absence of the clear diagnostic criteria. In recent years there have been works devoted to the study of connective tissue pathology in a number of gynecological diseases and conditions in obstetrics. The presence of connective tissue dysplasia in women is a big problem in obstetrics and gynecology. The obstetrician-gynecologist, when treating patients, should pay close attention to the phenotypic features of connective tissue dysplasia and carefully assess the state of the cardiovascular and pulmonary systems, the blood coagulation system in this group of patients to shun possible severe, often life-threatening complications.

Key words: connective tissue dysplasia, preterm birth, miscarriages, pelvic organ prolapse, urinary incontinence.

AKUSHERLIK VA GINEKOLOGIYADA BIRIKTIRUVCHI TO'QIMA DISPLAZIYASING AHAMIYATI

Referat

Biriktiruvchi to'qima displaziyasining akusherlik va ginekologiya amaliyotidagi ahamiyati haqida adabiyotlar sharhi keltirilgan. Bu sharhda atamalar izohi, kasallikning klassifikatsiyasi, klinik kechishi yoritilgan. Hozirgi vaqtda ko'plab mutaxassislar kasalliklar klassik klinik kechishining o'zgarishi va yildan yilga autoimmun hamda allergik kasalliklar uchrash chastotasining ortib borayotganligini ta'kidlamoqdalar. O'tgan asrning 90-yillaridan boshlab mutaxassislar bu o'zgarishlarni biriktiruvchi to'qima displaziyasi bilan bog'lay boshlashdi. So'nggi yillarda

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biriktiruvchi to’qima displaziyasining akusherlik va ginekologiyada uchrovchi ba’zi patologik holatlardagi ahamiyatiga bog’liq ilmiy ishlar paydo bo’la boshladi. Biriktiruvchi to’qima displaziyasi akusherlik va ginekologiya sohasida katta muammolarga sabab bo’ladi. Akusher-ginekologlar bemorlarni olib borishda biriktiruvchi to’qima displaziyasining fenotipik belgilariga katta e’tibor berishlari va yuzaga kelishi mumkin bo’lgan hayotga xavf soluvchi asoratlarning oldini olish maqsadida bu guruhdagi ayollarda yurak-qon tomir, nafas olish, qon ivish tizimi holatiga to’g’ri baho berishlari lozim.
Kalit so’zlar: biriktiruvchi to’qima displaziyasi, muddatdan oldingi tug’ruq, homila tushish xavfi, genitaliy prolapsi, siydik tuta olmaslik.

РОЛЬ ДИСПЛАЗИИ СОЕДИНИТЕЛЬНОЙ ТКАНИ В ПАТОЛОГИЧЕСКИХ СОСТОЯНИИИЯХ В АКУШЕРСТВЕ И ГИНЕКОЛОГИИ.

Реферат

Данный обзор литературы освещает роль дисплазии соединительной ткани (ДСТ) в развитии акушерско-гинекологических патологий. В статье освещены вопросы терминологии, классификации, клинических проявлений и диагностики. По мнению многих учёных в настоящее время изменяется классическое клиническое течение болезней и число аллергических и аутоиммунных заболеваний растёт. С 90-годов учёные начали связывать эту ситуацию с ДСТ. В основе формирования значительного числа соматических заболеваний лежит ДСТ, чем объясняется многообразная симптоматика и отсутствуют чёткие диагностические критерии. В последние годы появились работы, посвящённые изучению патологии соединительной ткани при ряде гинекологических заболеваний и состояний в акушерстве. Наличие ДСТ у женщин могли быть причиной многих осложнений в акушерстве и гинекологии. Практикующие акушер-гинекологи должны обращать внимание на фенотипические признаки ДСТ при патологии сердечно-сосудистых, дыхательных систем и системы свёртывания крови, так как наличие ДСТ может привести к угрожающим жизни состояния.

Ключевые слова: дисплазия соединительной ткани, преждевременные роди, угроза прерывания беременности, пролапс тазовых органов, недержание мочи.

Connective tissue dysplasia: definition and prevalence

In recent decades, research in various fields has been presented in the medical literature dedicated to the problem of connective tissue dysplasia (CTD). CTD determined as a group of inherited or congenital disorders of the connective tissue of multifactorial nature, characterized by genetic heterogeneity and a relatively benign

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course, combined into syndromes and phenotypes based on common external and/or visceral signs [13].

In recent decades, there have been works dedicated to connective tissue pathology in gynecological diseases and conditions in obstetrics [16]. Obstetrician-gynecologists give attention to the problem of CTD as one of the causes of prolapse of the genital organs and related methods of surgical treatment [19, 20]. In recent years, the number of supporters of the hypothesis about the development of genital prolapse in connection not only with childbirth, but also with its phenotypic conditionality have increased [14, 33].

