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Possibilities for predicting prelabor rupture of membranes

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Prelabor rupture of membranes occurs in 20% of all pregnancies, while in the structure of preterm labor it occurs in 40% of cases. Particular attention to prelabor rupture of membranes is primarily due to the risk of developing septic complications being increased as the duration of the anhydrous interval increases. Currently, there are no effective methods for preventing prelabor rupture of membranes. Therefore, the timeliness of prevention of fetal respiratory distress syndrome depends on the effectiveness of the prognosis of this condition. The aim of this study was to assess the possibilities for predicting prelabor rupture of membranes. This was achieved by using an analytical method including carrying out a detailed systematic analysis of modern domestic and foreign literature on predicting prelabor rupture of membranes. The study used databases such as eLIBRARY.RU, Scopus, PubMed, MEDLINE, ScienceDirect, Cochrane Library and FIPS from the creation until December 2020. An integrated approach to assessing the likelihood of prelabor rupture of membranes will allow optimizing the tactics of pregnancy and labor management, which in the future will reduce not only the incidence of maternal and perinatal morbidity, but also the frequency of operative delivery.

Keywords: prediction; rupture of membranes; wrong time; premature; preterm; prelabour; early intranatal; later intranatal.

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Возможности прогнозирования несвоевременного излития околоплодных вод

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Несвоевременное излитие околоплодных вод встречается в 20 % случаев общего числа родов, в структуре же преждевременных родов оно происходит в 40 % случаев. Особое внимание к преждевременному излитию околоплодных вод в первую очередь обусловлено повышением риска развития септических осложнений по мере нарастания длительности безводного промежутка. В настоящее время не существует эффективных методов профилактики преждевременного излития околоплодных вод, поэтому от точности прогноза данного состояния зависит своевременность профилактики респираторного дистресс-синдрома плода. Целью данного исследования явилось изучение возможностей прогнозирования несвоевременного излития околоплодных вод. Цель исследования была достигнута путем применения аналитического метода: проведен детальный систематический анализ современной отечественной и зарубежной литературы, посвященной прогнозированию несвоевременного излития околоплодных вод. В исследовании использованы такие информационные базы, как eLIBRARY.RU, Scopus, PubMed, MEDLINE, ScienceDirect, Cochrane Library и ФИПС, с момента создания до декабря 2020 г. Комплексный подход к оценке вероятности несвоевременного излития околоплодных вод позволит оптимизировать тактику ведения беременности и родов, а в перспективе позволит снизить частоту не только материнской и перинатальной заболеваемости, но и оперативного родоразрешения.

Ключевые слова: прогнозирование; излитие околоплодных вод; несвоевременное; преждевременное; дородовое; раннее; запоздалое; разрыв плодных оболочек.

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BACKGROUND

The terminology demonstrating the structure of the untimely discharge of amniotic fluid (UDAF) is rather confusing [1], mainly because a wide variety of opinions and classification approaches are applied to the concept [1–5]. The term "preterm discharge of amniotic fluid" (PDAF) is understood by most Russian authors as the rupture of the fetal membranes prior to the development of regular labor, regardless of gestational age [1–4]. In the current international classification, the term "prelabor rupture of membranes," which is identical in meaning to "prelabor discharge of amniotic fluid" (PLDAF), is used if the gestational period is 37 weeks or more [1]. When amniotic fluid (AF) discharge occurs at a gestational age of less than 37 weeks, the term "preterm prelabor rupture of membranes," which actually corresponds to PDAF, is used [1]. In general, the opinions of leading experts in obstetrics on the delayed discharge of AF coincide, that is, discharge is considered delayed if the fetal bladder remains intact with the full dilatation of the uterine orifice for a certain period of time [2–4]. The most controversial terminology in this context is the interpretation of "early discharge of amniotic fluid" (EDAF). While some authors consider this diagnosis legitimate in cases where AF discharge occurs when the uterine orifice opens by less than 6 cm, other authors consider the diagnosis only when the uterine opening is less than 7–8 cm; others consider EDAF valid so long as uterine orifice dilatation is incomplete [2–4]. According to O.R. Baev et al., AF discharge should be considered to occur early when the uterine orifice opens by less than 4 cm [5]. From the physiological point of view, each of these authoritative opinions certainly has a logical basis. In the active phase of labor, the tension of the fetal bladder increases with each contraction, and the rupture of the organ may lead to AF discharge. At the same time, the constant tension of the fetal bladder during contractions and in the pauses between them is normally registered only when the uterine orifice is nearly completely dilatated [4]. Given these inconsistencies, the issue of UDAF classification can only be resolved by creating clinical guidelines approved by the Ministry of Health of the Russian Federation.

