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Биомеханизмы ремоделирования шейки матки и современные подходы к оценке степени ее зрелости

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Уникальность шейки матки заключается в возможности ее ремоделирования: размягчения, сглаживания, полного раскрытия при рождении плода и обратной трансформации до исходного состояния — плотной длинной трубчатой структуры. Проблема нарушения цервикального ремоделирования рассмотрена в аспектах как преждевременных родов, так и перенашивания беременности при запоздалой трансформации шейки матки, ведущей к ее неготовности к родам. Гистологические, иммунологические и структурные динамические изменения шейки матки начинаются задолго до родов и отмечаются уже с I триместра гестации. Известно ограниченное количество способов оценки зрелости шейки матки, позволяющих прогнозировать преждевременные роды: во II и III триметрах это ультразвуковая цервикометрия и биохимический тест на определение содержания фосфорилированного протеина-1, связывающего инсулиноподобный фактор роста, в цервикальном канале, а при доношенной беременности — пальпаторная оценка степени готовности шейки матки к родам. Неадекватная оценка характеристик шейки матки является одним из факторов несвоевременной профилактики преждевременных родов, а при доношенной беременности ведет к некорректному выбору метода подготовки к родам. Необходима разработка новых подходов к комплексной оценке шейки матки (с применением существующих методов) и способов определения степени ее зрелости.

В данном обзоре на основании литературных данных таких баз, как PubMed, ResearchGate, Google Scholar, и электронных ресурсов Научной библиотеки им. М. Горького Санкт-Петербургского государственного университета, рассмотрена проблема диагностики созревания шейки матки. В обзоре проанализированы данные о молекулярно-биохимических и гистофизиологических процессах, происходящих в период созревания шейки матки на всех этапах гестации.

Исследователи сходятся во мнении, что основную роль в изменениях шейки на всех этапах гестации играют: реструктуризация/дезорганизация коллагеновых волокон, снижение концентрации коллагена и эластина, расщепление гиалуроновой кислоты высокой молекулярной массы, повышение уровня аквапоринов и гидрофильности тканей, усиление васкуляризации, изменение содержания гликозаминогликанов и матриксных металлопротеиназ. Пальпаторная методика и ультразвуковая цервикометрия — наиболее распространенные способы определения длины шейки матки, обладающие недостаточной чувствительностью. Это, вероятно, связано с тем, что они не охватывают все патогенетические пути ремоделирования и не позволяют оценить все характеристики шейки матки. Повышение эффективности измерения возможно за счет внедрения комбинированных методик, а также использования перспективных методов, таких как эластография, ультразвуковая диагностика шейки матки с допплерометрической оценкой ее сосудов, а также определение фосфорилированного протеина-1, связывающего инсулиноподобный фактор роста, плацентарного α1-микроглобулина в цервикальном секрете и релаксина в крови матери.

Понимание молекулярно-биохимических и гистофизиологических процессов, происходящих при ремоделировании шейки матки, имеет решающее значение для прогнозирования преждевременных родов, диагностики истмико-цервикальной недостаточности, понимания отсутствия своевременной готовности шейки матки, а также выбора способа преиндукции и индукции родов при необходимости. Недостаток клинических методов и отсутствие их объективности вызывает необходимость применения комбинированного подхода и поиска новых прогностических маркеров зрелости шейки матки.

Ключевые слова: ремоделирование; шейка матки; степень зрелости; релаксин; эластография.

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Biomechanisms of cervical remodeling and current approaches to maturity assessment

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The cervical remodeling process is unique and consists of softening, ripening, dilation at fetal birth, and repair to the original state, which is a dense long tubular structure. In this review, the problem of impaired cervical remodeling is discussed in both preterm birth and delayed transformation, which leads to the unpreparedness of the cervix for childbirth and prolongation of pregnancy. Histological, immunological and structural dynamic changes in the cervix begin long before delivery and are noted as early as the first trimester of gestation. There are a few ways to assess the maturity of the cervix. In the second and third trimester, in order to predict preterm birth, these are ultrasound cervicometry and a cervical phosphorylated insulin-like growth factor binding protein-1 test. At full term, in order to determine its readiness for delivery, this is a palpation assessment. Inadequate assessment of the cervical characteristics is one of the factors of untimely prevention of preterm birth, and at full term leads to inappropriate choice of method of preparation for labor. It is necessary to develop new approaches to the comprehensive assessment of the cervix, using existing methods, and to discover new ways to assess its maturity.

In this review, the problem of cervical maturation diagnosis is considered based on literature data from such databases as PubMed, ResearchGate, and Google Scholar, as well as from electronic resources of the M. Gorky Scientific Library (St. Petersburg State University, Russia). This review analyzes data on molecular, biochemical and histophysiological processes occurring during cervical maturation at all stages of gestation.

It is generally accepted that the main role in cervical changes at all stages of gestation is played by: collagen fiber restructuring / desorganization, decreased concentrations of collagen and elastin, high molecular weight hylauronic acid cleavage, increased aquaparin level and tissue hydrophilicity, increased cervical vascularization, as well as changes in glycosaminoglycan and matrix metalloproteinase content. Palpatory technique and ultrasound cervicometry are the most common methods of determining the cervical length, which have insufficient sensitivity, probably because they do not cover all pathogenetic pathways of remodeling and cannot assess all cervical characteristics. Improvement of efficiency is possible through the introduction of combined techniques and the use of promising methods such as elastography, ultrasound diagnosis of the cervix with Doppler assessment of its vessels, determination of a disintegrin and metalloprotease with thrombospondin-like repeats-1 and placental α1-microglobulin in cervical secretion, and relaxin in maternal blood.

Understanding the molecular, biochemical and histophysiological processes that occur during cervical remodeling is crucial for predicting preterm birth, diagnosing isthmic-cervical insufficiency, understanding the lack of timely cervical readiness, and choosing tactics – the method of preinduction and induction of labor if necessary. The lack of clinical methods and their lack of objectivity require a combined approach and the search for new prognostic markers of cervical maturation.

Keywords: remodeling; cervix; maturity; relaxin; elastography.

