improve the process of diagnosis and treatment of the specified category of patients, which will contribute to the improvement of the reproductive health of the future generation.

Key words: reproductive health, reproductive potential, adolescent girls, abnormal uterine bleeding.

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CURRENT STATE OF THE PROBLEM OF MENSTRUAL CYCLE DISORDERS IN WOMEN OF REPRODUCTIVE AGE WITH UNDIFFERENTIATED CONNECTIVE TISSUE DYSPLASIA (LITERATURE REVIEW)

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Based on the analysis of information from available sources of scientific literature, the article provides an overview of the problem of menstrual cycle disorders (MCD) in women of reproductive age and the impact of connective tissue diseases. MCD is the most common gynecological problem of reproductive health, and connective tissue diseases occur in up to 90% of cases in women of all ages. The pathogenic mechanism of these abnormalities can be presented as a connection between sex hormones and immunity. Undifferentiated connective tissue dysplasia (UCTD) has been shown to exert a negative effect on the course of pregnancy and the likely development of fetal disorders, to which the vast majority of research is devoted. The relationship between the pathological course of pregnancy of mothers whose daughters had menstrual disorders and phenotypic signs of connective tissue diseases is shown. In young women with connective tissue diseases, the most common menstrual dysfunction (MD) is dysmenorrhea and abnormal uterine bleeding (AUB), caused by immune dysregulation, autoimmune changes, and inflammation. The modern approach to the treatment of such patients involves the elaboration of individual treatment tactics taking into account concomitant diseases, current test results, pathogenic features of development and the course of MCD. Treatment involves the use of hormonal (synthetic and natural estrogens, gonadotropin hormones, progesterone, gonadotropin-releasing hormone analogues) and non-hormonal (nonsteroidal anti-inflammatory drugs, tranexamic acid) drugs, as well as non-drug methods (correction of lifestyle, physical activity, rational nutrition). UCTD remains an understudied problem due to its clinical heterogeneity, lack of uniform terminology, generally accepted criteria for diagnosis and assessment of severity. There is a lack of standardization of diagnostic methods and diagnostic criteria for UCTD compared to the criteria used for various forms of connective tissue diseases. Management of patients with connective tissue diseases and disorders of menstrual function is a complex problem, involving assessment of gynecological conditions (menstruation, fertility, sexuality) and an interdisciplinary approach (rheumatology, gynecology, etc.).

Key words: *menstrual cycle irregularities, women of reproductive age, undifferentiated connective tissue dysplasia, abnormal uterine bleeding, dysmenorrhea.*

Connection of the publication with planned research works.

The study was carried out within the scientific direction of the department of obstetrics, gynecology, pediatric gynecology and medical genetics of KhNMU "Optimization of clinical-diagnostic and therapeutic approaches to the management of gynecological patients taking into account age and the presence of extragenital disorders", state registration number 0122U000257.

Introduction.

Menstrual cycle (MC) is a natural event and a unique experience of women of reproductive age [1]. MC occurs during the reproductive period of a woman's life, characterized by cyclicity and rhythm. Menstrual cycle disorders (MCD) is one of the most common

gynecological problems of reproductive health, which is a combination of one or more pathological symptoms of MC, which strongly affects a woman's daily life and leads to infertility and other pathological conditions [2]. MCDs affect 75% of young women in developed and developing countries and constitute the majority of diseases of women of childbearing age [3]. These conditions, especially menorrhagia, are a serious reason for consulting a doctor [4]. MCDs not only impair the reproductive capacity of young women, but are associated with various pathological conditions, in particular with anemia, thyroid gland dysfunction, etc. [5, 6].

Researchers found general consequences of menstrual disorders, manifested by limitations in education or work due to a decrease in attention and concentration, the need to reduce normal physical activity [7]. So, the negative impact of menstrual dysfunctions on the quality of life of young women is obvious. At the same time, disorders of the menstrual function are manifested at the initial stage by such diseases of the reproductive system as uterine fibroids, endometriosis, adenomyosis [8].

