

**ОГЛЯД ЛІТЕРАТУРИ**

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**MODERN ASPECTS OF THE ETIOPATHOGENESIS OF ISTHMIC-CERVICAL INSUFFICIENCY**

I.V. Levitsky, N.M. Kinash

*Ivano-Frankivsk National Medical University, Department of Obstetrics and Gynecology ID Lanovij, Ivano-Frankivsk, Ukraine,**ORCID ID: 0000-0001-6197-1730, e-mail: igvollev@ukr.net;**ORCID ID: 0000-0002-2094-6026, e-mail: natalikinash78@gmail.com*

**Abstract.** Isthmic-cervical insufficiency (ICI), which results in the failure of the circular muscles of the internal os, isthmus and cervix of the uterus is important in the pathogenesis of preterm birth. The existing types are anatomical, functional and congenital ICI. ICI is a pathological condition of the cervix and the isthmus, in which they are unable to withstand the intrauterine pressure and keep a fertilized egg in the uterine cavity until birth. ICI is a serious complication of pregnancy. Genetic, hormonal, inflammatory-infectious, immunological, traumatic factors play a role in the occurrence of ICI. The aim of the study is to study the peculiarities of reproductive health and gestational process of pregnant women with ICI, according to the literature. For the study, we analyzed domestic and foreign publications on this topic in professional journals, as well as data from Internet resources. Results of the research show that ICI plays a special role among many causes that lead to preterm termination of pregnancy and premature birth in the II-III trimesters. The properties of the cervix depend on the ratio of connective and muscle tissue. Today, most authors distinguish between congenital, acquired, organic and functional isthmic-cervical insufficiency.

Organic (post-traumatic, secondary) ICI occurs due to mechanical damage to the cervix. Functional ICI is the result of a violation of the relationship between the muscular and connective tissues of the cervix, as well as the result of changes in the response of its structural elements to neurohumoral stimuli. Functional ICI most often occurs as a consequence of a violation of the hormonal background of women (ovarian hypofunction, hyperandrogenism). Congenital ICI occurs in malformations of the uterus, genital infantilism. Histological examination of cervical tissue in women with ICI reveals an increase in muscle tissue up to 50%, which leads to early softening of the cervix of the uterus and development of its functional insufficiency.

According to Kaufman KP (2021), the role of connective tissue in the development of ICI is confirmed by the fact, that this pathological condition of the cervix is found in women with Marfan syndrome and Ehlers-Danlos syndrome. The role of undifferentiated connective tissue dysplasia (UCTD) as a risk factor for complicated pregnancy, including ICI.

Research of Huang J and co-authors (2021) found the presence of nutritional imbalance in patients with UCTD, which was manifested by changes in serum concentrations of magnesium, calcium, zinc, iron, copper, selenium, inorganic phosphorus. The relationship between changes in the microcirculation system, tissue perfusion and cervical condition is currently being actively discussed and confirmed in numerous studies.

Fettweis JM (2019) believes that the mechanism of abortion at different stages of gestation is not the same in pregnant women with ICI. At the same time, all pregnant women with ICI at all stages of gestation have increased cytokine levels. However, an important factor in the premature termination of pregnancy in ICI is assigned to the infectious factor. The results of the study of the pathogenetic role of local immune responses in women with habitual miscarriage are often contradictory and dictate the need for further researches.

Eventually, isthmic-cervical insufficiency is a multifactorial complication of pregnancy, in which genetic, hormonal, inflammatory-infectious, immunological or traumatic factors play a role.

**Keywords:** isthmic-cervical insufficiency, extremely early premature birth, undifferentiated connective tissue dysplasia, hormonal imbalance, collagen metabolism disorders, nutritional disorder.

**Introduction.** The demographic situation in Ukraine at the moment is unfavorable. As a result, obstetricians and perinatologists face the challenge of maintaining every desired pregnancy and the birth of a healthy baby. The high frequency of miscarriage indicates the priority of the problem of thorough examination and adequate prevention of premature birth (PB). At the same time, timely diagnosis and effective treatment of isthmic-cervical insufficiency (ICI) in most cases can prevent miscarriage and give birth to a full-term and healthy baby [1, 4, 9].

Miscarriage has various and numerous causes.