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BACKGROUND

Characteristics of the uterine cervix (UC) in non-pregnant women vary depending on constitutional characteristics, age, and parity [1]. During pregnancy, the UC undergoes changes, and the mature UC becomes thin and easily extensible, unlike the dense UC in the early stages. This modification of tissue consistency is associated with histological changes in both the extracellular matrix and cellular composition. Changes in the UC by the type of softening were first described by Hegar in 1895. The main components of the subepithelial stroma in the UC are fibrillar proteins and cellular elements such as fibroblasts, lymphocytes, and histiocytes. The extracellular matrix mainly consists of polysaccharides, proteins, mucoproteins, water molecules, and electrolytes [2].

During pregnancy, cervical structures are partially reorganized, and endocervical epithelial cells proliferate, due to which the endocervical glands occupy approximately 50% of the entire UC mass by the end of pregnancy. Epithelial cells synthesize defensins, mucus, interleukin-6 and interleukin-8, enzymes (affecting the biosynthesis of prostaglandins), and protease inhibitors. The gradual decrease in the area of the cervical glands after week 31 of pregnancy correlates with the progressive softening of the cervix [2].

PHASES OF CERVICAL MATURATION

During pregnancy, the cervix undergoes significant structural changes, which Word et al. (2007) [3] divided conditionally into four phases, namely, softening, maturation, dilatation, and recovery. There are no clear boundaries between the phases, and they can proceed both synchronously and metachronously [4] (Fig. 1).

Softening phase

Softening (phase 1) is the longest phase, characterized by a change in the biomechanical properties of the UC, with a progressive decrease in tissue stiffness without loss of its strength. This phase starts with month 1 of gestation under the trophic influence of various hormones (mainly progesterone) and ovarian steroids [5].

The UC becomes more compliant, and its strength decreases due to the reorganization of collagen (type I by 70% and type III by 30%), increased vascularization, edema, stromal hypertrophy, hyperplasia of the cervical glands, and decreased matrix cellular proteins. Collagen is the most common protein component of the UC, and fibrillar collagen is the main structural protein that affects its extensibility. Some studies have found that the concentration of collagen in the UC progresses with increasing age, and its density correlates with parity [6]. Changes in the collagen structure are affected by the composition of glycosaminoglycans in the intracellular matrix. The total content of glycosaminoglycans in the UC increases with the progression of pregnancy and is accompanied by a sharp change in the composition [7]. Glycosaminoglycans include nonsulfated glycosaminoglycans, hyaluronic acid, and proteins containing sulfated glycosaminoglycan chains (dermatan sulfate, chondroitin sulfate, and heparin sulfate) and proteoglycans (versican, decorin, biglycan, fibromodulin, and asporin) [8].

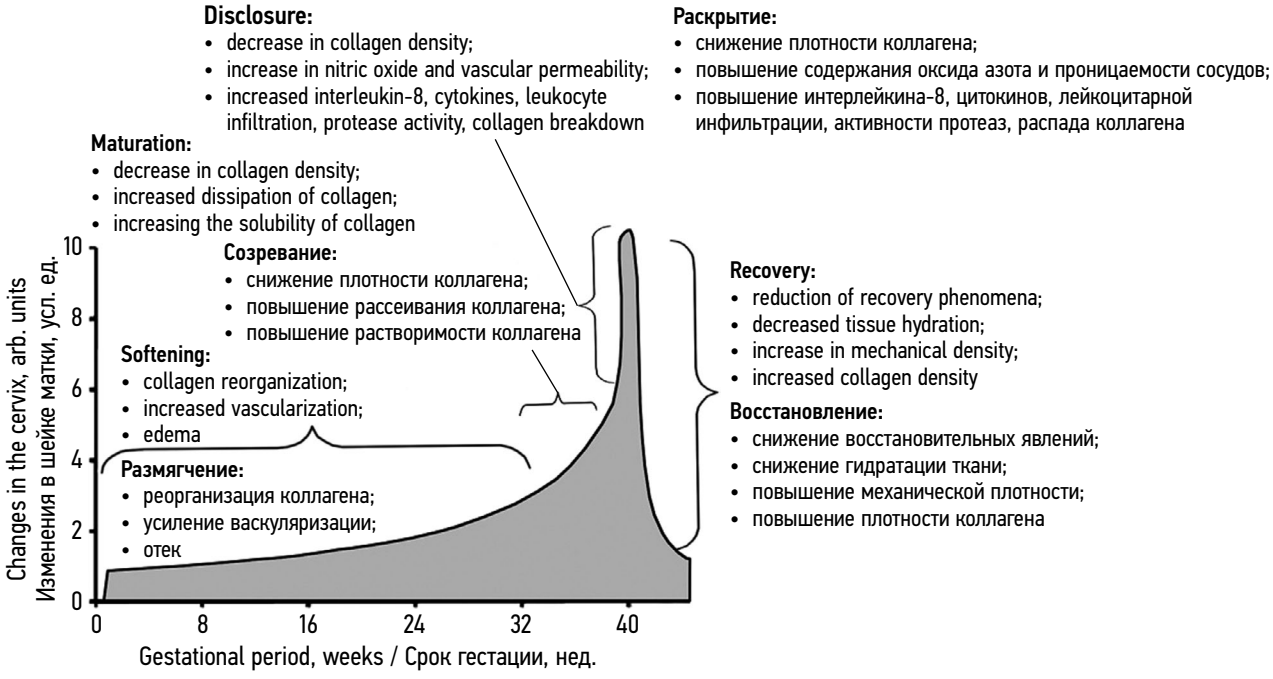

Fig. 1. Changes in the cervix during pregnancy [3] (transl. by A.V. Mokhnachyov and O.N. Bespalova)

Рис. 1. Изменения в шейке матки во время беременности [3] (перевод А.В. Мохначева, О.Н. Беспаловой)

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Elastin is encoded by the *ELN* gene (human elastin gene), is synthesized by fibroblasts to form a precursor, i.e., tropoelastin [9], and performs important functions in organs subject to constant extension and compression. During remodeling, elastin can undergo degradation with the participation of elastases of polymorphonuclear leukocytes and endopeptidases, with the formation of amino acids and cell migration pathways [10]. Rotten et al. (1988) revealed in the biopsy material of the UC of pregnant women a decrease in the content of elastin in UC tissues and constant disorganization and dissociation of its structures as pregnancy progresses [11].

