

# Differentiated tactics of pregnancy in women with premature rupture of membranes

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The problem of premature rupture of membranes (PROM) is unfortunately still relevant in modern obstetrics and perinatology, especially in preterm pregnancy, and leads to 20% of all cases of perinatal loss. Among the possible causes, a lot of attention has recently been paid to disorders of connective tissue structure of genetic origin. The article provides an overview of current medical literature on the causes and diagnosis of PROM. Preliminary own data on the positive effect of the advanced algorithm for detecting undifferentiated connective tissue dysplasia (UCTD) on obstetric and perinatal outcomes are also given.

*The objective:* to clarify the causes of PROM, the role of the severity of connective tissue dysplasia to predict risk factors for preterm birth, especially when combined in pregnant women with anemia.

*Materials and methods.* A total of 60 pregnant women with IDF were examined. During the survey, laboratory and instrumental methods were used. *Results.* The quality of life in women with UDCT had an inverse mean relationship between the well-being of patients and the number of phenotypes of furnace manifestations of connective tissue dysplasia ( $r=0.653$ ;  $p>94\%$ ). In addition, a high constitutionally determined level of personal anxiety was established. Quality of life depends on the number and severity of phenotypic disorders, ie the more signs of connective tissue dysplasia (hypermobility of joints, scoliosis, nephroptosis, increased bleeding, myopia, pronounced varicose veins of the lower extremities, etc.), the lower this indicator. As pregnancy progressed, worsening of health and decrease in quality of life in patients with NST were observed.

*Conclusion.* The advanced algorithm has demonstrated the positive effects in pregnant women with undifferentiated connective tissue dysplasia on obstetric and perinatal delivery, and the findings suggest that it is practiced in health care.

*Key words:* premature rupture of membranes, preterm pregnancy, undifferentiated connective tissue dysplasia.

## Диференційована тактика ведення вагітності у жінок з передчасним розривом плодових оболонок

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Проблема передчасного розриву плодових оболонок (ПРПО), на превеликий жаль, залишається актуальною у сучасному акушерстві та перинатології, особливо при недоношеній вагітності, та призводить до 20% всіх випадків перинатальних втрат. Серед можливих причин останнім часом багато уваги приділяють порушенням структури сполучної тканини генетичного походження. У статті наведено огляд сучасної медичної літератури щодо причин та діагностики ПРПО. Також наведені попередні власні дані про позитивний вплив удосконаленого алгоритму виявлення недиференційованої дисплазії сполучної тканини (НДСТ) на акушерські та перинатальні наслідки.

*Мета дослідження:* уточнення причин ПРПО, ролі вираженості дисплазії сполучної тканини для прогнозування факторів ризику передчасних пологів, особливо у разі поєднання їх у вагітних з анемією.

*Матеріали та методи.* Було обстежено 60 вагітних з ПРПО. Під час обстеження використовували лабораторні та інструментальні методи дослідження.

*Результати.* Якість життя у жінок з НДСТ мала зворотний середній достовірний зв'язок між самопочуттям пацієнток і кількістю фенотипічних проявів ДСТ ( $r=0.653$ ;  $p>94\%$ ). Крім того, встановлено високий конституціонально зумовлений рівень особистісної тривожності. Якість життя залежить від кількості і вираженості фенотипічних порушень, тобто чим більше ознак сполучнотканинної дисплазії (гіпермобільність суглобів, сколіоз, нефроптоз, підвищена кровоточивість, міопія, виражене розширення вен нижніх кінцівок тощо), тим нижче цей показник. У міру розвитку вагітності спостерігалось погіршення самопочуття і зниження якості життя у пацієнток з НДСТ.

*Заключення.* Удосконалений алгоритм продемонстрував позитивний вплив у вагітних з недиференційованою дисплазією сполучної тканини на акушерські і перинатальні результати розродження. Отримані дані дозволяють рекомендувати його впровадження у практичну охорону здоров'я.

