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## **THE ROLE OF UNDIFFERENTIATED CONNECTIVE TISSUE DISEASES IN THE DEVELOPMENT OF ISCHEMIC-CERVICAL INSUFFICIENCY IN PREGNANT WOMEN**

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### **Abstract**

The article analyzes clinical and anamnestic and biochemical markers of undifferentiated connective tissue diseases (UCTDs), the course of pregnancy and childbirth in 56 women with ischemic-cervical insufficiency (ICI) and 30 healthy pregnancies without ICI. The obtained data on the study of UCTDs point to its importance in the development of ICI along with other factors. The presence of pathology of connective tissue in the examined pregnant women can be assumed on the following factors: the pregravidar low Vargue index, the presence of phenotypic markers, diseases indicative of the presence of UCTDs, and the increase in the level of hydroxyproline in daily urine. Given the history of the particular pregnant woman, as well as the presence of markers of UCTDs, it is possible to predict the development of ICI with high probability. The findings indicate the need to examine women at high risk, with a threat or with miscarriage with the help of UCTDs markers, with the aim of taking measures for additional timely diagnosis and subsequent correction of ICI.

**Keywords: pregnancy, collagen, undifferentiated connective tissue diseases, markers, hydroxyproline, ischemic-cervical insufficiency, childbirth.**

Ischemic-cervical insufficiency (ICI) – softening, widening and shortening of the cervix until the 37th week of pregnancy in the absence of a threat of interruption [7, 9]. The emergence of ICI is possible as a result of a disruption in the proportional relationship between muscle tissue, the content of which increases to 50% (at a rate of 15%), which leads to an early softening of the neck [3]. One of the significant reasons for this condition can be connective tissue diseases (CTDs) [4].

According to the literature, clinical manifestations of this disease occur in 26-80% of cases in the general population [8]. It is believed that CTDs are a genetically determined states characterized by defects in fibrous structures and the basic substance of connective tissue, leading to a disruption in the formation of organs and systems, which has a progressive course that determines the characteristics of associated pathology [2]. At the heart of the formation of CTDs are inherited mutations of genes encoding the synthesis and spatial organization of collagen, structural proteins and protein-carbohydrate complexes, as well as mutations of the genes of enzymes and cofactors to them. Morphologically, all these changes are characterized by improper formation of collagen chains, resulting in the formation of so-called abnormal collagen trimmers that do not withstand the necessary mechanical loads; elastic fibrils, and glycoproteins, and proteoglycans with fibroblasts also undergo changes [1].

Modern classification distinguishes two main forms of CTDs: differentiated and undifferentiated [8]. Differentiated forms of CTDs are represented by the syndromes of Marfan, Ehlers-Danlo, imperfect osteogenesis, flaccid skin and even more than 100 syndromes in the description of hereditary human diseases. McKusick V.A. (1972) [5]. Diagnosis of this group of diseases usually does not cause difficulty, since they are associated with the defeat of a specific type of collagen, have vivid clinical manifestations and well-studied genetic markers.

The opposite of this is the undifferentiated forms of CTDs (UCTDs). The difference between UCTDs is the multiplicity and polysystemic nature of their clinical manifestations, and the defeat of different loci of genes encoding the synthesis of collagen, which complicates their genetic classification and diagnosis [5-7].

Clinically, UCTDs is manifested by heterogeneous symptoms and syndromes: locomotor lesions (hypermobility of joints, scoliosis, chest deformities, etc.), visceral pathology (myopia, nephroptosis, splanhoptosis, mitral valve prolapse, varicose veins, etc.) and many others (immunodeficiency, vegetative vascular dystonia, etc.) [8]. The most important phenotypic signs of dysplasia: asthenic constitution, increased skin extensibility, myopia, funnel-shaped deformation of the chest, scoliosis, longitudinal and transverse

flatfoot. The following diagnostic tests are also used: thumb test - the thumb easily fits across the palm and in this position stands for its ulnar edge; "Wrist test" - the patient easily covers the wrist with the little finger and thumb; the ring finger of the hand is smaller than the index finger; the second toe of the foot is greater than the first, between them is a "sandal-shaped" gap; hypermobility of the joints is assessed on the scale of Beiton (assessment of the ability of the subject to perform five movements, maximum score of 9 points): with a score of 0 to 2, joint mobility is assessed as a variant of the norm; 35 points - moderate hypermobility; 69 points - pronounced hypermobility of the joints [3].