In the late 1980s R. Beighton proposed the concept of "connective tissue dysplasia" to denote congenital connective tissue pathology. Translated from Greek "dysplasia" means "deviation information" [15]. However, despite the attention to the problem of CTD, there is still no consensus on the classification and terminology of this pathological status, as well as accurate data on the prevalence of CTD. At the moment, the term "connective tissue dysplasia" means anomaly of the tissue structure due to gene or chromosomal defects resulting from a certain type inheritance or mutagenic influences in the fetal period [18]. This pathology is characterized by defects in fibrous structures and basic substance of connective tissue, leads to weakness of the connective tissue, disorder of homeostasis in the tissue, organ and organism levels in the form of morphofunctional disorders of various visceral and locomotor organs, and has a progressive flow.

In some works, the frequency of CTD from 13 to 65% in the general population, and the presence of single phenotypic traits in 94% of young people [15]. In the studies of other authors signs of CTD are observed in 74–85% of adolescents [12]. Other studies indicate a small prevalence of CTD is up to 25%, with the largest proportion being women [15]. This difference is due to the lack of a unified approach to the diagnosis of CTD. In abroad there are also recommendations for diagnosis of individual syndromes, which are also used in our country.

– Berlin nosology of hereditary connective tissue disorders (1988) [28].

- International recommendations for the diagnosis of Marfan syndrome - "Ghent criteria" (1996) [30].

– International recommendations for the diagnosis of Ehlers-Danlos syndrome, "Villefranche criteria" (1998) [29].

– International recommendations for the diagnosis of joint hypermobility syndrome – Brighton Criteria (1998) followed by their revision (2000) [28].

– Guidelines for the treatment of patients with valvular heart disease (2006) [26].

Classification

The place of CTD is not defined even in the latest International Classification of Diseases (ICD-10, syndromes are reflected in various headings), and the CTD

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classification is one of the most controversial scientific questions. According to the classification, most recognized by foreign clinicians, adopted in1990 in Omsk, there are two forms of CTD [17]:

- differentiated CTD, which have certain clinical symptoms due to well-studied specific gene or biochemical defects (syndrome Marfan, Ehlers-Danlos syndrome, etc.);

- undifferentiated CTD (NCTD), which are manifested by external phenotypic signs of CTD, but do not fit into any known syndromes of connective tissue pathology; most authors believe that UCTD are the most common and occur in the general population with a frequency of 26 to 80% [2].

A classification with a post-syndrome approach:

- Syndrome of neurological disorders;
- asthenic syndrome;
- valvular syndrome (valve prolapse) heart, myxomatous valve degeneration);
- thoracodiaphragmatic syndrome (deformation of the chest, spine);
- arrhythmic syndrome (rhythm disturbances, atrioventricular and intraventricular blockade);
- sudden death syndrome;
- bronchopulmonary syndrome;
- syndrome of immunological disorders;
- visceral syndrome;
- syndrome of pathology of the organs of vision;
- hemorrhagic hepatomesenchymal dysplasia;
- joint hypermobility syndrome;
- disorders of the mental sphere (neurotic disorders, depression, anxiety, etc.).

The role of hereditary disorders of the connective tissue in obstetrics and gynecology

It is known that CTD underlies increased bleeding, hemoglobinopathy, thrombocytopathy, which can lead to juvenile uterine bleeding. Most patients with CTD have dysfibrinogenemia, development of secondary von Willebrand syndrome, various variants of thrombocytopathy - from a decreased platelet aggregation to endothelial platelet dysfunction. Factor Va resistance to activated protein C, hyperhomocysteinemia, the presence of lupus anticoagulant are identified often in patients with CTD[29]. All of the above may also cause a high risk of developing thromboembolic complications [6].

In the reproductive period, CTD causes menstrual and reproductive disorders (dysfunctional uterine bleeding, infertility, amenorrhea, isthmic-cervical insufficiency, etc.) [21]. There are many researches devoted to the CTD as a risk factor for adhesions in the pelvis [6, 10, 11]. CTD can cause complications during the pregnancy and

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childbirth (miscarriage, higher frequency of preeclampsia, preterm birth, placenta previa, anomalies of labor activity, hypotonic bleeding, more frequent birth trauma - ruptures of the perineum, vagina).

Extragenital manifestations of CTD can be the cause of severe complications and even deaths during or after gynecological and obstetric operations [31]. Insufficient attention to extragenital manifestations of CTD in obstetrics and gynecology can have catastrophic consequences.

It was noted that in patients with hereditary CTD often develops inferiority of the scar after caesarean section as a result of progressive disorganization of the connective tissue (up to fibrinoid necrosis) with a violation of the content of laminin and type 4 collagen[22]. Also in women in reproductive age with UCTD is often can be found varicose veins of pelvic, genital prolapse, various forms of urination disorders (incontinence urine, frequent urination, difficulty of urination, imperative urge) [1]. The opinions of scientists regarding CTD and urinary incontinence are divided, and each has quite a lot of supporters and opponents. So, V.E. Radzinsky, V.I. Krasnopolsky, S.N. Buyanova et al. believe that urination disorders are directly related to the state of the pelvic floor and prolapse of the genital organs [19].