Despite the uncertainty in some aspects of UDAF classification, from a practical point of view, the prediction of premature and prenatal AF discharge is of great interest. The risk of septic complications is well known to increase as the duration of the period without AF increases [1, 5]. In addition, PLDAF and PDAF are common complications of pregnancy; for example, the incidence of PLDAF (at full-term) is 8%–10% while that of PDAF (at premature terms) is 20%–40% [5]. Preterm rupture of membranes (PROM) is accompanied by a fourfold increase in the frequency of perinatal mortality and threefold increase in the frequency of neonatal morbidity. This finding may be attributed to the fact that the most common complications of PDAF are preterm labor and its associated conditions, such as prematurity, sepsis, and pulmonary hypoplasia [5]. However, at present, no effective methods to prevent PDAF are yet available. Therefore, the timely prevention of fetal respiratory distress syndrome depends on the accuracy of the prognosis of this condition. The possibility of predicting PLDAF holds significant value because AF discharge in case of an immature parturient canal is often accompanied by the development of abnormalities in labor, fetal distress, chorioamnionitis, and, often, cephalhematomas and prolapse of small parts of the fetus. Poor uterine contraction strength in the presence of untimely rupture of the fetal bladder has been recorded in approximately 60.5% of all women in labor [6]. A wide range of complications in UDAF affect the frequency of delivery by cesarean section, which is also an important risk factor for postpartum infectious complications; indeed, the frequency of these complications increases by 5–20 times in the presence of UDAF [7]. The efficiency of predicting the time of PLDAF onset determines the feasibility of the preventive preparation of the parturient canal upon reaching full-term gestation. Such a measure has been hypothesized to be able reduce the frequency of not only maternal and perinatal morbidity but also operative delivery.

The study aimed to analyze the possible prognoses of UDAF at the current stage. Specifically, a detailed systematic analysis of modern Russian and international literature on the prognosis of UDAF was performed. Studies published in popular informational databases, such as eLIBRARY, Scopus, PubMed, MEDLINE, ScienceDirect, Cochrane Library, and the Federal Service for Intellectual Property, from the time of creation until December 2020 were included in this analysis.

Assessment of risk factors for untimely discharge of amniotic fluid

Risk groups, including those determining the probability of UDAF [4], have been identified in the Russian Federation for many years. A number of maternal, fetal, and uteroplacental risk factors have been identified. Maternal risk factors include inflammatory diseases of the female genital organs and sexually transmitted infections; PDAF during a previous pregnancy (risk of recurrence, 16%–32%); uterine bleeding during the present pregnancy; long-term glucocorticoidal therapy; systemic connective tissue diseases; and isthmic-cervical insufficiency. According to the results of G.E. Guseynova and Z.S. Khodjaeva, PROM is often registered in primigravida primiparous women who are somatically burdened with frequent respiratory and odontogenic inflammatory diseases. In addition, PDAF often occurs when diseases of the cervix and uterine fibroids are present [8]. Uteroplacental risk factors include placental abruption, which is complicated by UDAF in 10%–15% of