In the early period of softening, the amount of mature cross-linked collagen proteins decreases and is replaced by immature collagen fibrils, which contributes to an increase in tissue compliance. During the softening phase, early changes in strength are partly the result of changes in the number and type of collagen cross-links and are associated with a decrease in the expression of two matrix cellular proteins, namely, thrombospondin 2 and tenascin C [12]. Increased expression of water channels (aquaporins) induces tissue hydration, which causes the dispersion of collagen fibers and increases their sensitivity to endogenous proteases [13].

Gene expression studies have revealed a potentially important role of the cervical epithelium in maintaining the immunomucosal barrier during its softening and maturation. The levels of protective barrier proteins, namely, trefoil factor 1 (TFF1) and serine protease inhibitor Kazal type 5 (SPINK5), increased, which prevented the penetration of infection. Reduced or absent expressions of these protective elements may contribute to the predisposition to preterm birth mediated by infection [14, 15] (Fig. 2).

The expression of the *Pcp4* gene encoding the cellular Purkinje's protein 4 (neuron-specific regulatory calmodulin protein that inhibits apoptosis) decreases as remodeling progresses [2]. Enzymes are also produced in the epithelium, whose activity increases during UC maturation, such as hyaluronan synthase 2 and 5-alpha reductase 1 (SRD5a1). SRD5a1 is involved in local progesterone metabolism in the UC. When this enzyme is inactivated, unmetabolized progesterone accumulates in the UC, which prevents the initiation of its maturation [16].

Involvement of steroid hormones. In most mammalian species, steroid hormones estrogen and progesterone have minimal effects on cervical maturation in the absence of the peptide hormone relaxin. Progesterone without relaxin or estrogen does not affect UC growth and extensibility.

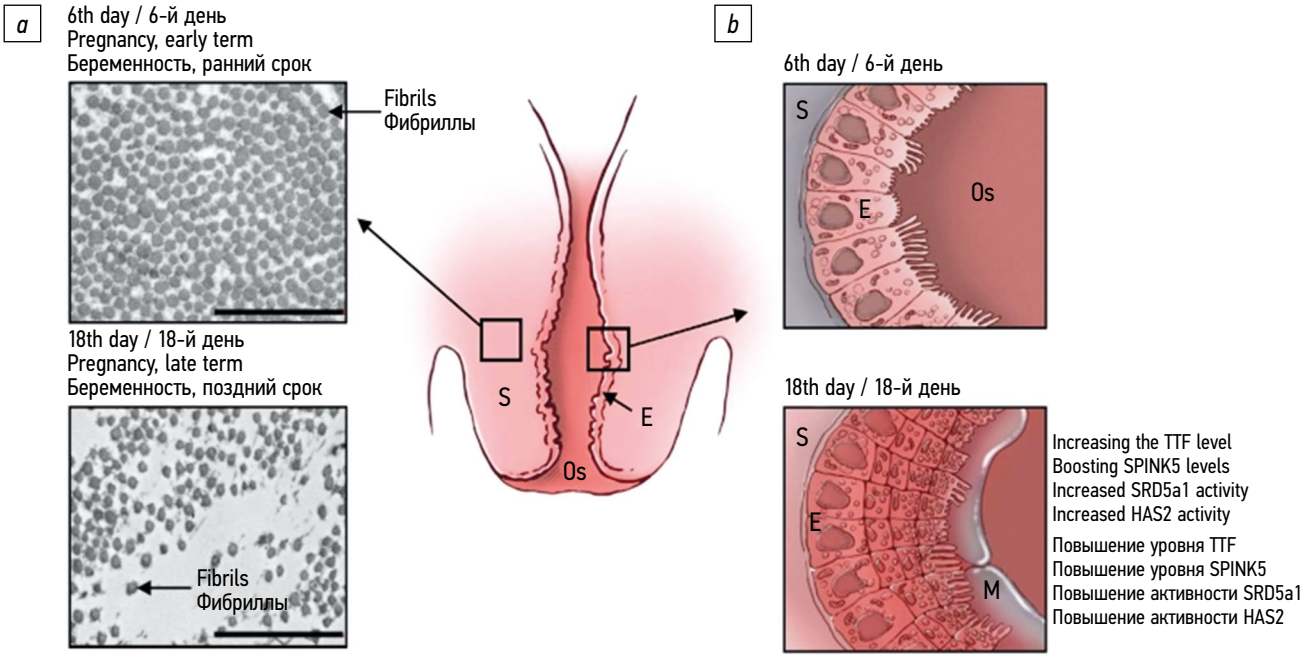

Fig. 2. Changes in the mouse cervical stroma and epithelia during the remodeling process [14]: *a*, changes in the stroma on the 6th and 18th day: the stage of disorganization of the extracellular matrix (transmission electron microscopy of a cross section of mouse cervical collagen fibrils, zoom ×20,500); *b*, changes in the epithelium on the 6th and 18th day: the increased expression of proteins. TFF1 — trefoil factor 1; SPINK5 — serine protease inhibitor Kazal type 5; SRD5a1 — steroid 5 alpha reductase type1; HAS2 — hyaluronan synthase 2; S — stroma; E — epithelium; Os — cervical opening; M — mucus

Рис. 2. Изменения в строме и эпителии шейки матки мыши в процессе ремоделирования [14]: *a* — изменения в строме на 6-й и 18-й дни: этап дезорганизации внеклеточного матрикса (трансмиссионная электронная микроскопия поперечного сечения коллагеновых фибрилл, увеличение ×20 500); *b* — изменения в эпителии на 6-й и 18-й дни: повышенная экспрессия белков. TFF1 — фактор трилистника 1; SPINK5 — ингибитор сериновой протеазы Kazal типа 5; SRD5a1 — 5-альфа-редуктаза 1; HAS2 — гилуронансинтаза 2; S — строма; E — эпителий; Os — зев шейки матки; M — слизистые включения

Hormonal regulation is probably the most studied aspect of UC maturation. Nevertheless, human hormonal regulation has not been fully recreated in animal models. Thus, the effect of progesterone decreases in proportion to the degree of UC maturity. In mice, this results from a decrease in progesterone synthesis in the ovaries and an increase in progesterone metabolism in the UC due to increased expression of SRD5a1. The inhibition of SRD5a1 activity resulted in the local metabolism of steroid hormones in the UC [14, 17].