Isthmic-cervical insufficiency (ICI), which is the result of the failure of the circular muscles of the internal os, isthmus and cervix, is important in the pathogenesis of preterm birth. The existing types are anatomical, functional and congenital ICI. Isthmic-cervical insufficiency is a pathological condition of the cervix and the isthmus, in which they are unable to withstand intrauterine pressure and keep a fertilized egg in the uterine cavity until delivery [1, 5, 18]. Isthmic-cervical insufficiency is a spontaneous smoothing and opening of the cervix not related to the contractile activity of the uterus, which leads to abortion, more often in the second trimester.

The diagnosis is often made retrospectively, as rapid and virtually painless opening of the cervix in the second or third trimester of pregnancy ends in miscarriage or early premature birth. There are no objective ICI criteria in the early stages. More often there is a set of causal factors that lead to ICI.

ICI is a multifactorial complication of pregnancy. Genetic, hormonal, inflammatory-infectious, immunological, traumatic factors, etc. play a role in the occurrence of ICI [5, 9, 12, 16]. A special place among the risk factors is occupied by undifferentiated connective tissue dysplasia, which is the result of impaired development with defects in the basic substance and fibers. Analyzing the changes in hormonal and nutritional homeostasis, the state of collagen metabolism in undifferentiated connective tissue dysplasia, the mechanisms of etiology and pathogenesis of asymptomatic cervical dilatation in premature pregnancy are considered.

The incidence of ICI according to the literature ranges from 20% to 65%. Most authors point out that late pregnancy loss, in almost half of cases, is due to cervical failure [2, 4, 21, 23].

Despite the large number of scientific publications on the ICI, the problem cannot be considered completely solved.

The problem of cervical failure (CF) during pregnancy has been known since the 19th century as the cause of 40% of late miscarriages and up to 30% of premature births. The reason is that due to the shortening and softening of the cervix, dilation of the internal os and cervical canal, the ovum loses its physiological support in the lower segment of the uterus [4, 10, 11, 17].

With increasing intrauterine pressure as the pregnancy progresses, the amniotic membranes protrude into the dilated cervical canal, become infected and rupture, after which the ovum is expelled from the uterine cavity. Loss of biomechanical function of the connective tissue of the cervix is accompanied by activation of collagenolysis and is observed in isthmic-cervical insufficiency [5, 9, 14, 19, 22]. It is possible that systemic connective tissue dysplasia plays a leading role in the pathogenesis of ICI development. The pathogenesis of dysplastic changes is based on the pathology of the fibrillar component of connective tissue [1, 12, 15, 19].

**The aim of the study.** To study the peculiarities of reproductive health and gestational process of pregnant women with isthmic-cervical insufficiency according to the literature.

**Materials and methods.** Analysis of domestic and foreign publications on the topic in professional journals, as well as data from Internet resources.

**Research results.** The frequency of ICI, according to the literature, reaches 1% of all obstetric and gynecological pathology (SOCG Clinical Practice Guidelines). Among the many causes that lead to premature termination of pregnancy and premature birth in the II-III trimesters, isthmic-cervical insufficiency plays a special role. Therefore, clinicians should pay considerable attention to the issue of ICI as one of the leading factors in premature birth [4, 7, 10, 14].

The cervix in a woman's body is a complex and heterogeneous organ that is subject to significant changes during pregnancy and childbirth. The properties of the cervix depend on the ratio of connective and muscle tissue.

The structure of the cervix is dominated by fibrous connective tissue, which consists of extracellular matrix, represented by collagen, elastin and proteoglycins, and the cellular part, consisting of smooth muscle, fibroblasts, epithelium and blood vessels.

Among the biochemical components that play an important role in the functioning of the cervix are proteins such as collagen and elastin, as well as glycoproteins and hydrocarbon components that are actively involved in the differentiation and mutual recognition of cells, intercellular contacts, adhesion, and receptors. Changes in the quantitative content of glycoproteins and their carbohydrate components affect the structural and functional characteristics of the cervix [9, 13, 15, 19, 22].

Changes that occur in the cervix affect changes in the mucus of the cervical canal, which allows you to use it for diagnostic purposes. Cervical shortening, confirmed by transvaginal echocervicometry, is an early marker of the threat of pregnancy loss - late miscarriage, premature birth.

Today, most authors distinguish between congenital, acquired, organic and functional isthmic-cervical insufficiency [7, 12, 16, 25].