Often MCDs are associated with other diseases, for example, connective tissue. Connective tissue dysplasia (CTD) causes a violation of the formation of connective tissue in many organs and systems. This abnormality occurs in up to 90% of cases in women of various ages [9]. Undifferentiated connective tissue dysplasia (UCTD) is diagnosed when the set of phenotypic features does not correspond to any of the differentiated diseases [9]. Among the disorders associated with this syndrome, in recent years, disorders of the reproductive system occupy a certain place, which constitutes an actual medical problem. There are well-known studies of the sexual function of women suffering from connective tissue diseases, which show the relationship between sexual and mental health and the underlying disease [10, 11]. All of the above cannot fail to affect the implementation of the reproductive plans of women with disorders of menstrual function and CTD. Violations of the reproductive system against the background of UCTD can be explained both by chronic inflammation, hormonal imbalance and the influence of medication, and by psychological problems [12]. The researchers' attention was mostly drawn to the issue of the relationship between the underlying disease and sexual problems, their impact on women's mental health, as well as vaginal symptoms, such as dryness of the vaginal mucous membranes [12, 13]. However, limited data are available on violations related to MC in the case of UCTD [12], which prompted us to pay attention to this problem.

The aim of the study.

Considering the available sources of literature, to analyze the state of the problem of menstrual cycle disorders in women of reproductive age with undifferentiated connective tissue dysplasia.

Object and research methods.

This review was conducted using PubMed, Medline, and the Cochrane Library databases. Key terms such as "problems of menstrual disorders", "women of reproductive", "abnormal uterine bleeding", "dysmenorrhea", "undifferentiated connective tissue dysplasia" were used to search for relevant studies published within 10 years. We have analyzed the abstracts of articles related to disorders of the menstrual cycle of women of reproductive age and the impact of connective tissue diseases on the functioning of the reproductive system of young women. Reference lists of publications on the topic and recent reviews on this issue were also studied.

Research results and their discussion.

The pathogenic mechanism of menstrual disorders in patients with UCTD can be presented as a connection between sex hormones and immunity. Autoimmune connective tissue diseases have been shown to more often affect women, so the issue of hormonal influence on the risk of developing connective tissue diseases attracts the attention of researchers [13, 14]. Women are known to have enhanced immunoreactivity against men due to a higher level of immunoglobulins and increased production of antibodies to antigenic stimulation. In women, the immune response is dominated by type 2 T-helpers, in contrast to men, who have a type 1 T-helper response [15]. At the same time, sex hormones estrogen, androgen and prolactin increase the susceptibility to autoimmune diseases by modulating the immune response through androgen and estrogen receptors [16]. The interaction of sex hormones is complex, affecting susceptibility to disease. Thus, cholesterol is a precursor to hormones such as estrogen, progesterone, and testosterone, and their common intermediate metabolites dehydroepiandrosterone and estradiol also interact with the immune system [17]. The study of the level of sex hormones is difficult due to the fact that it is not determined whether the disease itself or its treatment affects the level of hormones, and information about the level of hormones before the disease is not always known [18].

The level of sex hormones that circulate in women and men represent the relative transformation of androgens and estrogens [19]. Estrogen and progesterone levels decline with age, with the rate of decline increasing during premenopause and menopause, while progesterone levels decline faster than estrogen levels. Estrogen and prolactin are known to be pro-inflammatory hormones, which may explain the high prevalence of autoimmune disorders in women.

The prevalence of this disorder in women of reproductive age, which negatively affects obstetric and perinatal outcomes, also attracts attention.

An analysis of the specialized scientific literature on the problem of menstrual cycle disorders in women with UCTD revealed a large number of studies on the peculiarities of the course of pregnancy in women with connective tissue diseases. It has been established that UCTD has a negative effect on the course of pregnancy. D. Zucchi et al. [20] in a retrospective study found that 11% of pregnancies ended in miscarriage in the first trimester, and 29% in complications during pregnancy: preeclampsia was noted in 10%, intrahepatic cholestasis of pregnancy in 3%, premature rupture of membranes in 2%, gestational diabetes, TELA in 1%, in 10% of cases babies were born with low gestational weight. According to A. Spinillo et al. [21], the number of pregnancy complications in women with UCTD was 39 % against 13.4 % of healthy pregnant women.