In UCTDs, an increase in type 4 collagen occurs due to the destruction of fibronectin of the endogenous matrix, which leads to an increase in hydroxyproline. Hydroxyproline is one of the basic amino acids of collagen, which allows us to consider it a marker that reflects the catabolism of this protein. About 20% of hydroxyproline-containing peptides released from collagen molecules are excreted in the urine, and 80% are metabolized in the liver; almost 90% of hydroxyproline urine is a component of peptides of small molecular weight, and about 9% - large (mostly fragments of N-terminal propeptides of procollagen type 1); only about 1% of hydroxyproline is in free form; an increase in the amount of free and, correspondingly, a decrease in the level of bound hydroxyproline may indirectly indicate a violation of collagen synthesis.

The need for a biochemical study of the metabolism of structural components of connective tissue as an integral assessment of the state of pregnant women with ICI on the background of UCTDs is obvious. Understanding the peculiarities of connective tissue metabolism, including increased hydroxyproline in the blood and early detection of its disorders, can form the basis for preventing the formation and progression of many chronic conditions during pregnancy, including ICI.

Objective: to study the role of undifferentiated connective tissue diseases in pregnant women in the development of ischemic-cervical insufficiency.

### **Materials and methods**

86 pregnant women were examined, which were stratified into two groups: I group (main) (n = 56) - with ICI against the background of UCTDs, II control group - pregnant women with no signs of UCTDs with physiologically occurring pregnancy (n = 30). The severity assessment of UCTDs was performed according to the scale of clinical criteria for the expression of UCTDs [2].

In addition to the general and clinical examination of pregnant women, an assessment was made of the availability of UCTDs for the following parameters:

- 1) collection of the anamnesis data, including data on heredity, the past illnesses;
- 2) physical examination included: measurement of growth (cm); measurement of body weight (g); calculation of the Vargue index:  $IV = (\text{body weight, g} / \text{height}^2, \text{cm}) - (\text{age, years} / 100)$ . Normally, the Varga index is equal to or greater than 1.5;
- 3) at external examination, markers of UCTDs were detected, diagnostic tests were performed: a "thumb test", a "wrist test", a "sandal-shaped" slot; hypermobility of the joints;
- 4) the determination of hydroxyproline in daily urine was carried out according to the method of I Bergmann, R Loxley (1963) in the modification of AA Krel and LN Furtseva (1968). The patient collected daily urine in one container, measured its amount. The method is based on oxidation of hydroxyproline with chloramine T to pyrrole-2-carboxylic acid, which gives a colored compound with p-dimethylaminobenzaldehyde. The content of hydroxyproline in the urine was expressed in mg / day. The normal level of hydroxyproline was 16.5 to 30.5 mg / day.

The statistical processing of the material was carried out using the Microsoft Excel software package. The M was determined as the mean, SE as the standard deviation error, n as the volume of the subgroup analyzed, and p as the achieved significance level. To verify the normality of the distribution of the indicators, the Kolmogorov-Smirnov test was used. In the case of normal distribution, a statistically significant difference in sample mean was verified using Student's t-test; in other cases the nonparametric Mann-Whitney criterion was used. The statistical significance of the differences between the relative frequencies of events was checked by the  $\chi^2$ -criterion and the odds ratio (OR).

### **Results and its discussion**

The mean age of the patients in the main group was  $30.2 \pm 4.8$  years, the control group  $29.8 \pm 5.2$  ( $p > 0.05$ ). In 16 (28,57%) women mild degree of UCTDs was revealed, in 25 (44,64%) – average degree, in 15 (26,79%) – heavy degree. Women of the main group had a statistically significant prevalence of 5 or more stigma UCTDs in 69.4% of cases ( $p < 0.001$ ). Positive diagnostic tests of UCTDs were determined in 80.36% of pregnant women in the main group, including a positive thumb test in 46.43%, a wrist test – in 32.14%, a sandal-shaped slit (a large gap between I and II finger of the foot) – at 25.00%; hypermobility of the joints – in 60.71%.