Increased expression of 17β-hydroxysteroid dehydrogenase type 2 in the cervical epithelium maintains an elevated progesterone level at a reduced concentration of estradiol. During UC maturation and dilatation, the expression of this enzyme is suppressed, which contributes to an increase in the synthesis of estradiol and weakening of the action of progesterone. The continued activity of the reductive 20α-hydroxysteroid dehydrogenase (aldo-ketoreductase 1C1) also contributes to the further loss of local progesterone function [18].

Thus, the levels of circulating steroid hormones in the blood do not always indicate the local concentration of steroids in the cervical microenvironment, as was described in the experimental mouse model without SRD5a1 expression. Although UC maturation pathways are different in humans and mice, the local metabolism of steroid hormones is a common mechanism for the remodeling process [14]. Further studies of local hormonal activity in both animal and human models are necessary.

Maturation phase

Phase 2 starts before the development of regular uterine activity a few weeks or days before delivery. It is characterized by the maximum loss of tensile strength. The transition to this phase is mediated by hormonal influences, namely, a decrease in the synthesis and an increase in the metabolism of progesterone in the UC and an increase in the synthesis of estradiol and relaxin [14]. A study of collagen assembly genes [17] revealed the continuation of the processes initiated in the softening phase. These include increased synthesis of matrix-degrading proteoglycans such as hyaluronan and decorin, vascularization, increase in hyaluronic acid content, loosening of the collagen matrix with increased collagen solubility (degradation of cross-linked collagen), changes in the distribution of inflammatory cells (proinflammatory myeloid and lymphoid phenotypes, cytokines, regulators of chemotaxis, and cells capable of inducing oxidative stressors), increased growth, and hydration of cervical tissues [19, 20].

Increased expression of hyaluronic synthase 2, followed by an increase in the level of hyaluronic acid, is a distinguishing sign of UC maturation and dilatation [21]. Thus, in murine models, the molecular weight of UC hyaluronic acid is predominantly high before delivery and low immediately after delivery. At stage 1 (during maturation), a large molecular weight of hyaluronic acid and its association with the level of versican proteoglycan are necessary to increase the viscosity, elasticity, and extensibility of the tissues, as well as hydration and disorganization of the collagen matrix. Furthermore, the activity of hyaluronidase and the amount of disintegrin and metalloproteinase with thrombospondin 1 (ADAMTS1) motifs increased, which leads to the disruption of cross-links and destruction of hyaluronic acid. Thus, increased splitting into smaller structures can be step 2 in the loss of strength necessary for the UC dilatation [14].

In experimental studies on animal models (rats), an increase in the proliferation of the cervical mucosa epithelium in late pregnancy has been shown. In the epithelium, the number of vacuoles secreting and containing mucin increases [22, 23]. During softening and maturation, the cervical epithelium maintains fluid balance and a permeability barrier through regulated expression of aquaporins, gap junction proteins connexins 26 and 43, hyaluronic synthase 2, desmogleins, and claudin proteins [13]. In the maturation phase, the involvement of macrophages and neutrophils in the stroma is less significant than in the subsequent phases [2, 14].

Thus, it is the variations in changes in the content of proteoglycans and the proportions of various glycosaminoglycans (hyaluronic acid, dermatan sulfate, chondroitin sulfate, and heparan sulfate) that are a clinical sign of the UC maturation and dilatation [24].

In an experimental study, M. Ruscheinsky et al. (2008) [25] suggested that hyaluronic acid performs multiple cell-specific functions in cervical tissues, namely the modulation of tissue structure and integrity, and migration and differentiation of epithelial cells. Increased expression of hyaluronic synthase 2 and subsequent increase in hyaluronic acid concentrations are characteristic signs of UC maturation and dilatation [21]. Moreover, proteoglycans containing sulfated chains of glycosaminoglycans modulate the size of collagen fibrils, distance between them, and access to proteases [26].

Dubicke et al. (2016) [27] used flow cytometry and revealed an increase in the macrophage counts in biopsy specimens of the subepithelium and stroma of the UC in late gestation. This confirms the presence and probable activity of macrophages in UC remodeling. The macrophage expression of matrix metalloproteinases involved in the activation (CD147) and remodeling (CD169) of the cell matrix increases, and the activity of matrix metalloproteinases associated with adhesion (CD11bhigh) and migration (CD54) decreases. Thus, some authors characterize the normal maturation of the UC as a sterile inflammatory condition that causes its remodeling, which promotes dilatation [28]. Macrophages can synthesize nitric oxide and prostaglandins. Their inhibition suppresses