Since women are not always aware of the abnormality of uterine bleeding and do not seek

medical help, a thorough history is of great importance in identifying its cause. The relationship between the pathological course of pregnancy of mothers whose daughters had menstrual disorders and phenotypic signs of connective tissue diseases is shown. In this case, the most threatening factors are termination of pregnancy, premature birth, preeclampsia and asphyxia of the newborn [22].

F. Beneventi et al. [23] conducted a prospective cohort study and found during dopplerography more frequent presence of blood flow disorders in uterine arteries in pregnant women with UCTD in the first, second and third trimesters compared to the control group. The findings show that inadequate trophoblast invasion is common in pregnant women with UCTD. In addition, the detected disorder was associated with poor pregnancy outcomes. According to A. Spinillo et al. [24], antibodies are directly related to defective placentation and are the cause of adverse pregnancy outcomes. Also, antinuclear antibodies affect the quality of oocytes and the pathological development of the embryo due to the activation of the complement cascade [25]. The presence of antinuclear antibodies causes disruption of uterine blood flow in non-pregnant women who have experienced repeated pregnancy loss, which has been experimentally confirmed [26, 27]. Placentation defect in pregnant women with UCTD has been shown to be triggered by endothelial dysfunction and cytokine imbalance [28]. The researchers came to the conclusion that antinuclear antibodies and inflammation negatively affect the function of platelets, the balance of coagulation and anticoagulation mechanisms, causing a prothrombotic state, endothelial dysfunction, resulting in violation of remodeling of spiral arteries and development of the placenta, increase in the risk of preeclampsia, fetal development delays in pregnant women with UCTD, and a risk of premature birth [29].

UCTD is one of the causes of isthmic-cervical insufficiency due to a decrease in collagen and an increase in the mass of muscle tissue. Such an imbalance is characteristic of connective tissue diseases [30].

That is why, in recent years, experts in the medical field have been talking about the importance of pregnancy planning and pre-pregnancy preparation of women with connective tissue diseases, since complications of pregnancy and newborn impairments are mostly found in patients who are not sufficiently prepared for this [31].

While studying the problem of reproductive function in women with CTD, we have drawn attention to the small number of studies and limited information on disorders associated with MC and connective tissue diseases. The most common gynecological symptom associated with menstruation is dysmenorrhea — pain due to pathological contraction of the uterus [32].

According to López-Liria R, Bakhsh H et al., dysmenorrhea affects about half of women of childbearing age and adolescent girls [33, 34]. Dysmenorrhea is characterized by painful spasms before or during menstruation due to cyclic shedding of the inner lining of the uterus. Approximately 34 % of women rated the pain as 7–10 points on the VAS scale (visual analog scale) [35], which negatively affects the intellectual abilities and psychosocial existence of a significant number of adolescent girls and young women [36, 37].

A number of studies suggest that dysmenorrhea is a clinical manifestation of dysmorphic connective tissue disorders [38]. And according to M. Orlandi et al. [39], 72% of women of reproductive age with connective tissue diseases suffer from moderate or severe menstrual pain. A study conducted by N. Shigesi et al. [40], found a connection between connective tissue disorders and endometriosis. Endometriosis is often the cause of secondary dysmenorrhea due to ectopic localization of endometrial cells [41]. Quite often, a woman considers such menstrual pain “normal”, so patients with connective tissue diseases are a high-risk group for the development of endometriosis, especially if dysmenorrhea is established [39]. O. Yakubova et al. [42] concluded that there is a relationship between hypomagnesemia and connective tissue diseases in girls with primary dysmenorrhea. Since collagen fibers are the main component of connective tissue, their destruction occurs due to magnesium deficiency.

Abnormally heavy or prolonged menstrual bleeding was found in 38% of women of reproductive age and 52% of adolescent girls with connective tissue diseases [39].