all cases; abnormalities in the development of the uterus; and intra-amnial infection [5, 6]. Fetal risk factors include incorrect position and presentation of the fetus and multiple pregnancies, which could complicate PDAF in 7%–10% of the cases. A special risk group includes injuries and iatrogenic invasive interventions (e.g., amniocentesis, obstetric cerclage) [6]. According to a prospective study by D. Bouvier et al., which included nearly 7000 birth cases, the specific risk factors for PDAF are weight deficit (OR 2.00; 95% CI 1.09–3.67; $p < 0.05$), PDAF during a previous pregnancy (OR 2.75; 95% CI 1.19–6.36; $p < 0.05$), first birth (OR 2.52; 95% CI 1.77–3.60; $p < 0$ 05), gestational diabetes mellitus (OR 1.87; 95% CI 1.16–2.99; $p < 0.05$), and low educational level (OR 2.39; 95% CI 1.20–4.78; $p < 0.05$) [9]. However, for pregnant women with PROM, a combination of several risk factors in the present pregnancy is often observed [8]. Another approach involving the allocation of factors related to past and present pregnancy has been reported to describe the prognosis of UDAF [10]. However, the classification method is not of fundamental importance in determining the probability of UDAF. In addition, while the risk factors described herein are widely known, the time of the onset of UDAF cannot be predicted accurately because of its multifactorial etiology. According to E. Lorthe, the overwhelming majority of patients with PDAF have no risk factors, and individual predictions based on an assessment of risk factors and measures of primary prevention have not proven their efficiency [11].

Because no convincing data on the possibility of predicting the time of onset of UDAF via the assessment of risk factors are available, diagnostic measures are of great importance in such predictions. According to some authors, UDAF is mainly caused by the structural aspects of the collagen filaments of the fetal membranes, which determine their mechanical and biological properties; other authors do not exclude the role of the expression of long-chain non-coding RNAs that regulate the work of messenger RNAs and, thus, affect the proliferation, differentiation, and apoptosis of cells [12–15]. Some scholars believe that the most important role in the initiation of PROM is played by mechanisms mediated by the intensive aging of cells during oxidative stress, the indicators in the fetal membranes of which may include the shortening of leukocyte DNA telomeres, an increase in the activity of phospho-p38 mitogen-activating protein kinase, or a decrease in the activity of antioxidant enzymes, among others [16–19]. A direct study of the fetal membrane tissues or the AF structure could certainly provide accurate information on the probability of UDAF. However, given the desire of modern medicine for minimally invasive technologies, more accessible, reliable, but less invasive technologies are preferred, especially since invasive procedures, such as amniocentesis or biopsy of local tissues, to identify significant markers, can also induce UDAF [6, 20]. As such, today, along with instrumental and clinical research methods, preference is given to the biological fluids or body tissues most accessible for analysis, including whole blood/serum/plasma, saliva, urine, buccal epithelium, and cervico-vaginal contents.

Assessment of the probability of untimely discharge of amniotic fluid by analyzing the cervico-vaginal contents

Since the main risk factor of UDAF is intra-amnial and associated infection, analysis of cervico-vaginal contents is of great importance in assessing the prognosis of the condition. M.A. Kaganova et al. indicated that PLDAF occurs 2.6–3.8 times more often in patients with bacterial vaginosis than in those without, but the diagnosis of vaginal dysbiosis is not always a significant predictor [21]. In this case, studies on the state of the cervical canal biocenosis, as the most significant barrier delimiting the uterine cavity from the external environment and biocenosis of the vagina, are highly promising. The authors performed real-time polymerase chain reaction with the Femoflor-16 diagnostic panel to analyze a smear from the cervical canal at full-term pregnancy and determine the probability of PLDAF. According to the authors, decreases in the level of *Lactobacillus* spp. of less than 99.3%, increases in the levels of *Gardnerella vaginalis* / *Prevotella bivia* / *Porphyromonas* spp. of over 0.08%, and increases in the levels *Megasphaera* spp. / *Veilonella* spp./*Dialister* spp. of over 0.06% indicate a high risk of PLDAF (Table 1).