An important criterion for the clinical assessment of the condition of connective tissue is the determination of growth, body weight and the growth index of Varga. The initial mean growth and weight of the pregnant groups analyzed were not statistically significantly different: the growth in the main group was  $162.5 \pm 0.1$  cm and in the control group it was

163.4 ± 0.1 cm, the body weight was 62.1 ± 2.2 kg and 62.9 ± 2.5 kg. However, in the main group, a pronounced pregravidar decrease in body weight (Varga index to 1.5) was recorded in 7.14% of pregnant women, moderate – in 14.29%, i.e. 21.43% of women had a body weight loss before pregnancy. In the control group, there were no women with significant weight loss, a moderate deficit was observed in 23.33%.

Attention was drawn to the high incidence of childhood infections (chicken pox, measles, rubella, scarlet fever, infectious parotitis) that were registered in 67.86% of pregnant women with UCTDs. Among the infections in frequency, chickenpox was leading – in 51.79% of patients. In the control group, 20.00% of pregnant women had infectious diseases.

Extragenital pathology was detected in 71.43% of pregnant women, including 55.36% related to the pathology of connective tissue. In the structure of extragenital pathology it was dominated by myopia (32.14%) and cardiovascular disease (28.57%). Patients with UCTDs often complained of drowsiness, cephalgia, rapid heartbeat, a feeling of lack of air, dizziness, numbness in the limbs.

Mean age of menarche in the main group was 13,00 ± 0,13 years, in control – 12,52 ± 0,18 years, duration of menstruation – 5,22 ± 0,24 and 5,14 ± 0,32 days, duration of menstrual period cycle – 28.12 ± 0.95 and 28.01 ± 0.89 days, the age of onset of sexual activity is 17.50 ± 0.18 and 17.32 ± 0.24 days. Distinguishing characteristics of menstrual function was the presence of dysmenorrhea in pregnant women with UCTDs in 73.21% of cases compared with 26.67% in controls (OR 7.52, 95% CI 2.76-20.48) and profuse menstruation – 37.50% against 13.33% (OR 3.90, 95% CI 1.19-12.74).

This pregnancy in the main group was the first in 26.79% (15) women, in the control group - in 33.33% (10). Re-pregnant women with UCTDs in 34.15% (14/41) of cases had a miscarriage in the anamnesis, the average number of which was 1.96 ± 0.25 per woman. The average term of spontaneous termination of pregnancy was 15.60 ± 1.35 weeks of gestation. In anamnesis of re-pregnant women of the control group, miscarriages were registered in 10.0% of cases (2/20) (OR 7.26, 95% CI 1.51-35.00).

An increased level of hydroxyproline was detected in 73.21% of the pregnant women with UCTDs at the gestation period of 14-16 weeks. On average, in this group of pregnant women, the level of oxyproline in urine was 39.19 ± 2.28 mg / day, while in control group – 25.87 ± 2.19 mg / day, which can be regarded as a manifestation of disturbed collagen catabolism, which reflects complex pathogenetic relationships between macro- and microorganisms at UCTDs. Elevated levels of hydroxyproline are correlated with the severity of the disease. At a mild degree of UCTDs, the excretion of hydroxyproline in the urine

reached  $28.92 \pm 1.79$  mg / day; with an average degree of  $35.12 \pm 1.15$ ; at severe -  $46,23 \pm 2,54$  ( $p < 0,001$ ). The direct connection between these indicators was most adequately approximated by the exponential dependence (fig.) of the form:  $Y = 22.568e^{0.2345x}$ , at  $R^2 = 0.99$ ,  $p < 0.001$ .