Many other authors disagree with this and consider urinary incontinence as an independent pathological process [27]. As evidence, the prevalence of various forms of urinary incontinence among the women who have not given birth does not differ from the general population. A number of researchers revealed that these functional disorders are not based on damage pelvic diaphragm, and neurogenic dysfunction vesicourethral segment and pelvic diaphragm [5].

Most researchers consider that the most common manifestation of UCTD in gynecology is genital prolapse [9]. Today, there is an opinion that pathological changes in the connective tissue contribute to the development of pelvic organ prolapse, and without CTD, there are no significant changes in the pelvic floor after childbirth [3]. According to Allen-Brady (2009), genes that predetermine pelvic floor disorders localized on chromosome 9q [27]. T.Yu. Smolnova also showed that the form of CTD determines the form of genital prolapse and disruption of the structures of the pelvic complex [20].

Etiology and pathogenesis

The main component of the connective tissues serve as collagen fibers. It is known that collagen synthesis includes several stages, each of which requires the presence of various enzymes, macro- and microelements, and vitamins [8, 36]. Modern achievements in molecular biology have made it possible to identify the mechanisms of development CTD, in particular, three levels of pathology development [7]:

– gene level;

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- protein-enzymatic level - imbalance of enzymatic and protein metabolism, for which are characterized by increased activity proteases (metalloproteinases, lysyl oxidases, transglutaminase);

– violations at the nanolevel – imbalance micro and macro elements.

Genes related to a particular proteoglycan are classified according to their glucosaminoglycan chains. Major gene types include chondroitin sulfate proteoglycan (genes CSPG1, CSPG2, etc.) and heparan sulfate proteoglycan (perlecan, gene HSPG2). The development of hereditary CTD is based on mutations in the genes responsible for the synthesis or breakdown of extracellular components connective tissue matrix. There is a large group of monogenic CTD associated with mutation of extracellular matrix protein genes (various types of collagen, fibrillin, tenascin), growth factor receptor genes, in particular transforming growth factor β and matrix metalloproteinases. Mutations of these genes lead to the development of many variants CTD, the number of which today is >250 [15].

Important connective tissue proteins are also decorin (DCN gene) and lumican (LUM gene), which limit the diameter of collagen fibers.

More recently, it has been revealed that the “null genotype” of the xenobiotic detoxification system gene GST T1 is associated with the development of CTD [2]. Collagen is an important extracellular protein matrix and connective tissue. In humans about 50 genes encoding various types of collagen and forming 19 types of collagen fibers have been identified.

There are five main types of collagen fibers [24].

– Collagen type I – collagen of the skin, tendons, bones, cartilage, scars (genes COL1A1, COL1A2). Without this type of collagen, normal wound healing is impossible.

– Type II collagen (COL2A1 gene) – the main cartilage component.

– Collagen type III (COL3A1 gene) – forms reticular fibers, supports the extracellular matrix.

– Collagen type IV – forms the basal membranes to which the epithelium is attached (genes COL4A1, COL4A2, COL4A3, etc.).

– Collagen type V is a component of the wall of blood vessels.

Elastin is the main component of elastin fibers that give elasticity extracellular matrix and connective tissue, is controlled by the ELA2A, ELA2B genes, ElA3B and others. The human genome also contains about 200 matrix metalloproteinases. They affect the synthesis and intensity of connective tissue degradation structure of the cell matrix. For each proteinase is a specific inhibitor encoded by a specific gene. Balance between proteases and proteins promotes cellular proliferation, renewal and remodeling fabrics. An imbalance in this delicate system of connective tissue formation can lead to CTD [29].

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In the formation of connective tissue, an important role is played by macro- and microelements, the leading of which are magnesium, copper and zinc [23]. They are cofactors of enzymes involved in the synthesis of collagen, therefore, the development of UCTD. Magnesium, in addition, promotes the absorption of calcium and phosphorus, normalizes the processes neuromuscular transmission and indirectly influences the formation of collagen through higher the autonomic center is the hypothalamus [4, 25]. Magnesium metabolism is regulated by a number of genes, among which TRPM6 and TRPM7 are especially important [32]. Magnesium is involved in the formation specific connective tissue proteins, forms the structure of transport ribonucleic acid. There is evidence in the literature that weakness of pelvic diaphragm in CTD may be associated with a change in Ca-actinomyosin metabolism.

Thus, CTD is a developmental anomaly of the human body, which underlies the formation of a significant number of somatic diseases, with a variety of symptoms and the absence of clear diagnostic criteria. The presence of CTD in women is a big problem in obstetrics and gynecology. The obstetrician-gynecologist, when managing patients, should pay close attention for phenotypic signs of CTD and carefully evaluate the state of the cardiovascular, pulmonary systems, as well as the blood coagulation system in this group of patients to exclude possible severe complications, often threatening life. It must be taken into account that the presence of CTD can be the cause of insolvency postoperative scar. It is relevant to carry out deep studies devoted to more accurate diagnosis of the degree of CTD based on clinical and laboratory parameters, which will allow to determine treatment tactics, including when planning surgical interventions, taking into account the individual characteristics of patients.

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