The prognostic accuracy index combining the simultaneous presence of all three significant indicators is 78.7% [21] because dysbiosis leads to the stimulation of apoptosis and collagenolytic activity of matrix metalloproteinases of the fetal membranes. PLDAF most often occurs in cases where the predominance of anaerobic flora, a decrease in the concentration of *Lactobacillus* spp., and the appearance of

Table 1. Assessment of indicators of smear from the cervical canal in predicting predelivery discharge of amniotic fluid

Indicator	Sensitivity, %	Specificity, %
Lactobacillus spp. less than 99.3%	75.0	68.0
Gardnerella vaginalis / *Prevotella bivia* / *Porphyromonas* spp. of over 0.08%	64.3	73.7
Megasphaera spp. / *Veilonella* spp. / *Dialister* spp. of over 0.06%	66.7	52.6
Simultaneous presence of the three indicators mentioned above	85.5	68.4

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Raoultella spp. are observed in scrapings from the cervical canal [22].

According to T.N. Pogorelova et al., the study of vaginal contents presents sufficient prognostic value [23]. The researchers believe that assessment of neuraminidase activity in the vaginal contents represents the most pathogenetically valid test for predicting the outcomes of the condition. According to the authors' data, the high probability of PDAF is evidenced by neuraminidase activities equaling 2.5 mmol/l or higher. Determination of this enzyme activity may thus enable the prediction of PDAF with 100% accuracy [23]. While this conclusion must certainly be confirmed in multicenter studies, the prospective value of this indicator cannot be denied.

Assessment of the probability of premature discharge of amniotic fluid based on the analysis of body fluids most accessible for sampling

A large amount of research focusing on the role of cytokines in predicting UDAF has been published. Some authors believe that assessment of the level of interleukins (IL) in the AF presents the greatest predictive capability compared with other techniques. In particular, R.M. Holsi et al. believed that an increase in the levels of IL-8 and IL-6 in the AF indicates a high probability of PROM [24]. Proinflammatory ILs, as members of the chemokine family, stimulate neutrophil chemotaxis, changes in cell shape, polymerization and degranulation of actin, and increases in the production of reactive oxygen species in response to various inducers. Neutrophils attracted to the inflammation focus, in turn, enhance the production of elastase, which damages the membranes [25]. However, AF sampling is an independent risk factor for PDAF on account of its invasiveness; therefore, such measurements cannot be performed in a wide range of patients. In addition, the levels of cytokines with preterm and timely discharge of amniotic fluid (TDAF) are different ($p < 0.05$) both in the blood serum and in the AF (Table 2) [25].

Increases in IL-8 and TNF-α levels indicate pathological disorders in the cytokine network of the fetal-placental complex, which is probably associated with the progression of non-infectious inflammatory process [25]. The coordinated increase in the concentrations of TNF-α and IL-8 in both the AF and blood serum raises doubts as to whether invasive interventions are necessary to obtain an appropriate prognosis. A blood test is more accessible and does not cause stressful reactions in a pregnant woman; therefore, it may be the preferred approach.

In contrast to other authors, N.Yu. Sotnikova et al. obtained completely opposite results and found that PDAF could be characterized by IL-8 levels equal to 15.4 ng/ml or less determined in blood serum at 32–36 weeks of gestation. According to the researchers, the decrease in the IL-8 level in the peripheral blood of patients with PDAF indicates a transfer in the production of IL-8 from the systemic level to the local one, which leads to a process that triggers this pathology. The presented data revealed that the method described is simple in execution and allows PDAF prediction with high accuracy (86%), sensitivity (90%), and specificity (81%) [26]. Determining the level of IL-8 by this method does not exceed 2 h, therefore it can be widely used.

According to the results of S.M. Lee et al., who assessed the levels of IL-6, IL-8, MCP-1, MIP-1α, and MIP-1β in maternal blood plasma, cervico-vaginal contents, and AF, the levels of these proinflammatory cytokines in the cervico-vaginal contents strongly correlate with those in the AF but weakly correlate with their corresponding levels in blood plasma [27]. This finding casts doubt on the significance of these prognostic markers of blood plasma in predicting PDAF. According to S. Ronzoni et al., the level of endotoxin (EAA) in the blood of women with PDAF, which is equal to 0.43 ± 0.18, is 1.2 times higher than the reference values ($p < 0.02$); thus, this marker may be a promising biopredictor of PDAF [28]. Turkish scientists H. Ozturk et al. indicated that the combined increase in the level of serum alpha-fetoprotein (AFP) and human chorionic gonadotropin (hCG) relative to the reference values in the second trimester of pregnancy has a significant relationship with PDAF ($p = 0.001$). However, an isolated increase in the levels of hCG or AFP is not significantly associated with the development of PDAF ($p > 0.05$) [29]. D. Basbug et al. revealed contradictory findings and confirmed the

