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## HAMİLƏ QADINLARDA DÖL QIŞASININ VAXTINDAN ƏVVƏL CIRILMASININ KLİNİK-ANAMNESTİK VƏ LABORATOR PREDİKTORLARI

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**Xülasə.** Döl qişasının vaxtından əvvəl cırılması (DQVƏC) müşahidə edilmiş hamilələrdə klinik statusu qiymətləndirmək, qanda 25-OH-D vitamininin səviyyəsini və β-2-defenzin antimikrob peptidinin ekspressiyasının bu prosesin proqnozlaşdırılmasında əhəmiyyətini müəyyənləşdirmək məqsədilə tədqiqat aparılmışdır.

2 hamilə qadın qrupu (əsas qrup – 23-36 həftəlik hamiləlik dövründə DQVƏC törənmiş qadınlar və kontrol qrup – normal vaginal doğuş keçirmiş qadınlar) üzərində aparılmış tədqiqatdan aydın olmuşdur ki, DQVƏC anamnezində 2 və daha artıq abort, xronik pielonefrit, simptomuz bakteriuriya, hamiləliyin vaxtından əvvəl başa çatması təhlükəsi olan qadınlarda daha çox rast gəlinir. DQVƏC-in ən çox rast gəlinən ağırlaşması vaginal doğuş zamanı cift hissəciklərinin xaric olmasının ləngiməsidir.

Qanda 25-OH-D vitamininin orta qatılığı kontrol qrupunda  $52,9 \pm 2,37$  pq/ml olduğu halda, əsas qrupda  $26,32 \pm 0,87$  pq/ml, β-2-defenzinin qatılığı isə kontrol qrupda  $107,42 \pm 2,56$  pq/ml, əsas qrupda  $78,03 \pm 1,74$  pq/ml ( $p < 0,001$ ) olmuşdur.

Müəlliflərin fikrincə, DQVƏC törənmiş qadınlarda hamiləliyin klinik-anamnestik və laborator xüsusiyyətləri bu patologiyanın erkən diaqnostikasının, proqnozlaşdırılmasının və vaxtından əvvəl doğuşların alqoritminin hazırlanması üçün əsas ola bilər.

**Açar sözlər:** vaxtından əvvəl doğuş, döl qişasının vaxtından əvvəl cırılması, 25-OH-D vitamini, β-2-defenzinlər

**Ключевые слова:** преждевременные роды, преждевременный разрыв плодных оболочек, 25-OH витамин D, β-2-дефензины

**Keywords:** preterm birth, preterm premature rupture of membranes, 25-OH vitamin D, beta-2-defensins

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## CLINICAL, ANAMNESTIC AND LABORATORY PREDICTORS OF PRETERM PREMATURE RUPTURE OF MEMBRANES IN PREGNANT WOMEN

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A study was conducted to assess of the clinical status of pregnant women with preterm premature rupture of membranes (pPROM) and to determine the role of 25-OH vitamin D and the level of expression of antimicrobial peptides (beta-2-defensins) as prognostic markers of pPROM.

A study of two groups of women (pPROM at 23-36 weeks of gestation (main group) and with intact fetal membranes, who had a normal vaginal delivery (control group)) was found that pPROM is significantly ( $p < 0.05$ ) more common in the presence of such risk factors as: 2 or more abortions in the anamnesis, chronic pyelonephritis, asymptomatic bacteriuria, the threatened abortion. The most common complication of pPROM was retained placenta after vaginal delivery. The average

content of 25-OH vitamin D in the blood of pregnant women with pPROM was  $26.32 \pm 0.87$  pg/ml vs.  $52.9 \pm 2.37$  pg/ml in the control group, and the expression level of beta-2-defensins was  $78.03 \pm 1.74$  pg/ml vs.  $107.42 \pm 2.56$  pg/ml in the control group ( $p < 0.001$ ).

According to the authors, the established clinical, anamnestic and laboratory features of pregnancy and labor in pregnant women with pPROM may become the basis for the creation of algorithms for early diagnosis and prediction of pPROM and premature birth.