*Ключові слова:* передчасний розрив плодових оболонок, недоношена вагітність, недиференційована дисплазія сполучної тканини.

## Дифференцированная тактика ведения беременности у женщин с преждевременным разрывом плодных оболочек

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Проблема преждевременного разрыва плодных оболочек (ПРПО), к сожалению, остается актуальной в современном акушерстве и перинатологии, особенно при недоношенной беременности, и приводит к 20% всех случаев перинатальных потерь. Среди возможных причин в последнее время много внимания уделяют нарушениям структуры соединительной ткани генетического происхождения. В статье приведен обзор современной медицинской литературы о причинах и диагностике ПРПО. Также приведены предварительные собственные данные о положительном влиянии усовершенствованного алгоритма обнаружения недифференцированной дисплазии соединительной ткани (НДСТ) на акушерские и перинатальные исходы.

*Цель исследования:* уточнение причин ПРПО, роли выраженности дисплазии соединительной ткани для прогнозирования факторов риска преждевременных родов, особенно в случае сочетания у беременных с анемией.

*Материалы и методы.* Было обследовано 60 беременных с ПРПО. При обследовании использовали лабораторные и инструментальные методы исследования.

*Результаты.* Качество жизни у женщин с НДСТ имела обратный средний достоверная связь между самочувствием пациенток и количеством фенотипических проявлений ДСТ ( $r = 0,653$ ;  $p > 94\%$ ). Кроме того, установлен высокий конституционально обусловленный уровень личностной тревожности. Качество жизни зависит от количества и выраженности фенотипических нарушений, то есть чем больше признаков соединительнотканной дисплазии (гипермобильность суставов, сколиоз, нефроптоз, повышенная кровоточивость, миопия, выраженное расширение вен нижних конечностей и т.д.), тем ниже этот показатель. По мере развития беременности наблюдалось ухудшение самочувствия и снижение качества жизни у пациенток с НДСТ.

*Заключение.* Усовершенствованный алгоритм продемонстрировал положительное влияние у беременных с недифференцированной дисплазией соединительной ткани на акушерские и перинатальные результаты родоразрешения. Полученные данные позволяют рекомендовать его внедрение в практическое здравоохранение.

*Ключевые слова:* преждевременный разрыв плодных оболочек, недоношенная беременность, недифференцированная дисплазия соединительной ткани.

The spontaneous rupture of the fetal membranes is a component of the normal delivery process. Its premature rupture of membranes, which took place regardless of the gestational period at the beginning of regular contractions [1]. In the English literature, there is a separate terminology for premature rupture of fetal membranes (PROM) in terms of preterm pregnancy – prelabor membrane rupture and PPRM for preterm pregnancy – preterm prelabor rupture of membrane [1]. This distinction is appropriate because it reflects 2 different approaches to the continued management of patients. The rupture of the fetal membranes makes delivery unavoidable, and further prolongation of pregnancy in some cases leads to chorioamnionitis and infection of the fetus. PROM complicates from 8 to 10% of all term pregnancies [2], among premature births, the rate of premature rupture of the fetal membranes reaches 30%, among multiple births – 40% [6].

According to A. Wolfensberger (2006), PROM alone accounts for up to 20% of all perinatal deaths in the United States in preterm pregnancy. The incidence of perinatal complications depends on the duration of the PROM; in preterm pregnancy up to 28 weeks, the rate of early neonatal mortality is up to 70%. Development intraamniotichnoyi infection observed in 15–30% of cases PROM, in 2–13% of such women have postpartum endometritis [3].

Despite the obvious urgency of the problem, the issues of pathogenesis and possible prognosis of PROM have not been fully clarified. The formation of fetal membranes occurs in the first trimester of pregnancy, in this process involved the tissues of the fetus (chorion) and maternal origin (decidual membrane). The strength of the fruit shells depends on the state of the collagen, their composition and the contact density between the layers [11]. Normally rupture of membranes occurs at altitude Renane one of the first stage of labor, it is preceded by a softening of membranes in the internal os of the cervix, abuse the strength of links between chorion and amnion, which is influenced by the number Throne enzymes – protease and Foz prostaglandins and cytokines activated by lipases. In the case of PROM, similar changes in the membranes occur long before delivery and are predominantly due to the local inflammatory process [5].

