Volume 2, Issue 4, April - 2024 **ISSN(E):** 2938-3773

FEATURES OF THE COURSE OF PREGNANCY IN PATIENTS WITH CONNECTIVE TISSUE DYSPLASIA

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Abstract

The article is devoted to the problems associated with connective tissue dysplasia (CTD), predominantly undifferentiated forms of the disease (nDST). The relevance of the topic is due to the high prevalence of this pathological condition. The generalized nature of connective tissue damage with the involvement of the reproductive system in the pathological process significantly affects the course of pregnancy and Birth. Complications that may be associated with pregnancy, childbirth and the postpartum period in women with nDST and which cause a high need for surgical aids: amnio-, episio- and perineotomy, cesarean section are presented. Particular attention is paid to magnesium, which plays one of the determining roles in the complex biosynthesis of the extracellular matrix in the formation of connective tissue and in the morphofunctional state of fibroblasts. The methods used to detect connective tissue metabolism disorders (determination of the level of oxyproline and fibronectin in blood serum, pyrinx D and glucosaminoglycans in urine, etc.) are described. In view of the lack of reliable diagnostic (biochemical and genetic) criteria for nDST, special attention is paid to the need for an integrated approach to assessing the condition of patients using anamnesis data, the results of clinical, instrumental and laboratory examinations.

Keywords: connective tissue dysplasia, hemostasis, complications of pregnancy and childbirth, magnesium deficiency, endothelial dysfunction, markers of collagen breakdown, genital prolapse.

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Introduction

Considerable attention to the problem of connective tissue dysplasia (CTD) is associated with the wide prevalence of its individual manifestations in the population, which ranges from 26 to 80% [1, 2]. For example, the incidence of small undifferentiated forms is 68.8% [3, 4].

Various combinations of external and internal manifestations of DST cause a variety of connective tissue syndromes and non-syndromic forms [5–7].

DST is a nutritionally and genetically determined condition that develops as a result of impaired connective tissue metabolism in the embryonic and postnatal periods and is characterized by abnormalities in the structure of the components of the extracellular matrix (fibers and the main substance of the gel-like medium) with progressive morphofunctional changes in various systems and organs [8–13].

Depending on the etiology, differentiated and undifferentiated forms of DST are distinguished. Differentiated (syndromic) forms of DST include diseases of a monofactorial nature with an established gene defect, a known type of inheritance, and with a pronounced and well-defined clinical picture. Classic examples of syndromic forms of DST are Marfan and Ehlers-Danlos syndromes, osteogenesis imperfecta, and some other rare genetic syndromes [14–17].

Undifferentiated forms of DST (nDST) have a polygenic-multifactorial nature. That is, the causes of the development of this pathological process are polymorphisms or mutations of a large number of genes in various combinations, as well as the impact of various environmental factors. Clinical manifestations of dCST (scoliosis, severe flat feet, joint hypermobility, varicose veins, hemorrhoids, mitral valve prolapse, hernias, myopia, genital prolapse, etc.) do not fit into any of the known differentiated hereditary diseases, although sometimes the clinical picture may be similar [1, 5, 10, 18, 19]. However, despite the high prevalence of nDST in the population, its recognition rate does not exceed 2.4% [3, 5, 9].

Interestingly, the combination of individual features of dST is the basis for the diagnosis of DST, but a single feature may not be strictly specific to dysplasia [10, 20]. The generalized nature of connective tissue damage with the involvement of the reproductive system in the pathological process significantly affects the course of pregnancy and childbirth. However, this aspect of the problem of cSTT remains insufficiently studied [3, 9].

Control of collagen synthesis is carried out at all its stages and depends on specific enzymes (at different stages these are ascorbic acid, copper, calcium, iron, selenium, zinc, etc.) [1, 21]. It is known that magnesium plays one of the determining roles in the complex biosynthesis of the extracellular matrix in the formation of connective tissue and the morphofunctional state of fibroblasts [22, 23].

Magnesium is one of the main elements that participates in the provision of important biochemical and physiological processes in the human body, it takes part in energy, plastic and electrolyte metabolism, and stimulates many cellular processes [1, 22]. Physiologically, magnesium metabolism in the body is a prerequisite for human health [10, 24]. In 1994, the World Health Organization classified magnesium deficiency as a disease with its ICD-10 code: E 61.3. The diagnosis of magnesium deficiency is more common as a concomitant. In Russia, the prevalence of magnesium deficiency among the population ranges from 16 to 42% [25], i.e. it is one of the most common types of nutrient deficiency in the population, which, of course, cannot but affect the quality of pregnancy [26, 27].