Table 2. Level of cytokines during the timely and premature discharge of amniotic fluid

Cytokine	Peripheral blood serum		Amniotic fluid	
	TDAF	PDAF	TDAF	PDAF
IL-8, pg/ml	10.6 (95% CI 8.0–23.1)	13.0 (95% CI 9.0–58.2)	7668.3 (95% CI 2053.3–24774.2)	11687.2 (95% CI 908.4–26335.9)
TNF-α, pg/ml	11.9 (95% CI 8.3–22.6)	15.7 (95% CI 9.0–65.2)	4964.6 (95% CI 660.7–9286.2)	7100.3 (95% CI 867.8–14171.0)

Note. TDAF — timely discharge of amniotic fluid; PDAF — preterm discharge of amniotic fluid; IL-8 — interleukin-8; TNF-α — tumor necrosis factor alpha; CI — confidence interval.

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existence of a significant relationship between an isolated increase in serum AFP and the high incidence of PDAF [30]. According to H.D. Zhang et al., a decrease in serum copper levels may also be a significant predictor of PDAF. According to the data obtained, the level of serum copper could be correlated with the concentrations of copper, lysyl oxidase (LOX), and type III collagen in the AF of women with PDAF during preterm pregnancy. At full-term pregnancy, no such correlation is observed, likely because an increase in the volume of the uterine cavity results in greater fetal bladder degeneration [31]. A study by Chinese scientists showed that the risk of developing PDAF is correlated with the concentration of lead in the urine of the mother (OR 1.51; 95% CI 1.27–1.80; $p < 0.05$). Some scholars have examined the finding that the relationship between the concentration of lead and PDAF is more pronounced in primiparous women than in non-primiparous women ($p < 0.01$). This relationship indicates that exposure of lead on the mother's body is a risk factor for PDAF but, unfortunately, does not allow an increase in urine lead level to be considered a universal predictor of UDAF in the general population [32].

The decidual membrane serves as a source of tissue factor (TF), which is one of the most powerful natural procoagulants. Consequently, the progression of degradation of the fetal bladder structure may be accompanied by an increase in TF concentration. In contrast to TF, a TF inhibitor exerts protective effects by inhibiting the release of TF. O. Erez et al. reported that the average concentration of TF in the blood plasma is nearly 1.3-fold higher than the reference values ($p = 0.001$) and that the concentration of TF inhibitor is 1.1-fold lower in women with PDAF than in women with a normal course of pregnancy ($p = 0.02$). The authors also revealed that the concentrations of the inhibitor and TF are independent of the gestational age and development of intra-amnial infection [33].

Assessment of the probability of premature discharge of amniotic fluid according to the expression of signaling molecules

According to M.Kh. Afanasyeva et al., the expression level of matrix metalloproteinase (MMP)-9, connexins-37 and -40, and vascular endothelial growth factor (VEGF) in the buccal epithelium should be considered as non-invasive markers for predicting PDAF [34] (Table 3).

The results of this study are consistent with the opinion of a number of authors, who believe that PDAF occurs as a result of the destruction of collagen fibers of the fetal membranes under the action of MMP [35, 36]. Fetal membranes contain tissue inhibitors of matrix metalloproteinase (TIMMP), which weaken the enzymatic activity of the latter by covalent bonding with MMP [34]. Consequently, an increase in the concentration of MMP and a decrease in the level of TIMMP are accompanied by an increase in the risk of PDAF. Thus, V.M. Bolotskikh stated that the area (5413.1 ± 343.0 conditional units) and optical density (0.8 ± 0.04 conditional units) of MMP-1 expression in the placenta are significantly higher ($p < 0.001$) in women with PDAF than in women with TDAF; by contrast, indicators of TIMMP-1 expression are significantly lower ($p < 0.001$). Here, the area and optical density of TIMMP-1 expression in the case of PDAF were 1945.2 ± 65.5 and 0.2 ± 0.05 conditional units, respectively [37]. According to M. Tchirikov et al., MMP-8, which predominantly affects type I collagen, is equally important in the genesis of PDAF [38]. R. Menonet et al. considered the detectable activity of MMP-9 in saliva as a potential predictor of PDAF; in this work, peak MMP-9 activity (i.e., 2.5 ± 1.7 conditional units) was noted with PDAF, and high activity (i.e., 2.1 ± 1.6 conditional units) was registered with PLDAF; under normal circumstances, the activity of this enzyme does not exceed 2.0 conditional units [39]. If the described regularity is confirmed in studies with sufficiently large samples, this test may be used as a screening test.