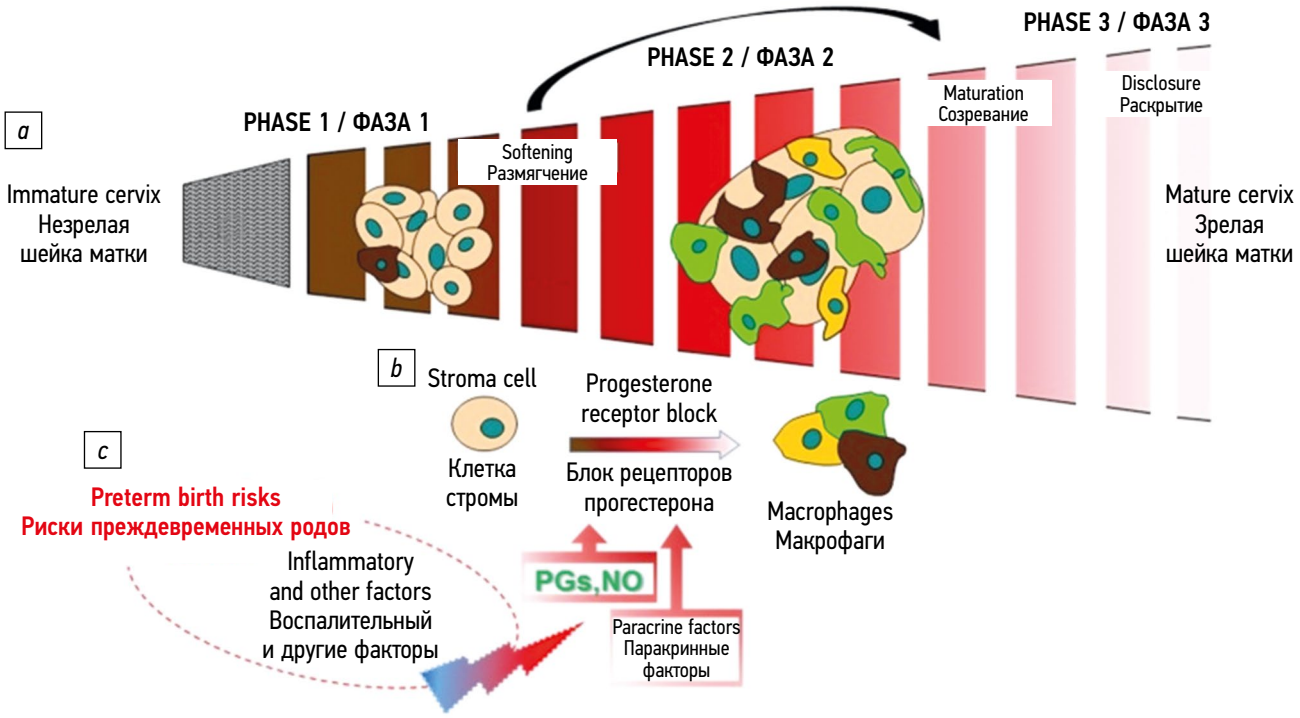

Fig. 3. Schema of preterm labor [5]: *a*, morphological structure changes in the cervix during the transition from the softening phase to the maturation phase, characterized by an increase in the number of macrophages; *b*, changes in the cervix in the transition from the phase of maturation to the phase of opening under the influence of progesterone and paracrine factors (PGs, NO); *c*, inflammatory and other factors are able to increase the risk of preterm birth when affecting the remodeling processes. PGs — prostaglandins; NO — nitric oxide

Рис. 3. Схематическая модель преждевременных родов [5]: *a* — изменения в шейке матки при переходе с фазы размягчения к фазе созревания, характеризующиеся увеличением количества макрофагов; *b* — изменения в шейке матки при переходе с фазы созревания к фазе раскрытия под влиянием прогестерона и паракринных факторов (PGs, NO); *c* — воспалительные и другие факторы способны увеличивать риски преждевременных родов при влиянии на процессы ремоделирования. PGs — простагландины; NO — оксид азота

UC softening and maturation, whereas the stimulation of nitric oxide production or the use of prostaglandins accelerate its remodeling and maturation in both animals [29] and humans [30].

Yellon et al. (2020) [31] evaluated preterm birth models and hypothesized that stromal fibroblasts combine local and systemic factors through paracrine (prostaglandins, particularly F2α, nitric oxide, proinflammatory and phagocyte-associated cytokines, chemokines, hypoxia-associated molecules, vasculoendothelial growth factors, etc.) influence on progesterone receptors and regulate the functions of resident macrophages mediating changes in the extracellular matrix of the cervical stroma. Fibrillar collagens in the extracellular matrix of the stroma are gradually replaced by less cross-linked collagens [5] (Fig. 3).

Progranulin is a glycoprotein that helps in regulating cell proliferation and differentiation. Akiba et al. (2022) observed an increase in the levels of progranulin in the blood serum in late pregnancy compared with the levels in mid-pregnancy and during childbirth. The most significant correlation was revealed between the levels of progranulin in the cervical mucus and the Bishop scale score in points before the onset of labor [32].

Dilatation phase

Phase 3 is characterized by complete dilatation of the UC to 10 cm to ensure the passage of the fetus through the birth canal at all stages of gestation. Given the short duration of the maturation and dilatation phases, identifying the processes that distinguish these two parallel phases is difficult. The dilatation phase is characterized by leukocyte infiltration with the release of collagenases and proteases into the extracellular matrix of the cervical stroma. This is the most studied phase because biopsy materials can be taken during this phase.

According to the experimental work of Mendelson (2009) [33] in mice, both term and preterm labor are associated with an inflammatory response. In preterm births, an infectious agent causes an increase in the levels of inflammatory markers in the amniotic fluid and the migration of inflammatory cells [34]. The cause of the characteristic changes in term delivery has not yet been studied.

Accumulating evidence suggests that during full-term delivery, mechanical stretching [35] caused by the growing fetus and associated hormonal signals [36] promote the production of chemokines that attract macrophages. The regulation

of inflammatory response pathways with cytokine release and activation of inflammatory transcription factors NF-κB and AP-1 are also activated by myometrial stretching. Thus, NF-κB activation promotes uterine contractility through direct activation of contractile genes (e.g., cyclooxygenase 2 and oxytocin and connexin receptors) [37] and resistance to progesterone receptors.

Radnaa et al. (2021) reconstructed a model of artificial exosomes containing HMGB1 (amphoterin, a nuclear non-histone protein involved in inflammation, being a cytoactive mediator that influences the RAGE and TLR4 receptors) and confirmed paracrine signaling by amnion exosomes that promote the preparation of the birth canal. The study also revealed that exosomes containing other protein structures (DAMP, SASP, and MAPK) can also form the inflammatory threshold required to initiate labor. To confirm this, Gomez-Lopez (2021) proved that intra-amniotic injection of HMGB1 induces inflammasome activation to enhance local inflammation associated with preterm birth in a murine model [38].