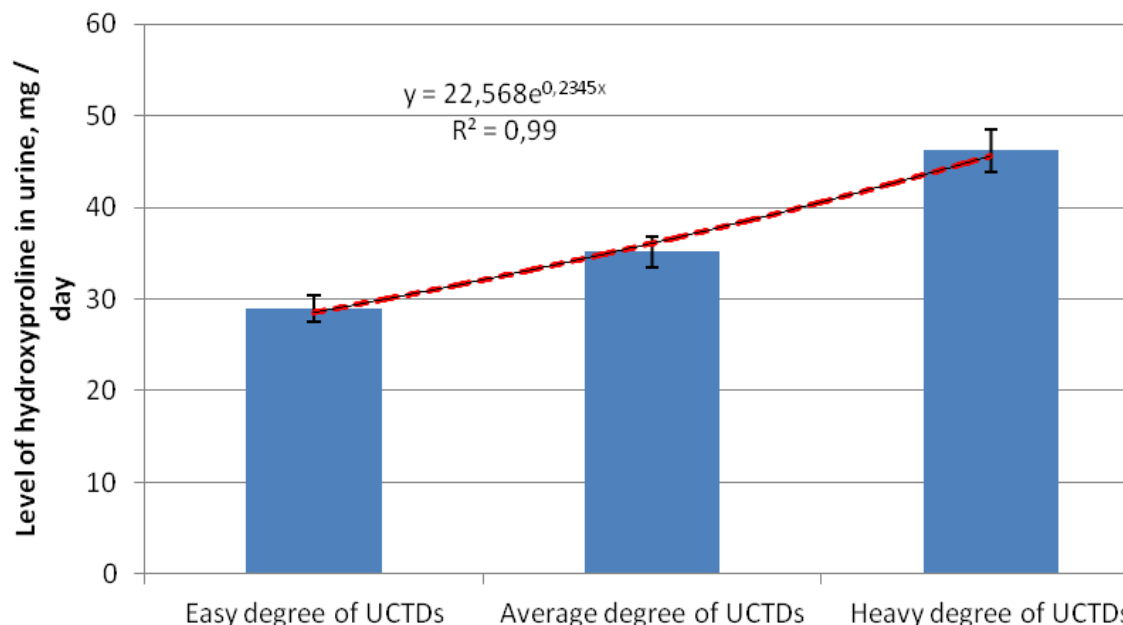


Fig. Correlation field, regression formula and coefficient of hydroxyproline excretion in urine and severity of UCTDs.

One of the main types of fibers of connective tissue are collagen, which consists mainly of collagen – fibrillar protein, which is the main component of the extracellular matrix of connective tissue. A peculiarity of the structure of this protein is that 1/3 of all amino acid residues is glycine, 1/3 is proline and hydroxyproline, about 1% is hydroxylysine. The most important indicator of the metabolism of collagen is the content of hydroxyproline. With violations of collagen synthesis, cross-links in collagen fibrils decrease, which leads to an increase in the content of readily soluble collagen. Therefore, in patients with impaired metabolism of connective tissue, the serum content of its free fraction increases and the content of the bound fraction decreases. Thus, we can consider the free fraction of hydroxyproline as a marker of destruction and development of the ICI [6].

Isthmiko-cervical insufficiency was established according to cervicometry in the main group in the period of 11-12 weeks in 39.29% of pregnant women, in the period of 14-16 weeks – in 60.71%.

In all cases, the course of the observed pregnancy in the main group was at least complicated by the threat of interruption. Iron deficiency anemia was observed in 51.79% of women, placenta dysfunction – in 42.86%, low placentation – in 26.78%. In 3.57% of cases, pregnancy was complicated by preeclampsia, 10.71% – with low salinity, 16.07% with polyhydramnios, premature rupture of membranes – at 8.93%.

In all pregnant women of the main group, after the diagnosis of ICI against the background of UCTDs, a perforated obstetric pessary of Dr. Arabin was used, and magnesium preparations were prescribed up to 36 weeks of gestation.

In one case (1.79%) in a pregnant main group with habitual miscarriage, a miscarriage occurred in the 21-week period. In 10.71% (6/56) of women with UCTDs, the delivery was premature, 87.50% (49/56) – urgent. Bleeding during childbirth and the puerperium, purulent-septic complications were absent.

Thus, connective tissue is a complex structural and multifunctional system that unites the various organs and tissues of the body. Therefore, the processes of adaptation of the organism, the stability of its organs and systems, including the cervix of the uterus during pregnancy, depend on the metabolic processes taking place in the connective tissue. Understanding the peculiarities of connective tissue metabolism, including increased hydroxyproline in the urine, and early detection of its disorders can form the basis for preventing the formation and progression of ischemic-cervical insufficiency during pregnancy [3].

### **Conclusions**

The obtained data on the study of UCTDs indicate its importance in the development of ICI along with other factors. The presence of pathology of connective tissue in the examined pregnant women can be assumed on the following factors: the pregravid low Vargue index, the presence of phenotypic markers, diseases indicative of the presence of UCTDs, and the increase in the level of hydroxyproline in daily urine. Given the history of the particular pregnant woman, as well as the presence of markers of UCTDs, it is possible to predict the development of ICI with high probability. The findings indicate the need to screen high-risk women, threaten or miscarry with the help of UCTDs markers and to take measures for additional timely diagnosis and subsequent correction of ICI.

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