Organic (post-traumatic, secondary) ICI occurs due to mechanical damage to the cervix and cervix. The most common causes are previous operations accompanied by mechanical dilatation and trauma of the cervix, deep ruptures of the cervix in abnormal births (obstetric forceps, vacuum extraction of the fetus, manual removal of the placenta and membranes and control of the uterine cavity, cervical surgery), secondary cervical healing with the growth of scar tissue, which cannot ensure the functional state of the cervix during the next pregnancy [14, 17, 25, 26].

Functional ICI is the result of a violation of the relationship between the muscular and connective tissues of the cervix, as well as the result of changes in the response of its structural elements to neurohumoral stimuli. Functional ICI most often occurs as a consequence of a violation of the hormonal background of women (ovarian hypofunction, hyperandrogenism).

Functional isthmic-cervical insufficiency (FICI) is most often the result of hormonal imbalance in the pre-pregnancy stage. According to modern domestic and foreign authors, hyperandrogenism of any genesis, ovarian hypofunction, luteal phase insufficiency (NLF), metabolic syndrome of various etiologies FICN during pregnancy is diagnosed in every third woman [3, 17, 19, 24].

During the physiological biphasic menstrual cycle in the follicular phase in conditions of estrogen saturation, which is dominated by  $\alpha$ -adrenoceptors, against the background of increased uterine muscle tone, there is some expansion of the isthmic region and the opening of cervix. In the physiological luteal phase due to increased biosynthesis of progesterone (PG) sensitivity of  $\alpha$ -adrenoceptors decreases, which leads to a decrease in uterine tone, narrowing of its isthmic region and reducing the size of the inner uterine cell. At NLF restoration of a tone of a myometrium of a uterus and isthmic department does not occur, the internal cervical os remains in the expanded state [16, 19, 20].

With hyperandrogenism, the cervix "softens" and with excessive load or uterine tone and may open. An increase in the likelihood of pathology is observed when combining this problem with a deficiency of progesterone

production. The most common cause of cervical insufficiency is hormonal disorders. With the onset of pregnancy in a woman's body is actively synthesized progesterone. In the early stages, the corpus luteum is responsible for production, and from the second trimester this function is assumed by the placenta [6, 24].

The hormone relaxes the muscle fibers of the uterus and maintains the elasticity of the internal os. Lack of progesterone causes hypertension, and spasms lead to dilation and shortening of the cervical canal. A similar process occurs in the absence of other important hormones, such as androgens and estradiol.

An aggravating factor in ICI is multiple pregnancy. Along with increased pressure on the cervix in such cases is often an increase in the production of the hormone relaxin. For the same reason, isthmic-cervical insufficiency is sometimes diagnosed in patients who underwent gonadotropin-induced ovulation. The probability of developing this pathology increases in the presence of a large fetus, polyhydramnios

Congenital ICI occurs in malformations of the uterus, genital infantilism [19, 20, 23].

For the first time in 1963 a group of scientists proved that cervical insufficiency is associated with structural and functional changes in the isthmic part of the uterus, the size of which varies depending on the phases of a woman's menstrual cycle. At a two-phase menstrual cycle in the 1st phase increase in a tone of uterine muscles and, accordingly, expansion of isthmic department is noted, and in the second - decrease in a tone of a uterus and narrowing of its isthmic department. It follows that functional ICI most often occurs as a consequence of a violation of the hormonal background of women [6, 10, 16, 18].

Histological examination of cervical tissue in women with ICI reveals an increase in muscle tissue up to 50%, which leads to early softening of the cervix and the development of its functional insufficiency. It has also been suggested that reduced concentrations of collagen and elastic fibers in cervical tissue lead to ICI. It is believed that these changes in cervical tissue are observed both during and outside pregnancy [15, 18, 26].

Studies by authors have shown the stimulation of osteoclasts responsible for collagen degradation, reactive oxygen species, interleukin-6 and tumor necrosis factor. Others authors argue that increased collagen synthesis and excessive accumulation of fibrous tissue cause impaired reproductive function, and hyperandrogenism before and during pregnancy stimulates collagen formation. It is also believed that a possible factor influencing collagen metabolism is the action of glucocorticoids, the level of which increases in the presence of inflammation and chronic stress [3, 8, 14, 20, 26].