The search for possible causes of PROM has long interested researchers. In recent times, much attention has been paid to the connection of premature rupture of the fruiting membranes with the disruption of the connective tissue structure of genetic origin.

So, in 1997, H. Qiu sang. showed an increase in paracrine production of relaxin by the deciduous membrane, which led to the activation of a different plan of collagenases and a decrease in the strength of collagen [8].

Among the genetic causes of PROM, polymorphisms of the collagen structure gene 1a2, endothelin and serine peptidase inhibitor are distinguished [11].

Research [11] shows that the incidence of various forms, including undifferentiated connective tissue dysplasia in which raised its elastic properties PROM group is 80%. Given the impossibility of screening genetic screening for pregnant women, the authors propose to pay attention to such anamnestic risk factors as involuntary miscarriages, miscarriage in the 1st trimester, neuro-circulatory dystonia, etc., which in the structure of their etiological factors also have abnormalities.

Considering the origin and structure of the fetal membrane, which is layered by layers of the amniotic epithelium, basement membrane, connective tissue, chorion and decidual membrane, the violation of the structure and metabolism of its tissues can be explained by both fetal and maternal causes. Traditionally, activation of apoptosis processes, decrease of collagen fibers content, increase of its solubility, increase of collagenolytic activity, etc., are considered to be the cause of reduction of elasticity of the amniotic membrane [10].

Among the latest biochemical prognostic factors for preterm birth (PB) is a special place in the concentration of fetuin in amniotic fluid. Fetuin is a glycoprotein, at the ends of which are sialic acids, designed to bind free calcium. For the first time the substance was isolated from the blood of animal fruits, where the name comes from. In addition, in the international nomenclature the substance is also called a2-HS-glycoprotein [10].

Thus, the pathogenesis of premature rupture of the fetal membranes has not been sufficiently studied to develop sensitive diagnostic criteria and preventive measures. Therefore, most doctors are in contact with the problem of PROM at the stage of inevitability of childbirth and the need to choose tactics in view of the immaturity of the fetus, readiness of maternity tracts and the risk of infection of the fetal egg. Over the last 10 years, the views on preterm and preterm pregnancy complicated by PROM have changed significantly [6].

Given the inevitability of childbirth as a result of premature rupture of the fetal membranes, many attempts have been made to prevent further leakage of amniotic fluid. Fruit membranes are extremely poor in blood supply, so they show an almost complete absence of healing in the experiment. It is believed that the closure of the defect of membranes after amniocentesis is due to their adhesion, and not by cell proliferation and the typical healing process [3].

There are three groups of factors contributing to PROM: uterine factors of the general plan, uterine-placental factors and factors of other origin [2].

Maternal factors of the overall plan:

- PROM in previous pregnancies (16–32% compared with 4% in women who had no previous pregnancy with this complication);
- bleeding during pregnancy;
- long-term corticosteroid therapy;
- connective tissue diseases (such as Ehlers-Danlos syndrome, systemic lupus erythematosus);
- abdominal trauma;
- premature birth;
- smoking;
- addiction;
- anemia;
- low body mass index (less than 18.8 kg/m<sup>2</sup>);
- low socio-economic status.

Uterine placental factors include:

- abnormalities of uterine development (such as uterine septum);
- premature placental detachment (10–15% of PROM);
- isthmio-cervical insufficiency;
- anamnesis cervical conization;
- shortening of the cervix in the 2<sup>nd</sup> trimester is less than 25 mm;
- overstretching of the uterus (polyhydramnios, multiple fertility);
- intra-amniotic infection (chorioamnionitis).