For women of childbearing age, the need for magnesium, provided that its content is initially normal, is 280 mg/day, for women during pregnancy — 350 mg/day, during lactation — 390 mg/day [10]. A more precise daily requirement for magnesium for pregnant and lactating women is 10–15 mg per 1 kg of body weight and 5 mg per 1 kg of body weight for healthy adults [10].

Magnesium deficiency in pregnant women with DST exacerbates existing disorders of collagen synthesis and forms a vicious circle that worsens the course of pregnancy. In general, patients with DST, especially those with magnesium deficiency, have a significantly higher risk of complications during pregnancy and childbirth than in the general population [26, 27]. Deficiency of the above-mentioned vitamins and minerals can also cause pregnancy complications [2, 5].

Features of the course of pregnancy in patients with DST

DST is a condition associated with the risk of developing various obstetric complications [9, 28–30].

Connective tissue forms a supporting framework for all tissues and organs and has a shape-determining significance, so its condition has a significant impact on the course and outcome of pregnancy, among other things. It is known that preeclampsia is significantly more common in connective tissue pathology, which ranks 2nd–3rd in the structure of causes of maternal mortality and is the main cause of perinatal mortality and morbidity [3]. 12.5–21.9% of women with nDST have preterm birth [3, 31]. In this category of patients, abnormalities of labor are often observed, untimely outpouring of amniotic fluid, and primary weakness of contractions is more often developed [32, 33]. Premature rupture of amniotic fluid, in turn, significantly increases the risk of placental abruption and the development of infectious complications [26, 29, 33]. Bleeding in the postpartum and early postpartum periods occurs in 7–12.7% of parturient women with nDST [34], which may be caused by impaired contractile activity and changes in the vascular system. Changes in blood flow velocity and venous pressure in patients with nDST with visceral manifestations, especially in cardiovascular pathology, affect uteroplacental circulation and, ultimately, uterine contractile activity and fetal condition [35]. Also, in women with nDST, the incidence of birth injuries (perineal, vaginal, and cervical ruptures) reaches 21.7–26.8%, which is associated with a systemic defect of the connective tissue [3, 9]. In addition, patients with DST often have uterine scar failure [36].

These complications during pregnancy, childbirth and the postpartum period are the reason for the high need for surgical aids: amnio-, episio- and perineotomy, cesarean section [36].

DST plays an important role in the development of isthmic-cervical insufficiency. Some authors argue that with a low Varge index, the presence of phenotypic markers of DST, and an increase in the level of oxyproline in daily urine, the development of isthmic-cervical insufficiency can be predicted with a high probability [37, 38].

The more pronounced the manifestations of DST at the multi-organ level, the more often rapid and rapid labor occurs. In this case, pathological childbirth is a provoking factor that triggers the mechanism of genital prolapse formation, which progresses rapidly, is more difficult to surgically correct, and is characterized by a high recurrence rate in the postoperative period [4, 5]. The severity of genital prolapse and the timing of its occurrence are directly related to the severity of the clinical manifestations of nDST [4].

In women with nDST, fetal and newborn pathology, intrauterine growth retardation, chronic fetal hypoxia are more often registered, premature babies are born three times more often, and the percentage of sick newborns is higher. Congenital malformations (cryptorchidism, hip dysplasia) are more common in the morbidity of newborns from mothers with nDST. Babies are born with a lower birth weight and a low Apgar score [9, 29].

Both pregnancy and nDST adversely affect collagen metabolism. Deficiency of a number of micronutrients in pregnant women with nDST contributes to its aggravation. Magnesium is one of the main cofactors of connective tissue metabolism enzymes. Magnesium deficiency is known to contribute to the development of placental insufficiency with a 12-fold increase in the incidence of fetal growth retardation (odds ratio 12.6; 95% confidence interval 1.5–106; p=0.0015) [36].

Physiological pregnancy is characterized by an increase in coagulant potential and an almost twofold increase in the content of all coagulation factors against the background of a decrease in fibrinolytic and anticoagulant activity [39]. Trophoblast invasion and normal functioning of

the placenta are complex processes of endothelial-hemostasiological interactions with complex regulation. Disturbance of trophoblast invasion processes against the background of endothelial dysfunction syndrome does not lead to physiological reorganization of spiral arteries, and they remain sensitive to pathological changes in the hemodynamics of the maternal body. The progression of pregnancy in such conditions leads to impaired placental perfusion and subsequent complications, such as miscarriage, preeclampsia, placental insufficiency, premature abruption of the normally located placenta, and fetal growth retardation [29, 34, 36]. Probably, it is endothelial dysfunction that develops in pregnant women suffering from diabetes mellitus, chronic arterial hypertension, autoimmune diseases, and thrombophilias, which leads to impaired microcirculation in the placenta and prevents the normal course of pregnancy [7].