Menstrual disorders in women with connective tissue diseases are pathogenically related to sex hormones and immunity: estrogens and progesterone are involved in the modulation of immune system signals, which affects the maturation of lymphocytes, activation and synthesis of antibodies and pro-inflammatory cytokines. At the same time, immune dysregulation and inflammation play a significant role in the development of some gynecological disorders (endometriosis, adenomyosis), which affects the development of menstrual disorders in women with connective tissue diseases [43, 44].

In patients with autoimmune diseases, the expression of sex hormones changes, which is one of the factors of immune dysregulation. The causes of menstrual cycle disorders can be autoimmunity and inflammation, even independent of connective tissue diseases. At the same time, menstrual disorders can cause a hormonal imbalance, which affects the contractility of the uterus, the condition of the endometrium [45]. Considering this, women with CTD represent a population associated with the risk of menstrual cycle disorders.

Treatment of women with MC disorders and connective tissue diseases is a difficult task for specialists. Scientific literature has a large amount of information on the specifics of MCD treatment in patients with extragenital impairments. The main principle of treatment of gynecological disorders in these cases is the treatment of the underlying disease [46, 47]. At the same time, little attention has been paid to the problem of treatment of women with menstrual cycle disorders and UCTD, so we can talk about the lack of specific treatment recommendations. The modern approach to solving this problem consists in the development of individual treatment tactics taking into account concomitant diseases, current test results, pathogenic features of MCD development and course [48]. The principles of therapy consist in the use of medicinal and non-medicinal methods.

The basis of medication is the use of hormonal and non-hormonal drugs. Among the latter, non-steroidal

anti-inflammatory drugs (NSAIDs) are prescribed, which act on the endometrium and reduce the level of prostaglandins due to inhibition of the enzyme cyclooxygenase [49]. NSAIDs are used only during menstruation to reduce pain in case of dysmenorrhea. At the same time, it was found that in 75% of women, these drugs reduce blood loss by 25–35% [50]. NSAIDs are quite well tolerated, but there are contraindications for them in case of blood coagulation disorders, gastric ulcer disease, kidney diseases [51].

The antifibrinolytic agent tranexamic acid reduces menstrual blood loss by 26–50 %, but has a minimal effect on dysmenorrhea [52, 53]. This medicine is used independently and with NSAIDs. But unlike NSAIDs, tranexamic acid does not increase the risk of thromboembolic events [54].

The main method of treatment of abnormal uterine bleeding (AUB) is hormonal therapy, the choice of which depends on the nature of their disorders. Estrogens of synthetic and natural origin, gonadotropin hormones, progesterone, analogues of gonadotropin-releasing hormone are widely used [55]. Estrogen, progesterone, and combined oral contraceptives are used for MC irregularity, amenorrhea, oligomenorrhea, and anovulatory bleeding [56, 57]. Ovulatory bleeding is managed by intrauterine systems releasing hormones with levonorgestrel [58] and antifibrinolytic drugs [59].

Management of patients with UCTD involves adherence to a diet rich in protein, trace elements, unsaturated fatty acids, vitamins and minerals, and collagen-forming elements. The selection of the diet should be individualized, taking into account the level of deficiency of these substances confirmed by the tests. Thus, vitamin D3 is additionally recommended for normalizing phosphorus-calcium metabolism in patients with UCTD, as it has powerful immunomodulatory properties. Some researchers even believe that the deficiency of this vitamin in patients with UCTD may contribute to the progression of the specified disorder to well-defined connective tissue diseases [60]. Given the availability of vitamin D3, it should be noted that there is a lack of evidence-based recommendations for the treatment of UCTD.

Physical activity is an important part of the treatment of connective tissue diseases, because with the simultaneous normalization of body weight, which contributes to the regularity and quality of menstrual function, muscle tone improves, which compensates for the insufficient development of connective tissue [61, 62].

Conclusions.