A possible factor that affects the expression of proteins, particularly connexin, is taurine (a sulfonic acid generated in the body from the amino acid cysteine). Yan et al. (2022) established that taurine enhances the expressions of α-SMA (actin) and SM-22 (smooth muscle heavy chains 22) while attenuating UC smooth muscle cells and suppressing the expression of connexin 43. Moreover, the authors concluded that taurine may play a role in the preterm maturation of the UC [39].

Stjernholm et al. (2000) demonstrated that dendritic cells and myeloid antigen-presenting cells in the cervical tissue biopsy samples of non-pregnant women are scarce or almost undetectable; however, these cells are abundant during childbirth [40]. An increase in T-lymphocytes with a predominance of $CD4^+$ in the UC during full-term pregnancy and an increase in their level by 10 times during childbirth is characteristic. The number of resident macrophages also increased in both stroma and subepithelial regions of the UC of mice during term delivery compared with those in preterm pregnancy (week 30 of gestation) [12].

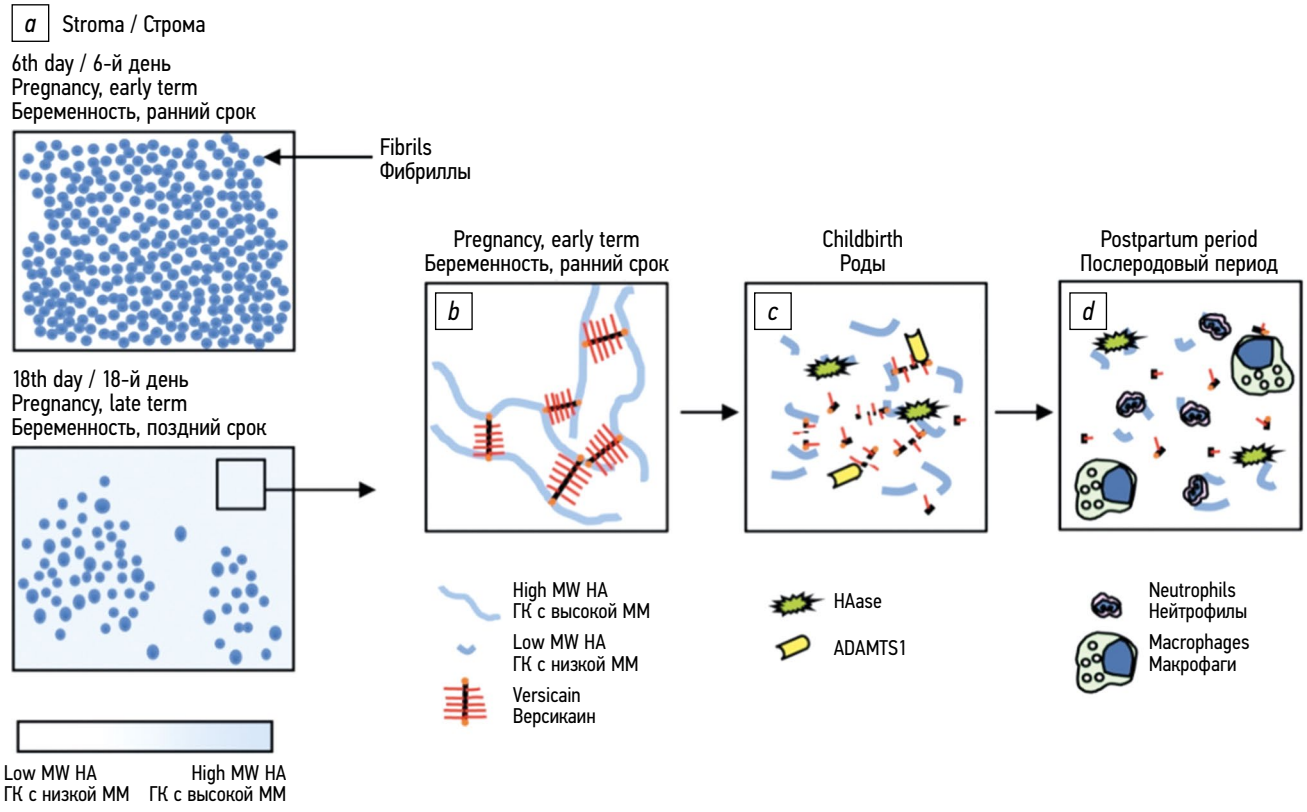

Fig. 4. Cervical stroma changes during the remodeling process [14]. *a*, change of pattern in fibril arrangement and the increase in high molecular weight hyaluronic acid; *b*, pregnancy: cross-linking between hyaluronic acid and versican; *c*, late pregnancy, labor: cleavage of cross-links between hyaluronic acid and versican by hyaluronidase and a disintegrin and metalloprotease with thrombospondin-like repeats-1; *d*, postnatal stage: repair involving neutrophils and macrophages. HA — hyaluronic acid; MW — molecular weight

Рис. 4. Изменения в строме шейки матки в процессе ремоделирования [14]. *a* — изменение расположения фибрилл и преобладание гиалуроновой кислоты с высокой молекулярной массой; *b* — беременность: образование перекрестных связей между гиалуроновой кислотой и версиканом; *c* — поздние сроки беременности, роды: разрушение гиалуронидазой, а атекже дезинтегрином и металлопротеиназой с мотивами тромбоспондина-1 перекрестных связей между гиалуроновой кислотой и версиканом; *d* — послеродовый этап: репарация с привлечением нейтрофилов и макрофагов. ГК — гиалуроновая кислота; ММ — молекулярная масса

Several researchers [41] revealed the relationship between childbirth and a significant increase in the expressions of interleukin-1β, interleukin-6, and interleukin-8 mRNA in the UC and myometrium, expressions of interleukin-6 and interleukin-8 mRNA in the choriodecidual membrane, and expressions of interleukin-1β and interleukin-8 mRNA in the amnion. Increased levels of inducible nitric oxide synthetase in the UC stroma in women with full-term pregnancy are also characteristic, regardless of labor onset [42].