Generalized decrease in collagen content in tissues in pregnant women is often associated with inferiority of the vascular-platelet link of hemostasis, weakening of the ability of platelets to aggregate and impaired release reaction, platelet adhesion, clot retraction [40], and impaired coagulation hemostasis, characterized by a quantitative decrease in blood coagulation factors (VIII, IX) [40–42].

Thrombohemorrhagic syndrome in pregnancy in patients with nDST is characterized by scattered intravascular coagulation of the blood with the formation of many microclots of fibrin and aggregates of blood cells that block microcirculation in vital organs. However, shifts in the hemostatic potential of blood in patients with nDST also occur due to an imbalance of macro- and microelements, and an insufficient content of essential metals [40]. There is evidence in the literature that micro- and macronutrient deficiencies in pregnant women with nDST contribute to the disruption of the hemocoagulation cascade and uteroplacental blood flow [43].

Diagnosis of DST

There are clinical criteria for assessing the severity of DST [4]. Each symptom is scored in points, the number of points is summed up, and the severity of DST is determined. The sum of points up to 9 corresponds to mild severity (mild), from 10 to 16 - moderate severity (moderate), from 17 and above - severe (pronounced).

In older patients, it can be difficult to differentiate between involutive changes and manifestations of DST, since dysplastic signs after the age of 25 often reflect a genetically programmed process of connective tissue degradation [44]. Specialists have calculated coefficients for many external and internal signs of DST, which determine their importance in making a diagnosis. For example, the diagnostic coefficient for spinal scoliosis from adolescence is 13.53, for myopia — 5.74, etc. If the sum of the points when adding up the diagnostic coefficients of symptoms reaches the minimum threshold of 17, then this indicates with a probability of 95% that the patient has DST [2].

As mentioned above, despite the high prevalence of nDST in the population and the developed special diagnostic criteria [1, 2, 4] based on clinical manifestations, the recognition of this pathological process does not exceed 2.4% [3, 5, 9].

Due to the imperfection of methods for diagnosing DST, there is an obvious need for a biochemical study of the metabolism of structural components of connective tissue. For this purpose, metabolites of collagen breakdown are determined, which are actively used as

laboratory markers of osteoporosis, indicating the degree of bone tissue resorption. Based on the results of the research, we can indirectly judge the degree of severity of DST. In addition, biochemical techniques can be used in the course of dynamic observation to assess the effectiveness of measures taken to prevent connective tissue complications and to predict the course of the dysplastic process [5].

Of the protein components of the fibrous part of the connective tissue, *oxyproline is most often studied* in serum according to the method of R.E. Neuman and M.A. Logan, and in urine according to the method of L. Bergman and R. Loxley. Biomaterial sampling is carried out after following a restrictive diet for the previous three days [1, 2, 5].

The ratio of total and free oxyproline in daily urine can be used to judge the degree of connective tissue metabolism disorders. However, for diagnostic purposes, it is important that the intensity of oxyproline release significantly depends on the patient's age, time of day, and diet [1, 4]. The amount of oxyproline in the urine depends on the intake of collagen with food, so some authors suggest that this method of study should be carried out after a 12-hour fast, which, in their opinion, excludes the influence of food collagen on the examination result [9, 45, 46].

There is also evidence of a high correlation between increased serum oxyproline levels and the results of immunohistochemical examination of tissues, indicating pelvic floor muscle failure. In the course of the study, it was revealed that the determination of the level of oxyproline has low specificity and is not informative in itself. To improve the quality of nDST diagnosis, it is necessary to compare laboratory markers with clinical data [45, 46].

The content of C-terminal (carboxyterminal) and N-terminal (aminoterminal) telopeptides (breakdown products of type I collagen) *in blood serum is also of certain importance*. These are the non-spiralyzed ends of procollagen that are cleaved during collagen maturation [1, 4]. There is an inverse relationship between the amount of these telopeptides and collagen synthesis in the cell, i.e., the more telopeptides outside the cell, the less collagen synthesis [4]. Determination of the level of pyrilink D (DPID, deoxypyridinoline) in the urine, traditionally used as a marker of bone resorption, allows us to judge the destruction of type I collagen, the filaments of which are connected by pyridine ligaments: pyridinoline and deoxypyridinoline. The latter is excreted into the bloodstream and excreted unchanged in the urine, and its levels are not affected by food intake. Pyrinx D content is assessed in the morning urine portion [45, 46].

Catabolism of the intercellular substance of connective tissue can be judged by the amount of excretion of *glycosaminoglycans* (GAG) in daily urine. In patients with various clinical variants of connective tissue diseases, there is usually an increased excretion of GAG in the urine [2, 9].

To assess collagen metabolism, serum *fibronectin* levels can also be determined . Fibronectin is a high-molecular-weight glycoprotein that binds collagen fibers, GAG, fibrin, etc. [45, 46]. Fibronectin deficiency usually indicates impaired collagen synthesis, which is also observed in DST.