VEGF is responsible for restoring the impaired blood supply to tissues in case of damage. Z.A. Savasan et al. proved that a lower concentration of VEGF in the AF is characteristic of PDAF, which, according to M.Kh. Afanasyeva, is strongly related to its concentration in the buccal epithelium [34, 40]. Connexins, which enable the metabolic cooperation of neighboring cells, are also involved in the amniotic membrane stabilization. Consequently, the results of the authors' study are substantiated not only from the statistical point of view but also from the pathophysiological point of view. Given the non-invasiveness and painlessness of the procedure for collecting

Table 3. Assessment of the degree of parallelism of changes in the expression of signaling molecules in the amniotic fluid and buccal epithelium

Signaling molecule	Pearson correlation coefficient	Bond strength according to the Chaddock scale	Statistical significance, p
MMP-9	0.76	High direct	<0.05
Connexin-37	0.25	Weak direct	<0.05
Connexin-40	–0.28	Weak inverse	<0.05
VEGF	0.72	High direct	<0.05

Note. MMP-9 — matrix metalloproteinase 9; VEGF — vascular endothelial growth factor.

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the buccal epithelium, prediction of PDAF via assessment of the expression level of signaling molecules seems to be a promising approach [34].

Instrumental methods for assessing the probability of untimely discharge of amniotic fluid

According to A.M. Gromova and A.Z. Khasina, PLDAF can be predicted on the basis of resisto-cervicometry. The authors performed hysterography for 10–15 min in women with full-term pregnancy. Here the hysterograph probe was placed on the anterior abdominal wall in the projection zone of the fundus and the lower segment of the uterus, and 0.09–0.11 IU of oxytocin solution was injected intramuscularly into the upper outer quadrant of the buttocks. After injection of oxytocin solution, the contractile activity of the uterus in the region of the fundus and the lower segment was recorded for 10–15 min. If the value of the cervix resistance exceeded 240 ohms and the ratio of the effectiveness of the contractile activity of the uterus in the lower segment to that in the bottom exceeded 0.52, PLDAF could be predicted. According to the results presented by the authors, the sensitivity, specificity, and accuracy of the pattern revealed are 87%, 100%, and 90%, respectively [41]. However, the disadvantages of this method, including its labor intensiveness and invasiveness, render it unsuitable as a screening approach. Consequently, assessing the possibility of predicting UDAF by evaluating the parameters of ultrasound examination is of some interest.

While assessing the significance of ultrasound markers, A.O. Odibo et al. established that PDAF is often combined with shortening of the cervix by less than 25 mm ($p < 0.001$) and opening of the cervical canal by more than 25% ($p < 0.001$). This finding may be attributed to the fact that the shortening and opening of the cervix lead to the prolapse of the fetal bladder, an increase in the contact of the fetal membranes with the vaginal microflora, and activation of collagenolysis. According to the authors, the shortening of the uterine cervix by less than 25 mm is accompanied by a nearly 8-fold increase in the risk of PDAF at a gestational age of less than 35 weeks (OR 7.9; 95% CI 3.6–17.5; $p < 0.05$) and a 10-fold increase in risk at a term of less than 32 weeks (OR 10.1; 95% CI 3.2–32.0; $p < 0.05$). The sensitivity and specificity of this pattern were 73% and 69%, respectively, at a gestational age of less than 35 weeks and 85% and 68%, respectively, at a term of less than 32 weeks [42]. M.T. Canda et al. revealed that exceeding the length of the nasal bone of the fetus by more than the 95th percentile is often combined with PDAF (accuracy = 94%, $p = 0.001$) and that exceeding the 99th percentile is statistically significantly associated with preterm labor and oligohydramnios (accuracy = 95%, $p = 0.006$; accuracy = 97%; $p = 0.014$, respectively) [43].