The convergence of inflammatory stimuli and risk factors can be assumed to contribute to UC dilatation in time. Various proinflammatory stimuli (bacterial or viral biome in the vagina), pathophysiological factors (susceptibility), or genetic predisposition can eventually change the balance between local anti-inflammatory processes and prostaglandin metabolism and exceed the threshold for accelerating the cervical remodeling, resulting in preterm birth [14, 31].

A study described the effect of increased cortisol secretion by the human fetal adrenal glands on the expression of the prostaglandin synthase 2 gene in the placenta, which causes an increase in the production of prostaglandin E2 in the cervical area and subsequent remodeling of its matrix [43].

This phase is histologically manifested by the cleavage of hyaluronic acid and versican by hyaluronidase and ADAMTS [14] (Fig. 4).

Recovery phase

Phase 4 aims to restore the integrity and barrier function of the UC for subsequent births.

Postpartum remodeling is characterized by increased expressions of genes involved in the assembly of mature collagen and the synthesis of matrix proteins that promote the formation of dense connective tissue [25]. During postpartum recovery, low-molecular-weight hyaluronic acid, versican fragments, and damaged collagen were destroyed by neutrophils and macrophages. During this period, metalloproteinases, extracellular matrix proteins (SPARC, thrombospondin-1, thrombospondin-2, and tenascin C) [44], genes that control epithelial differentiation pathways [45], and eosinophils [46] are also activated. The postpartum activation of M1 macrophages and neutrophils generates proinflammatory molecules necessary for matrix clearance, whereas the activation of M2 macrophages prevents an excessive inflammatory response and promotes tissue regeneration. Thus, the postpartum period is characterized by a proinflammatory response [14, 47].

An important component in the recovery phase is elastin fibers, which provide reverse extensibility and restoration of cervical structures. Their role is confirmed by a decrease in the content of elastin fibers in women with isthmic–cervical insufficiency and an increase in the incidence of cervical insufficiency in women with a genetic mutation of fibrillin (a component of elastin microfibrils) [48].

ASSESSMENT METHODS OF CERVICAL MATURITY

Based on fundamental information about the biochemical and histophysiological processes that occur during UC maturation, cervicometry (for preterm birth) and palpation assessment (for full-term pregnancy) are most often employed in clinical practice to assess labor onset. A combined approach to assessing UC maturity, in addition to the above methods, may include elastography, ultrasound diagnostics of the UC, and measurement of the levels of insulin-like growth factor binding protein-1 (IGFBP-1), placental α1-microglobulin (PAMG), and relaxin.

Bishop scale. This method is used to predict the nature of labor according to UC maturity, which is determined by vaginal examination. This scale was modified by Burnett (1966), and it represents a system for UC assessment, which is most often used in clinical practice. In 1964, Bishop first introduced the pelvic score for the subjective assessment of the readiness of the UC for the induction of term labor in multiparous women; however, it was later repurposed as an indicator of cervical maturation during pregnancy and childbirth. UC maturity assessment according to Bishop is carried out manually; thus, its main disadvantage was the subjectivity of interpretation of the results of manual examination [4]. However, this method is the most common and least expensive.

Ultrasonic cervicometry. In 1986, O'Leary and Ferrell made the first attempt to assess UC maturity using a transabdominal ultrasound transducer. In 2000, Ware and Raynor used a transvaginal transducer for this purpose [49]. Ultrasound techniques enable us to estimate the length of the UC more accurately (with cervicometry) than manually, but they cannot determine the consistency and elasticity of the organ.

The abovementioned methods have low sensitivity (25%–30%) for gynecological examination and 35%–40% for cervicometry; therefore, they cannot be used independently as a screening for the risk of preterm birth [50]. The shortcomings of these clinical methods and the lack of their objectivity enable the search for new prognostic approaches for assessing UC readiness for childbirth.

Histological invasive techniques for the study of the UC are applied only in experimental animal models. The method is extremely difficult to interpret because of the complexity of obtaining biological material and the lack of diagnostic criteria.

Elastography. Elastometry/elastography of the UC was first described by Yamaguchi in 2007. It is based on the measurement of tissue density and is intended to predict preterm labor and assess the readiness of the UC for childbirth [51]. The subtypes of elastography include shear wave elastography, compression elastography (qualitative and quantitative), and E-cervix. The disadvantage of the methodology is the lack of generally accepted rating scales; nevertheless, attempts were made to create them, which lead to the development of the Preis 2010 color scale, V.E. Gazhonova scale (2008), and S.V. Nagorneva scale (2021). Although elastography has a minimal role in clinical practice, it is used to predict the successful preparation of the UC for childbirth more accurately than palpation assessment [52].

Dopplerometry. A few studies have analyzed the hemodynamics of the UC in pregnant women, limited by data on Doppler indicators in the descending branches of uterine arteries without taking into account blood flow in the vessels of the cervical stroma. Yannaeva et al. claimed that the change in the last 2 weeks of gestation is characterized not only by an increase in blood flow in uterine arteries but also by an increase in the UC blood filling due to constantly increasing arterial inflow, decreased peripheral vascular resistance, and increased volume of the UC venous bed in the presence of cavernous-like transformation of veins.

Ultrasound determination of the degree of maturity of the UC on the eve of childbirth involves the prediction of the development of adverse obstetric outcomes in the diagnosis of immature UC 1–5 days before delivery (with a vascularization index of <2%). For this purpose, an ultrasound transvaginal examination is performed in a three-dimensional Doppler mode, taking into account indicators such as the vascularization index, blood flow index, and vascularization–flow index [53].

Biochemical methods. In addition to biophysical methods, biochemical methods have been developed for UC maturity assessment. According to clinical guidelines, additional effective markers for diagnosing preterm labor are the levels of IGFBP-1 (sensitivity 92.1% and specificity 90.5%) and PAMG-1 (sensitivity 96.8% and specificity 98.3%) [50]. Very high levels of PAMG-1 are detected in the amniotic fluid, and very low concentrations are found in vaginal secretions. An attempt was made to create a Partosure clinical test. The test is recommended to determine PAMG-1 levels in vaginal secretion simultaneously with cervicometry, as a method with high specificity and predictive value in determining the possibility of outpatient treatment in the case of threatened preterm labor [54].