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In recent decades, there has been an upward trend in the incidence of preterm births worldwide. Thus, in European countries, from 1.1 to 1.6% of children are born extremely preterm. [1]. Premature birth occupies one of the leading places in the structure of perinatal morbidity and mortality. About 60-70% of early neonatal mortality and 65-75% of infant mortality are registered in the population of premature infants [1,2]. It should be noted that over 50% of premature births begin with premature rupture of membranes (pPROM), which requires a comprehensive comparative analysis of approaches to the management of complications depending on the duration of latency interval based on maternal and neonatal outcomes [2,3,4]. Approximately 50% of women experiencing pPROM (<37 weeks of gestation) give birth within 24–48 hours after the rupture, and 70% to 90% within 7 days. Patients experiencing pPROM require clinical management in a hospital that provides the necessary care for premature newborns. Management of pPROM consists of antibiotic prophylaxis and corticosteroids for fetal lung maturation after the fetal viability threshold have been reached [5]. Many scholars consider inflammatory changes of amniotic membranes to be one of the leading causes of pPROM [6-10]. Considering the high incidence of infectious complications in pPROM, such as chorioamnionitis, new prognostic markers should be considered, one of which could be  $\beta$ -2-defensins [5,8,11].

The aim of the study was to assess the clinical status of pregnant women with preterm premature rupture of membranes (pPROM) and to determine the role of 25-OH vitamin D and the level of expression of antimicrobial peptides (beta-2-defensins) as prognostic markers of pPROM and the development of complications of pregnancy, labor and the postpartum in such women.

**Material and methods of the study.** The study was performed on the clinical basis of the

Department of Obstetrics, Gynecology and Perinatology, Faculty of Postgraduate Education, Dnipro State Medical University in obstetrics departments of the Municipal Enterprise "Dnipropetrovsk Regional Perinatal Center" of the Dnipropetrovsk Regional Council, Dnipro. A total of 120 women aged from 15 to 52 years (median - 31 years) whose pregnancies were complicated by pPROM at 23-36 weeks of gestation (study group) were examined. The control group consisted of 20 pregnant women aged from 17 to 38 years (median - 27 years), with intact fetal membranes, who had a normal vaginal delivery.

We investigated the patient's medical history, course of pregnancy, labor and postpartum, the duration of the latency period, clinical and laboratory parameters, including 25-OH vitamin D levels, and serum expression of antimicrobial peptides ( $\beta$ -2-defensins). Studies of general clinical blood parameters were performed using the MicroCC-20Plus analyser, the level of 25-OH-vitamin D was determined by the enzyme-linked immunosorbent assay (test system AccuBind Elisa microwheels 25-OH Vitamin D Total (Vit D-Direct)), expression of  $\beta$ -2 defensins – by the enzyme linked immunosorbent assays (test system Elabscience human DEF $\beta$ 2/DEFB2(Defensin Beta 2) ELISA Kit).

Statistical processing of the study data was performed using the licensed software package Statistica v.6.1 (Statsoft Inc., USA, №AGAR909E415822FA). Data are presented as arithmetic mean (M) or frequency (F) with standard error ( $\pm m$ ), median (Me) and interquartile range (25%; 75%). Comparison of the mean values was performed by Student's t (t) and Mann-Whitney (U) criteria, for relative values – bilateral Fisher's exact test (FET) and Pearson's Chi-square test ( $\chi^2$ ); assessment of the relationship between features was assessed by Spearman's rank correlation coefficients (r). The results were considered statistically significant at  $p < 0.05$ , the trend was determined at  $p < 0.1$ .

#### **Research results and their discussion.**

Analysis of anamnestic and clinical characteristics of patients did not reveal significant differences between the study groups in the frequency of fertilization, birth parity, pregnancy loss (miscarriage, missed abortion) and pre-