Summarizing the information presented in the review, it can be noted that young women with UCTD show a high prevalence of various gynecological symptoms and diseases. MCDs significantly affect a woman's quality of life and health, so this issue needs attention. With a view to clinical practice, a more complete understanding of the underlying phenomena associated with menstrual dysfunction will help to achieve the goals of personalized treatment. UCTD remains an understudied problem due to its clinical heterogeneity, lack of uniform terminology, generally accepted criteria for diagnosis and assessment of severity. Summing up, attention should be paid to the lack of standardization of diagnostic methods and diagnostic criteria for UCTD. Solving this problem will create an opportunity to determine the degree of clinical manifestations of dysplasia, select a set of treatment measures, assess the prognosis of the course of the disease and the possibility of complications that negatively affect the reproductive function of young women. Therefore, the management of patients with UCTD is a complex problem of modern medicine, which consists in the assessment of gynecological conditions (menstruation, fertility, sexuality) and an interdisciplinary approach (rheumatology, gynecology, etc.).

Prospects for further research.

Since menstrual cycle disorders in women of reproductive age remain an urgent problem of modern medicine, and connective tissue diseases are a widespread abnormality, it is advisable to continue studying the links of the pathogenesis of these impairments in order to develop acceptable treatment methods that will contribute to strengthening the reproductive health of young women.

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СУЧАСНИЙ СТАН ПРОБЛЕМИ ПОРУШЕНЬ МЕНСТРУАЛЬНОГО ЦИКЛУ У ЖІНОК РЕПРОДУКТИВНОГО ВІКУ З НЕДИФЕРЕНЦІЙОВАНОЮ СПОЛУЧНОТКАНИННОЮ ДИСПЛАЗІЄЮ (ОГЛЯД ЛІТЕРАТУРИ)

Ракитянський І. Ю.

Резюме. На основі аналізу доступних джерел наукової літератури представлено огляд проблеми порушень менструального циклу у жінок репродуктивного віку та впливу на них захворювань сполучної тканини. Порушення менструального циклу вражають 75 % молодих жінок у розвинених країнах і країнах, що розвиваються, та становлять більшість захворювань жінок дітородного віку. Патогенез цих станів можна описати як статево-гормонально-імунну асоціацію. Добре відомо, що недиференційована дисплазія сполучної тканини (НДСТ) має негативний вплив на перебіг вагітності та можливий розвиток уражень плода. Ця проблема є в центрі уваги більшості досліджень. Виявлено зв'язок між патологічним перебігом вагітності та фенотипічними ознаками захворювань сполучної тканини в матерів, чиї доньки мають порушення менструальної функції. У молодих жінок із захворюваннями сполучної тканини дисменорея та аномальні маткові кровотечі є найпоширенішими порушеннями менструального циклу, які зумовлені імунною дисрегуляцією, аутоімунними процесами та запаленням. Сучасний підхід до лікування таких пацієнток полягає в розробці індивідуального плану лікування, зважаючи на супутні захворювання, поточні лабораторні показники, патологічні особливості дебюту захворювання та перебігу порушень менструального циклу. Лікування складається з призначення гормональних (синтетичних і природних естрогенів, гонадотропін-рилізинг-гормонів, аналогів прогестерону та гонадотропін-рилізинг-гормону) та негормональних засобів (нестероїдних протизапальних препаратів, транексамової кислоти), а також немедикаментозного лікування (модифікація способу життя, фізична активність, раціональне харчування). На сьогодні відсутня єдина термінологія та загальноприйняті критерії діагностики та оцінки тяжкості НДСТ. Діагностичні методи та критерії НДСТ не стандартизовано порівняно з іншими захворюваннями сполучної тканини. Ведення пацієнтів із захворюваннями сполучної тканини та менструальною дисфункцією є комплексним питанням, відповідь на яке базується на оцінці гінекологічних проблем (менструація, фертильність, сексуальність) та мультидисциплінарному підході із залученням фахівців інших спеціальностей.

Ключові слова: порушення менструального циклу, жінки репродуктивного віку, недиференційована дисплазія сполучної тканини, аномальні маткові кровотечі, дисменорея.