In order to detect *magnesium* deficiency, its level in peripheral blood, as well as in serum and blood plasma, is determined. Determination of magnesium content in blood plasma is currently considered to be more physiological compared to the determination of magnesium levels in

serum, as it interacts with plasma proteins. Based on the results of numerous studies, optimal levels of magnesium in blood plasma have been determined. which range from 0.80 to 0.85 mmol/L [10, 47]. Comparing plasma magnesium levels to serum magnesium levels is a diagnostic error. An actively developing area of modern clinical research is the establishment of reference values for magnesium levels in various blood biosubstrates [10, 45].

Magnesium can also be detected in daily urine. However, it should be noted that the content of magnesium in daily urine as a biomarker of its deficiency is characterized by a fairly wide variability [10]. In this regard, today the determination of the level of magnesium in the urine is mainly used to assess the saturation of the body's magnesium depot when taking magnesium-containing drugs and drugs that affect magnesium metabolism [10].

For early diagnosis of magnesium deficiency, its content in saliva is determined, which is normally 0.4–0.9 mmol/L. However, studies have found a correlation between the electrolyte composition of the consumed water and the content of magnesium ions in saliva, which affects the informative value of the results obtained [10, 48, 49].

In the literature, there is evidence of a statistically significant relationship between the concentration of matrix metalloproteinases (MMPs) in peripheral blood (MMP-1, MMP-9), magnesium levels, and the severity of varicose veins of the lower extremities. That is, according to the authors, the determination of the level of MMP and magnesium ions that characterize DST makes it possible to predict the development of chronic venous insufficiency of the lower extremities and assess its severity [50].

Prevention and treatment of DST

The management of patients with various manifestations of connective tissue dysplasia is currently being discussed by many specialists. The issues of supervision of patients with scoliosis, myopia, mitral valve prolapse, flat feet, and Marfan syndrome have been developed [2, 9]. However, there is still no unified program for the management of patients with multiple manifestations of DST.

There are treatment regimens and follow-up for patients with hereditary connective tissue diseases. Mandatory components of this observation are diet therapy, therapeutic exercises, massage, physiotherapy, psychotherapy, intake of vitamins, trace elements and metabolites [2, 3, 9]. The main purpose of these therapeutic measures is to stimulate collagen formation and correct disorders in the synthesis and catabolism of GAG.

The principles of diet therapy include the consumption of foods rich in protein, amino acids, individually selected dietary supplements containing essential amino acids, especially lysine, arginine, methionine, leucine, isoleucine and valine. In addition, foods enriched with macro- (calcium, phosphorus, magnesium) and microelements (copper, zinc, selenium, manganese, fluorine, vanadium, silicon, boron) are prescribed, which are cofactors of enzymes that activate collagen synthesis and are necessary for normal mineralization of the skeletal system [1–3, 9].

To normalize collagen synthesis, B vitamins are needed: B1, B2, B3, B6, which also normalize protein metabolism. Vitamins C and E, in addition to their positive effect on collagen synthesis, have antioxidant activity. Zinc is a component of the body's 200 metalloenzymes, it is necessary for the synthesis of RNA, DNA, insulin, growth hormone, testosterone, the metabolism of proteins and lipids, as well as for the regulation of the function of T-

lymphocytes. Selenium increases the protective properties of the immune system and has antioxidant activity [2, 3].

A regimen of drugs aimed at normalizing collagen metabolism should activate plastic processes in connective tissue and stimulate its biosynthesis. In order to stabilize the synthesis of collagen and other components of connective tissue, to stimulate metabolic and correct bioenergetic processes, according to the majority of specialists dealing with this problem, at least 3 courses of basic therapy should be prescribed with breaks during the year [2, 3, 9]. According to the results of biochemical analyses (determination of oxyproline, C-terminal telopeptides, pyrinx D), on the basis of which it is possible to judge the degree of breakdown of collagen structures, it was found that longer rehabilitation therapy (3 courses within a year) brought a more stable result compared to 1 or 2 courses of therapy.

Conclusion

Patients with connective tissue pathology are at high risk of developing complications of pregnancy and childbirth, such as abortion, preeclampsia, placental insufficiency, labor abnormalities, etc., which requires special approaches to their management. Unfortunately, to date, most of the biochemical and genetic methods used in the diagnosis of DST are not available to practitioners. In addition, there are no uniform principles of clinical and instrumental examination of the patient and unified diagnostic criteria. Improvement of methods for diagnosing connective tissue pathology, implementation of adequate preventive and therapeutic measures will prevent the development of complications and increase the likelihood of favorable pregnancy outcomes [9, 21, 26].

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