Factors of other origin include: repeat vaginal examinations (does not apply to studies using sterile mirrors or transvaginal ultrasound); amniocentesis in this pregnancy; suturing of the cervix; vaginal infections and dysbiosis.

After specifying the duration of pregnancy, it is necessary to assess the condition of the mother and the fetus to determine the indications and contraindications to the continuation of pregnancy. To this end, study the data of the anamnesis of the mother, the features of the course of this pregnancy, indicators of clinical and laboratory studies.

In assessing the condition of the fetus use the results of ultrasound, including the definition of amniotic index, which allows to determine the degree of shallow water, and, when deciding on the expense of waiting tactics, to control the situation in the dynamics. Use Doppler measurement of blood flow in the fetoplacental

**Criteria for the severity of connective tissue dysplasia (Smolnova T.Y., 2003)**

<b>Small signs (1 point each)</b>	Asthenic constitution type or underweight The absence of structures on the skin of the anterior abdominal wall in women who had a history of childbirth Violation of refraction at the age of 40 years Muscle hypotension and low manometry Flattening of the arch of the foot Tendency to easy bruising, increased tissue bleeding Postpartum bleeding Vegetative-vascular dysfunction Disorders of the heart rhythm and conduction (ECG)
<b>Great signs (2 points each)</b>	Scoliosis, kyphosis, kyphoscoliosis Flatfoot of 2–3 degree Elastosis of the skin Hypermobility of the joints, tendency to dislocation, stretching of the joint apparatus of the joints Tendency to allergic reactions and colds Tonsillectomy Varicose disease, hemorrhoids Dyskinesia of the biliary tract Disorders of the evacuation function of the gastrointestinal tract The threat of premature birth at 32–35 weeks of gestation, premature birth Fast and rapid births with a history of hypotonic bleeding in or without childbirth Genital prolapse and hernia in first-line relatives
<b>Severe manifestations and conditions leading to, or indicative of, surgical interventions, as well as anatomical changes that led to impaired organ function (3 points each)</b>	Hernia Splanchnoptosis Varicose disease, hemorrhoids (surgical treatment), chronic venous insufficiency with trophic disorders Usual dislocations of joints or dislocations of more than two joints Disorders of the motor function of the gastrointestinal tract, confirmed by radiological examination methods Diverticula, dolichosigma. Polyvalent allergy, severe anaphylactic reactions

system and cardiocographic examination, determine the fetal biophysical profile (FBP).

**The objective:** of our study was to clarify the causes of PROM, the role of the severity of connective tissue dysplasia to predict the fact that pts are at risk of preterm birth, especially when combined in pregnant women with anemia.

**MATERIALS AND METHODS**

We examined 60 pregnant women with PROM at the age of 25–11 (18.3%), from 26 to 30 years – 19 (31.6%), from 31–35 years – 19 (31.6%), over 36–11 (18.3%). There were 23 births (38.3%) and 37 (61.7%). The gestational age (term of delivery) was within 22–28 weeks – 13 (21.6%), pregnant women 29–30 weeks – 12 (20%), 31–36 weeks – 35 (58.4%).

**RESULTS**

Laboratory and instrumental methods were used during the survey. The prevalence of untreated bacterial vaginosis in 31.8% of cases, acute viral infection – in 24.3%, urogenital candidiasis – in 19.2%, kidney disease: asymptomatic bacteriuria, chronic cystitis, chronic pyelonephritis – was specified in the anamnesis in 17.8%. Bad habits: smoking, abuse of beer, wine – in 5.8% of cases. Complications of Pregnancy: gestational hypertension without proteinuria – 10.3%, iron deficiency anemia – 38.4%, early preeclampsia – 13.5%, varicose veins of the lower extremities was identified in 35% of pregnant women.