CURRENT STATE OF THE PROBLEM OF MENSTRUAL CYCLE DISORDERS IN WOMEN OF REPRODUCTIVE AGE WITH UNDIFFERENTIATED CONNECTIVE TISSUE DYSPLASIA (LITERATURE REVIEW)

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Abstract. Based on the analysis of available sources of scientific literature, an overview of the problem of menstrual cycle disorders in women of reproductive age and the impact of connective tissue diseases on them is presented. Menstrual disorders affect 75% of young women in developed and developing countries and constitute the majority of diseases in women of childbearing age. The pathogenesis of these conditions can be described as a sex-hormonal-immune association. Undifferentiated connective tissue dysplasia (UCTD) is known to exert a negative impact on the course of pregnancy and the possible development of fetal impairment. This problem is the focus of most research. The relationship between the pathological course of pregnancy and phenotypic signs of connective tissue diseases in mothers whose daughters have menstrual disorders was revealed. In young women with connective

tissue diseases, dysmenorrhea and abnormal uterine bleeding are the most common menstrual disorders, caused by immune dysregulation, autoimmune processes, and inflammation. The modern approach to the treatment of such patients consists in the development of an individual treatment plan, taking into account concomitant diseases, current laboratory findings, pathological features of the onset of the disease and the course of menstrual cycle disorders. Treatment consists of prescribing hormonal (synthetic and natural estrogens, gonadotropin-releasing hormones, progesterone and gonadotropin-releasing hormone analogues) and non-hormonal agents (nonsteroidal anti-inflammatory drugs, tranexamic acid), as well as non-drug treatment (lifestyle modification, physical activity, rational nutrition). To date, there is no unified terminology and generally accepted criteria for diagnosing and assessing the severity of UCTD. Diagnostic methods and criteria for UCTD are not standardized compared to other connective tissue diseases. Management of patients with connective tissue diseases and menstrual dysfunction is a complex issue, the answer to which is based on the assessment of gynecological problems (menstruation, fertility, sexuality) and a multidisciplinary approach involving specialists from other branches.

Key words: menstrual cycle irregularities, women of reproductive age, undifferentiated connective tissue dysplasia, abnormal uterine bleeding, dysmenorrhea.

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INFLUENCE OF HEAVY METALS ON MORPHO-FUNCTIONAL STATE OF BONE TISSUE

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The article presents an analysis of scientific literature on the impact of heavy metal compounds on bone and cartilage tissue. The most common environmental toxicants in the group of heavy metals are mercury, cadmium and lead salts, which, when ingested, accumulate in the body, provoke a hypoxic state and compete with biogenic metals for binding to the active site of many proteins and enzymes, causing a violation of their functions. Modern scientific research has shown that chronic cadmium intoxication creates an imbalance in the process of bone remodelling, inducing the development of osteopenia and osteoporosis. The ability of the toxicant to accumulate in the extracellular bone matrix has been experimentally determined, leading to its bioaccumulation and an increase in the half-life of the metal from the body. The accumulation of cadmium in bone tissue leads to a decrease in calcium and zinc levels, which disrupts the basic processes of ossification and negatively affects cartilage and joint tissue. Understanding the mechanisms of osteo- and chondrotoxicity of cadmium will help to find adequate therapy methods for cadmium-induced osteoporosis and prevent the negative impact of the toxicant on bone and cartilage tissue. Studies of the accumulation level of trace elements in bones and their changes under the influence of negative factors are also relevant. It is perspective not only to determine the accumulation level of heavy metal salts but also to search for possible bioantagonists of heavy metal salt accumulation.

Key words: *bone tissue, femur, lower jaw, microelements, dyselementoses, cartilage tissue, rats, heavy metals, cadmium, zinc, iron, influence, accumulation.*

Connection of the publication with planned research works.

The work was carried out in accordance with the scientific theme of DSMU “Morphological and functional features of organs and tissues under the influence of external and internal factors”, state registration number 0120U105219.

Introduction.

Increasing rates of environmental pollution in industrialised countries require studying the impact of environmental factors on human health. One of the most widespread and dangerous environmental pollutants is heavy metals, which, when ingested by the human body, lead to acute and delayed complications, change the balance of trace element systems, cause diseases or