At the same time Kaufman KP and co-authors claim that increasing the production of endogenous opiates by interleukin-1-dependent means reduces the collagen-synthesizing function of fibroblasts. The role of connective tissue in the development of ICI is confirmed by the fact that this pathological condition of the cervix is found in women with Marfan syndrome and Ehlers-Danlos syndrome. The role of connective tissue dysplasia as a risk factor for the development of ICI [14, 25, 26]

It has been suggested that reduced concentrations

of collagen and elastic fibers in cervix tissue lead to ICP. Connective tissue dysplasia is a group of genetically heterogeneous and clinically polymorphic pathological conditions characterized by impaired connective tissue formation in the embryonic and postnatal periods

The role of undifferentiated connective tissue dysplasia (UCTD) as a risk factor for complicated pregnancy, including ICI, is confirmed by numerous domestic and foreign authors. Development of placenta-associated complications of pregnancy in UCTD Vogel JP and co-authors explain the pathological growth of defective CT in primary microvilli at the stage of placentogenesis, which subsequently leads to the formation of pathological secondary and tertiary microvilli at the stage of vascularization and after it [9, 16, 17, 24].

At the same time, the stroma of the villi themselves is CT, which is represented by a network of collagen fibers and cellular elements in the form of fibroblasts and histiocytes, which in UCTD have a defective structure that closes the "vicious circle" in the vascular bed of the placenta. Today, CT dysplasia is understood as a disorder of its development, which is characterized by defects in the basic substance and fiber. Among the main causes of UCTD are changes in the rate of synthesis and construction of collagen and elastin, synthesis of immature collagen, disruption of the structure of collagen and elastin fibers due to their insufficient lumbar crosslinking [7, 11, 15, 19].

This explains the variety of manifestations of CT defects in its dysplasia. Authors link UCTD to severe menstrual disorders that develop in the setting of hormonal, metabolic dysfunction, and hypomagnesemia, which are characteristic of CT dysplasia. Authors emphasize the leading role of disorders of functional adaptation of the myometrium, which is inherent in UCTD [5, 9, 14, 19, 26]. As a result of impaired trophic muscle fiber and connective tissue of the uterus with an increase in CT between individual myocytes in the capillaries of the vessels with a simultaneous decrease in the number of functioning, mostly sinusoidal, capillaries with no adventitia and high permeability develops the so-called growth retardation syndrome. The latter is a premorbid background for the development of complications of pregnancy and childbirth in women with UCTD.

Research Vink J and co-authors [26] found the presence of nutritional imbalance in patients with UCTD, which was manifested by changes in serum concentrations of magnesium, calcium, zinc, iron, copper, selenium, inorganic phosphorus. The imbalance of these macro- and microelements causes metabolic disorders in the CT and creates a premorbid background for the manifestation of pathological processes in various organs and systems of the body. Some authors notes the regularity of premature maturation of the cervix during pregnancy on the background of magnesium deficiency, linking it with disorders of collagen synthesis by fibroblasts in UCTD [11, 16, 20, 26].

In recent years, studies have shown that ICI is the maturation and disclosure of the cervix, which morphologically corresponds to the general remodeling and reorganization of connective tissue. The extracellular component of connective tissue consists of collagen and elastic fibers, as well as the main (amorphous) substance.

Traditionally, isthmic-cervical insufficiency has been regarded as a result of trauma to the cervix in previous births or as a consequence of endocrinopathies leading to hyperandrogenism. However, currently a large number of studies consider the cervix primarily as an organ with a connective tissue structure. The fundamental difference between connective tissue and any other type of tissue is the excess of the extracellular matrix with a relatively small number of cells. In molecular biology, this structure is defined as a complex network formed by macromolecules of proteoglycans, collagen and elastin. By interacting with cells, these structural macromolecules maintain the structural integrity of tissues. All macromolecules are synthesized by fibroblasts, numerous chains of proteoglycans are attached to a special type of glucosaminoglycans - a polymer of hyaluronic acid called hyaluronan. Hyaluronan filaments bind the structure of the tissue together, and this polysaccharide "gel" can resist compression and stretching of the extracellular environment and at the same time provide rapid diffusion between blood and connective tissue cells. Impaired capacity of the processes underlying the premature maturation of the cervix can be considered as manifestations of undifferentiated connective tissue dysplasia. Therefore, the definition of diagnostic markers of connective tissue dysfunction is of considerable interest in terms of prevention of ICI [2, 3, 8, 26].

Some authors [1, 15] found a connection between the development of functional ICI and ICI of combined genesis with undifferentiated connective tissue dysplasia and magnesium deficiency. It is known that the cervix consists of collagen and proteoglycans. Thus, the content of connective tissue in the lower uterine segment reaches 90-95%, and in the cervix - 75%. It is known that magnesium, a deficiency of which is widespread among the population, plays an important role in the metabolism of collagen, the change of which causes premature maturation of the cervix. The author found a high frequency of the "A" allele of the ESR +2014 G A gene in the group of pregnant women with bladder prolapse [1, 15, 22, 26].