Cesarean delivery was completed before this pregnancy in 6 (10%) women. In 11 pregnant women under 25 years of age, 13 children were born alive (twin – 3), 1 premature baby died within 27–28 weeks. Pregnant women aged 31–35 years, all living mother, but the children, who died – 4, including one – with twins. In pregnant women older than 36 years who gave birth to 5 twins, premature deaths was 7 causes of death were preterm

infants changes in microbiology placenta, perinatal hypoxic-hemorrhagic lesions of the central nervous system, intraventricular bleeding, necrotizing enterocolitis in stage 3B, bowel perforation, prematurity, jaundice of premature baby.

In our study, gram-positive and gram-negative microorganisms were found in pregnant women among potentially pathogenic infectious agents. Thus, almost every third pregnant with intermediate type of vaginal biocenosis identified Staphylococcus epidermidis and Enterococcus Faecalis (30.3% and 30.3%, 29.63% and 33.33%, respectively, in the group of women 25–30 years and after 31–35 years), in every fifth Streptococcus group B (18.18 and 18.52%); in 12.12% and 14.81 % of women, respectively, of Escherichia coli, which is also associated with inflammatory diseases of the urinary tract and pelvic organs; Gardnerella vaginalis, a known causative agent of bacterial vaginosis – in 15.15% and 14.81% of pregnant women, respectively. At the same time, the contamination of the vagina with these microorganisms and fungi of the genus Candida saprophyte did not reach a diagnostically significant level.

To understand the pathogenesis of complications of prematurity, PROM reasons, it was necessary to analyze not only the risk (violation habitat vagina untreated in den paths and contribution and extra-genital diseases), but the presence UDCT our patients.

To establish a link between anemia and UDCT and pregnancy and childbirth all pregnant women were analyzed according to the criteria of severity undifferentiated connective tissue dysplasia according to Table 1 (for. Smolnova T.Y., 2003).

In recent years, most authors have paid attention to the issue of pregnancy and childbirth in women with connective tissue dysplasia and iron deficiency anemia [11], given that our patients with PROM also had connective tissue dysplasia and anemia, and we consider it advisable to discuss these issues for extension.

Dysplasia of the connective tissue is characterized by a combination of numerous phenotypic features that represent

**Prevalence of DCT phenotypic features in pregnant women who had elevated iron levels in placental tissues. Significant differences in the frequency of prevalence of these states are presented**

Metric, %	The Fe ↑ group	Fe ↓ groups	p
Curvature of the nasal septum	0	0.12	0.041
Skin hypertension	0	0.24	0.006
Allergy	0	0.24	0.006
Sinus tachycardia	0	0.12	0.041
Nephroptosis, 1st degree	0	0.16	0.021
Gastroesophageal reflux	0	0.12	0.041
Deviation of the little fingers	0.57	0.20	0.053
Hemorrhoids	0.57	0.04	0.019
Myopia unchanged on the fundus	0.57	0.12	0.034

impaired formation of the connective tissue framework. In general, the clinical and morphological manifestations of DCT are extremely wide:

- cartilage disorders,
- disproportionately long extremities,
- arachnodactyly,
- chest deformity,
- spinal scoliosis,
- flat feet,
- pathology of development of teeth,
- bite,
- cysts,
- pathology of joints (tendency to subluxation),
- susceptibility to skin trauma,
- varicose veins and many other symptoms.

Undifferentiated DCT (UDCT) in obstetrics is of particular importance, often leading to various complications of pregnancy and childbirth. Pregnancy and DCT are characterized by a negative effect. Deficiency of a number of trace elements in pregnant women with UDCT, lead to its complication. One of the major cofactors of enzymes in connective tissue metabolism is iron.

In 45% of pregnant women, mild anemia (Hb <100 g/l, but not less than 90 g/l) was formed in the second trimester, the color index was  $0.84 \pm 0.06$  units, the volume of erythrocytes of patients fluctuated on average  $83 \pm 5 \mu\text{m}^3$ , microcytosis occurred in 12% of the examined, anisocytosis – in 12% of the examined. When necessary, in clinical manifestations of iron deficiency anemia, pregnant women received trivalent iron, the purpose of which was justified by a decrease in the level of ferritin in the serum.