Insulin-like growth factors play important roles in the growth of the fetus and placenta. Phosphorylated IGFBP-1 is synthesized by decidual cells, whereas fetal fluid contains a significant amount of non-phosphorylated and, to a lesser extent, phosphorylated forms of IGFBP-1-6. As the due date approaches, the fetal membrane begins to separate from the decidua, resulting in a small amount of phosphorylated IGFBP-1 entering the cervical discharge [55].

To assess UC maturity, tests for the determination of phosphorylated IGFBP-1 (Aktim Partus, Aktim Prom) in cervical secretion have a high prognostic value and are indicated in clinical guidelines for widespread use [50]. Dalnikovskaya et al. established that in addition to shortening UC length, elevated levels of matrix metalloproteinase-9, fibronectin, and IGFBP-3 in the blood serum of pregnant women in the second trimester were reliable prognostic signs of a high-risk of preterm labor or late abortion [56]. The study of IGFBP offers a promising laboratory direction in the comprehensive assessment of the body's readiness for childbirth.

Relaxin. Several authors consider determining relaxin levels to be a highly effective method for predicting a non-developing pregnancy even before its implementation to identify high-risk populations and subsequently select an optimal pathogenetically substantiated approach for their management and exclusion of polypharmacy [57].

Relaxin is a double-stranded peptide hormone with a structure similar to insulin and insulin-like growth factors, first discovered in 1926 by Hisaw. Like insulin, mature relaxin is formed as a result of the processing of prorelaxin into a double-stranded peptide (chains A and B) using convertases. It is produced by the corpus luteum, decidua, and placenta. The highest concentration of relaxin in the blood was registered at weeks 13–14 of gestation [57].

Seven relaxin peptides were identified, namely, human relaxins 1, 2, and 3; insulin-like peptides 3 and 5, whose effects were implemented through RXFP-1, RXFP-3, RXFP-2, and RXFP-4 receptors; and native receptors for insulin-like peptides 4 and 6, which have not yet been identified. Relaxin-2 is mainly expressed in the corpus luteum, whereas relaxin-1 is expressed in the decidua, the trophoblast. Both peptides may be involved in cervical remodeling during pregnancy. The role of relaxin in mesenteric, renal, and uterine blood vessels has been evaluated the most. However, it may be also involved in the placental vasculature. In animals, relaxin prepares the birth canal for delivery, including UC maturation, thickening of the uterine endometrium, increased vascularization, and changes in collagen synthesis (Table) [59].

Researchers focused on the autocrine and paracrine roles of relaxin in the premature rupture of the membranes, which accounts for 30%–40% of preterm births, and demonstrated that the expression levels of relaxin genes and proteins in the decidua and placenta are increased in patients with the premature rupture of the membranes. Moreover, Anumba et al. revealed that patients with a history of recurrent miscarriage had low levels of circulating relaxin in all

Table. Role of relaxin during gestation [59]

Таблица. Роль релаксина в период гестации [59]

Early term	Late term
• When the cells of the endometrium stroma change, it plays an important role in its decidualization (the transformation of elongated fibroblast-like mesenchymal cells of the uterine stroma into rounded epithelial-like cells). • Modulates the MMP activity (inhibits the activity of MMP-1 and MMP-3 and enhances the activity of MMP-2). • Increases the local concentration of immunocompetent cells, selectively increases the count of neutrophils, CD56-positive (uterine natural killers) and CD68-positive (macrophages) cells in the endometrium, and does not affect CD3-positive (T-lymphocytes) cells, expression of nitric oxide synthase 2, and nitric oxide production. • Enhances angiogenesis and thus supports embryo implantation (endometrial vascularization). • Inhibits the activation of steroid hormone receptors and receptors activated by peroxisomal gamma proliferators, which can disrupt cytotrophoblast differentiation and invasion, and decreases the level of vascular endothelial growth factors	• Stimulates cervical maturation by regulating the sequential processes of degradation and remodeling of collagen. • Causes the relaxation of the ligaments of the pubic symphysis of the pelvic bones, which contributes to the optimal preparation of the female body for physiological childbirth. • Stimulates the increase in the levels of interleukin-6 and interleukin-8 in the fetal membranes, inducing labor. • Is associated with lactation and, according to some reports, activates the growth of mammalian tissues. • Plays a role in the adaptation of the female cardiovascular system with the use of RXFP1 (angiotensin II receptor), which has a cardioprotective effect.

Note. MMP, matrix metalloproteinase.

trimesters of pregnancy, in contrast to female patients without miscarriage [60]. Taking into account its histophysiological effect, relaxin can be considered a promising new predictor of the degree of UC maturity.

CONCLUSION

In the summary of data from various experimental and clinical studies, cervical remodeling can be assumed to proceed through the implementation of aseptic inflammation. UC changes at all stages of gestation are mainly attributed to restructuring or disorganization of collagen fibers, decreased concentration of collagen and elastin, cleavage of high-molecular-weight hyaluronic acid, increased content of aquaporins and tissue hydrophilicity, increased vascularization of the UC, and changes in the levels of glycosaminoglycans and matrix metalloproteinases. The palpation technique and ultrasonic cervicometry are the most common methods for determining the UC length, which have insufficient sensitivity. This may be because they do not cover all pathogenetic pathways of remodeling and do not enable us to assess all the characteristics of the UC.

Understanding the molecular biochemical and histophysiological processes that occur during UC remodeling is crucial for predicting preterm labor, diagnosing isthmic–cervical insufficiency, understanding the lack of timely UC readiness, and choosing the preinduction and induction methods of labor if necessary.

This study describes the structural processes that occur in each of the four phases of UC maturation. However, individual assessment of each phase is difficult because they can proceed in parallel, sequentially, or crosswise. Thus, the approach to assessing UC maturity cannot be one-sided and based on only one diagnostic method. The shortcomings of clinical methods and the lack of their objectivity necessitate the use of a combined approach and the search for new prognostic markers of UC maturity.

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