Authors point to a significant association between vitamin D deficiency and an increased risk of preeclampsia and eclampsia, gestational diabetes, miscarriage and anemia. Vitamin D also plays an important role in regulating calcium and phosphate levels by stimulating their absorption in the small intestine, thereby increasing the efficiency of intestinal calcium absorption by 30-40%, and stimulating the reabsorption of these trace elements in the proximal renal tubules. The end product of double hydroxylation of total vitamin D, first in the liver and then in the kidneys - 1,25-dihydroxyvitamin-D or calcitriol - stimulates the release of ionized Ca<sup>2+</sup> from bone tissue by maintaining the differentiation of monocytes and macrophages into osteoclasts and reduces type I collagen synthesis, which, of course, affects the state of ST, in particular CU [5, 7, 13, 18, 23].

The relationship between changes in the microcirculation system, tissue perfusion and cervical condition is currently being actively discussed and confirmed in numerous studies, as various authors have suggested that capillary blood flow disorders play a key role in the genesis of various diseases. Disorders of local microcirculation contribute to the emergence and development of pathological processes of the cervix, including connective tissue defects, trophics in tissues.

Thus, according to the author, in pregnant women with premature labor in the period of 28-34 weeks of pregnancy there is a significant increase in the concentration of pro-inflammatory cytokines. At this time, the activator of interleukin synthesis can be both infectious-inflammatory process and local thrombosis in the placenta, which indicates that thrombophilia has developed. In the serum of pregnant women with ICI noted an increased concentration of proinflammatory cytokines, which is a trigger for the activation of the synthesis of metalloproteinases, collagenases and other enzymes. This disrupts the normal structure of uterine cervix. Such processes are not characteristic of extremely early premature births. At the same time, all pregnant women with ICI at all stages of gestation have an increase in cytokine levels. Activators of their synthesis are usually intrauterine infection, polymorphism of genes of the second phase of detoxification, GHG deficiency, which triggers the mechanism of premature termination of pregnancy [3, 8, 10, 27].

Another hypothesis describes ICI as induced premature cervical maturation due to an increased inflammatory response associated with elevated cytokines, prostaglandins, and matrix metalloproteinases.

The pathogenesis of ICI development is insufficiently studied. However, an important factor in the premature termination of pregnancy in ICI is assigned to the infectious factor. The cervix together with the vagina is the first line of anti-infective protection, it is the place of greatest immunological activity. Factors of local immunity, cellular and humoral, prevent and limit the reproduction of microorganisms, preventing them from entering the upper genital tract. Thus, the cervix is the border organ between the sterile uterine cavity and the bacterially contaminated vagina [2, 12, 21, 27].

In 2020 Al-Memar M, Lee YS and co-authors found [2] the frequency and significance of intraamniotic inflammation in patients with ICP. Through amniocentesis, they collected amniotic fluid and inoculated it with aerobic and anaerobic flora, ureaplasma urealiticum, mycoplasma hominis, and also studied the activity of metalloproteinases (MMP-8), as it was previously found that the level of MMP-8 is specific and sensitive.

Intraamniotic inflammation found in 81% of women with ICI and was a direct risk factor for preterm birth and adverse neonatal outcome, and the presence of inflammation was not always combined with the presence of an infectious agent as such [2, 7, 19, 27].

At the same time, as many authors suggest, more than 75% of miscarriages are due to immunological disorders, especially in groups of pregnant women with viral and bacterial contamination of the vagina and cervical canal. The most important immunopathological changes that accompany pregnancy rejection are associated primarily with local immune processes and impaired cytokine activity, which, in turn, can affect the structure of collagen fibers and the state of the extracellular matrix of cervical tissues [2, 3, 8, 10, 27]. The results of the study of the pathogenetic role of local immune responses in women with habitual miscarriage are often contradictory and dictate the need for further research.

Abortion, both in organic and functional ICI, is probably due to several mechanisms.

First, the gradual shortening of the vaginal part of the cervix and the gaping of the cervical canal promotes

the ascending spread of vaginal flora to the amniotic membranes, which leads to their infection and violation of plastic properties.

Second, the fertilized egg, which has no physiological support, descends in the caudal direction, the amniotic membranes protrude into the dilated cervical canal and open. The contractile activity of the myometrium joins, the ovum is expelled.