We needed to study the effect of iron content in serum and in placental tissues by mass spectrometry on pregnancy and preterm birth in UDCT patients. In the study group of pregnant UDCT (n=47) prevalence of phenotypic traits of UDCT in pregnant women with low and high levels of iron was different (Table 2).

Iron deficiency anemia is usually associated not only with iron deficiency but also with deficiency of copper, manganese and other trace elements [10]. For the formation of the normal placenta and gestational process, it was necessary to ensure adequate content of these trace elements not only at the stage of pre-gravid preparation, but also during pregnancy, taking into account the presence of UDCT and premature birth, which were complicated by PDO.

Thus, a comprehensive study of the interaction between the manifestations of DCT, the metabolism of connective tissue, such trace elements as iron, copper, manganese, complications of pregnancy and childbirth is quite a promising area for research. It is important to note the extremely complex nature of these interactions. First, UDCT is characterized by a combination of numerous phenotypic manifestations, and secondly, there are a large number of connective tissue abnormalities. Obviously, the analysis of so many severe traits requires the use of specific methods of studying such clinical trial data.

Given the systemic damage of undifferentiated dysplasia of the connective tissue (UDCT), which adversely affects the course of pregnancy (exacerbation of urogenital infection, impaired functional status of the fetoplacental complex, miscarriage, perinatal morbidity and mortality birth). Thus, the risk of miscarriage reached 51.7% in women with UDCT, placental dysfunction, premature rupture of the fetal membranes (100%) were very often observed.

The quality of life in women with UDCT had an inverse mean relationship between the well-being of patients and the number of phenotypes of furnace manifestations of connective tissue dysplasia ( $r=0.653$ ;  $p>94\%$ ). In addition, a high constitutionally determined level of personal anxiety was established. Quality of life depends on the number and severity of phenotypic disorders, ie the more signs of connective tissue dysplasia (hypermobility of joints, scoliosis, nephroptosis, increased bleeding, myopia, pronounced varicose veins of the lower extremities, etc.), the lower this indicator. As pregnancy progressed, worsening of health and decrease in quality of life in patients with NST were observed.

## CONCLUSIONS

1. The results of the study showed the positive effect of our improved algorithm in pregnant women with undifferentiated connective tissue dysplasia on obstetric and perinatal delivery.
2. The obtained data allowed us to recommend an improved algorithm of diagnostic and treatment-and-prophylactic measures (except for the use of medication correction in accordance with obstetric complications arising and functional condition of the fetoplacental complex), for widespread implementation in practical health care, especially in pregnant women with premature rupture of membranes.

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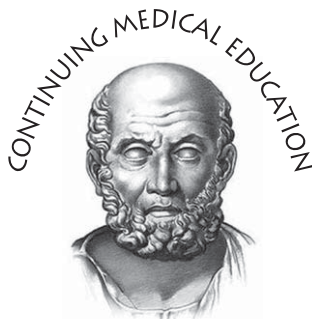


ВСЕУКРАЇНЬСЬКА АСОЦІАЦІЯ  
БЕЗПЕРЕРВНОЇ  
ПРОФЕСІЙНОЇ ОСВІТИ  
ЛІКАРІВ  
ТА ФАРМАЦЕВТІВ



ГО «ВСЕУКРАЇНЬСЬКА АСОЦІАЦІЯ НЕПЕРЕРВНОЇ ПРОФЕСІЙНОЇ ОСВІТИ ЛІКАРІВ І ФАРМАЦЕВТІВ»  
НАЦІОНАЛЬНА МЕДИЧНА АКАДЕМІЯ ПІСЛЯДИПЛОМНОЇ ОСВІТИ ІМЕНІ П.Л. ШУПИКА

## «ГІППОКРАТ» – сучасна електронна платформа післядипломної медичної освіти для лікарів



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