Assessment of the probability of preterm discharge of amniotic fluid based on the analysis of genetic predisposition

V.V. Astafiev et al. believed that the high association of PDAF with hypotonic neurocirculatory dystonia and undifferentiated connective tissue dysplasia substantiates the necessity of searching for genetic predictors of PDAF [44, 45]. The search for polymorphisms of PDAF-associated genes could enable the identification of a group of women with unmodifiable risk factors [44]. As this group is most vulnerable to the adverse effects of environmental factors, women in this group require more careful dynamic monitoring. However, the genetic aspects of PDAF development have not been sufficiently studied, mainly because of to the complexity of the pathogenesis of the condition [12].

According to V.M. Bolotskikh, carriage of the –308A allele of the *TNFA1* gene reduces the risk of PDAF by over twofold (OR 2.1; CI 95% 1.16–4.03; $p < 0.05$), thus confirming the protective role of the gene in relation to PDAF. Meanwhile, the –308G/–308G genotype is 1.4 times more common in patients with PDAF ($p = 0.02$) than in those without. Carriage of the GSTT 1 0/0 genotype increases the risk of PDAF by over twofold (OR 2.2; CI 95% 1.0–4.9; $p \leq 0.05$) [37]. H. Wang et al. revealed a statistically significant relationship between three haplotypes of minor alleles (i.e., –799T/–381A/+17C; –799C/–381G/+17G; –799T/–381G/+17G), which determine the high activity of the MMP–8 promoter in trophoblast cells, and PDAF (OR 4.63; $p < 0.001$). Here, the promoter of the main allele (i.e., –799C/–381A/+ 17C) appeared to confer protective effects (OR 0.52; $p < 0.001$), and none of the minor alleles were bound in isolation with PDAF [46]. Some authors have established a relationship between PDAF and polymorphism in the genes of the hemostasis system and folate metabolism [47, 48]. Thus, according to M.G. Nikolaeva et al., polymorphism in the *PAI-I* gene (–675 5G/4G) is a significant risk factor for PDAF in full-term pregnancy, as heterozygous carriage of PAI-I polymorphism increases the risk by 3.6-fold and homozygous carriage increases it by 1.7-fold [48]. T. Fujimoto et al. concluded that the 2G allele exerts strong promoter activity in amnion cells by increasing the sensitivity of amnion cells to MMP-1, thereby promoting PLDAF [49]. A 10-fold increase in the expression of the *MMP-2* gene in PROM was obtained in the study of S.J. Fortunato et al. According to the authors, increases in the production of MMP-2 are highly likely to be caused by the activation of the expression of the proapoptotic *p53* and *bax* genes and the suppression of the expression of the antiapoptotic gene *bcl-2* [12, 50]. S. Sagol et al. did not confirm that apoptosis in PDAF is mediated by the *bcl-2* and *bax* genes [51]. However, despite the inconsistency of the data, the possibility of determining the genetic determination of PDAF is highly relevant, and further research is required in this field [12].

CONCLUSIONS

While clear opinions regarding the classification, etiology, and pathogenesis of UDAF are available, a fairly large number of methods have been developed to predict this complication. Most researchers believe that assessing the probability of untimely discharge of the fetal bladder is best performed using an integrated approach, and the results of several of the most sensitive and specific methods should be taken into account. The results from the analyzed studies indicate that the absolute predictive value of some predictors should be verified in multicenter studies. Confirmation of the predictive value of individual or a certain set of predictors will optimize the approach of pregnancy and childbirth management and, in the future, reduce the frequency of not only maternal and perinatal morbidity but also operative delivery.

ADDITIONAL INFORMATION

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