As for the timing of abortion in ICI, they range from 11 to 28 weeks of pregnancy. However, according to authors, women in whom spontaneous abortions occurred before 24 weeks of gestation have a higher risk of cervical shortening in subsequent pregnancies than those in whom preterm births occurred after 24 weeks [19, 24, 26].

Impairment of the obstructive function of the uterine cervix during pregnancy remains one of the most significant problems of modern obstetrics, as they lead to extremely early premature birth and the birth of infants with profound morphofunctional immaturity. It is these newborns that form the indicators of perinatal morbidity and mortality, disability from childhood. Approximately 75% of perinatal deaths are due to premature births, and the risk of stillbirth is 8-13 times higher than in preterm births [5, 16, 25].

Thus, risk factors for ICI development are: congenital malformations of the uterus, genital infantilism, hormonal imbalance due to hyperandrogenism, luteal phase deficiency, induction of ovulation by gonadotropins, undifferentiated connective tissue dysplasia and vitamin deficiency.

Thus, the issues devoted to the study of modern approaches to the search for the most adequate methods of diagnosis and prevention of miscarriage in women with ICP are limited and are the basis for further development and implementation of prevention methods.

#### Conclusions:

1. In the pathogenesis of late pregnancy loss in almost half of the cases the cause is ICI.

2. ICI is a multifactorial complication of pregnancy, in which genetic, hormonal, inflammatory-infectious, immunological, traumatic factors, etc. play a role.

3. Impairment of uterine cervix obturation during pregnancy remains one of the most significant problems of modern obstetrics, as they lead to extremely early premature birth and the birth of infants with profound morphofunctional immaturity.

**Prospects for further research.** The pathogenesis and early diagnosis of ICI is poorly understood and requires further research to improve algorithms for care and prevention of pregnancy loss.

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### СУЧАСНІ АСПЕКТИ ЕТІОПАТОГЕНЕЗУ ІСТМІКО-ЦЕРВІКАЛЬНОЇ НЕДОСТАТНОСТІ

І.В. Левицький, Н.М. Кінаш

*Івано-Франківський національний медичний університет, кафедра акушерства та гінекології ім. І. Д. Ланового, Івано-Франківськ, Україна, ORCID ID: 0000-0001-6197-1730, e-mail: igvollev@ukr.net; ORCID ID: 0000-0002-2094-6026, e-mail: natalikinish78@gmail.com*

**Резюме.** Невиношування вагітності має різноманітні багаточисельні причини. Важливе значення у патогенезі передчасних пологів має істміко-цервікальна недостатність (ІЦН). Існуючими типами є анатомічна, функціональна, вроджена ІЦН. Тому метою нашого дослідження стало вивчення особливостей репродуктивного здоров'я і гестаційний процес у групи вагітних з ІЦН за даними спеціалізованої літератури. Для дослідження ми використали такі методи як аналіз вітчизняних і зарубіжних публікацій за темою у фахових журналах, а також дані інтернет-ресурсів. За результатами досліджень на сьогодні більшість авторів розрізняють вроджену, набуту, органічну та функціональну істміко-цервікальну недостатність.

Органічна (посттравматична, вторинна) ІЦН виникає внаслідок механічного пошкодження перешийки та шийки матки. Функціональна ІЦН є наслідком порушення співвідношення між м'язовою і сполучною тканинами шийки матки, також результатом змін реакції її структурних елементів на нейрогуморальні подразники. Вроджена ІЦН зустрічається при генітальному інфантилізмі. Є гіпотеза, що знижена концентрація колагену і еластичних волокон у тканині шийки матки веде до виникнення ІЦН. Інтраамніотичне запалення, виявлене у 81% жінок з ІЦН, є фактором ризику передчасних пологів, несприятливого неонатального результату. Фактори ризику розвитку ІЦН: вроджені аномалії розвитку матки, генітальний інфантилізм, гормональний дисбаланс, недостатність мікроелементів, вітамінів, які забезпечують функціонування сполучної тканини та виношування вагітності. Отже, ІЦН є мультифакторним ускладненням вагітності, у виникненні якого відіграють роль генетичні, гормональні, запально-інфекційні, імунологічні, травматичні фактори.

**Ключові слова:** істміко-цервікальна недостатність, передчасні пологи, недиференційована дисплазія сполучної тканини, гормональний дисбаланс, метаболізм колагену, нутритивні порушення.

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