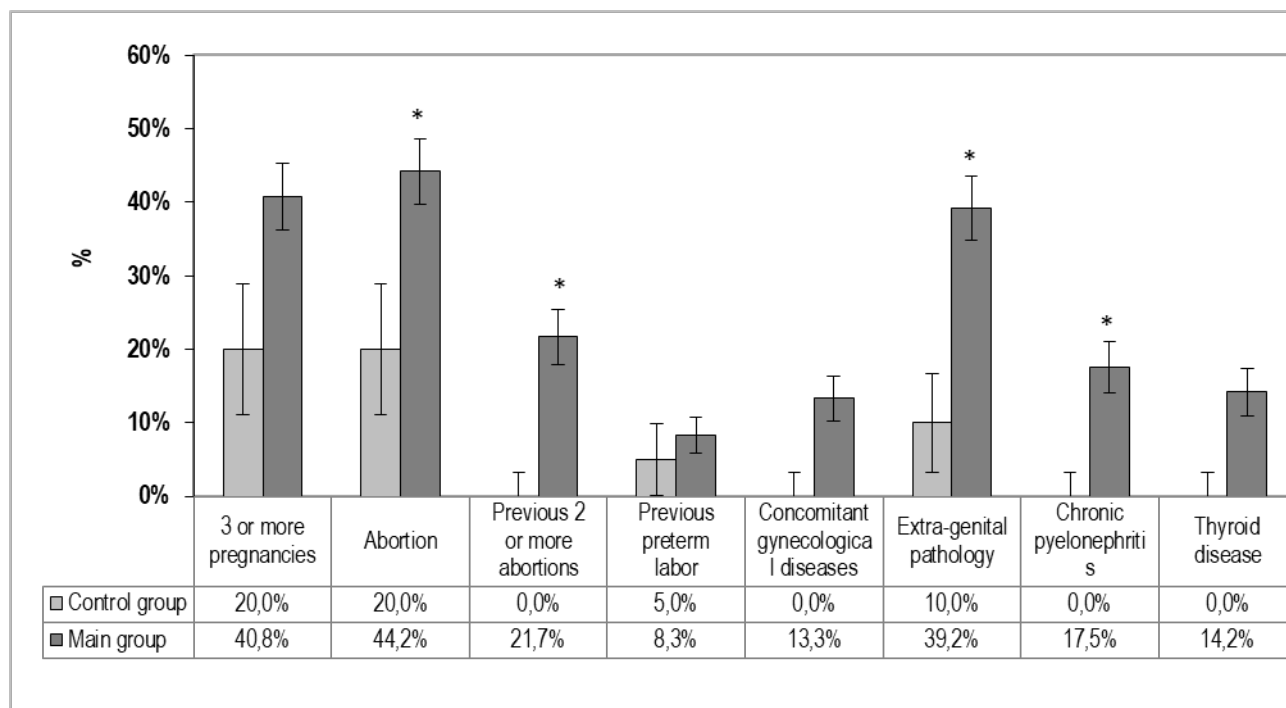
term delivery ( $p > 0.05$ ). At the same time, an increasing tendency in the average number of pregnancies was detected in the main group –  $2.98 \pm 0.23$  vs.  $1.95 \pm 0.21$  in control group ( $p_U = 0.098$  by U-test), in particular due to increasing of the proportion of women with 3-rd pregnancy and more –  $40.8 \pm 4.5\%$  vs.  $20.0 \pm 8.9\%$  ( $p_{FET} = 0.086$ ). Preterm delivery had  $8.3 \pm 2.5\%$  of women with pPROM and  $5.0 \pm 4.9\%$  of women in the control group. The overall abortion rate in anamnesis in the main group was significantly higher than in control group –  $44.2 \pm 4.5\%$  of cases versus  $20.0 \pm 8.9\%$  ( $p < 0.05$ ), additionally one in five women with pPROM ( $21.7 \pm 3.8\%$ ) and no patients in the control group ( $p < 0.05$ ) had 2 or more abortions (Fig. 1).

When assessing the somatic medical history in the study groups it was noted that 47 ( $39.2 \pm 4.5\%$ ) women with pPROM and only 2 ( $10.0 \pm 6.7\%$ ) women in the control group had extra-genital pathology ( $p < 0.05$ ). One case of 1-st degree obesity and chronic cystitis was registered in the control group. In the main group obesity was detected in 8 ( $6.7 \pm 2.3\%$ ) patients, urinary tract pathology – in 23 ( $19.2 \pm 3.6\%$ ), 21 ( $17.5 \pm 3.5\%$ ) of them had chronic pyelonephritis ( $p < 0.05$ ); pathology of

the thyroid gland – in 17 ( $14.2 \pm 3.2\%$ ) pregnant women, including hypothyroidism – in 9 ( $7.5 \pm 2.4\%$ ), diffuse goiter I-II degree – in 5 ( $4.2 \pm 1.8\%$ ), multinodular goiter, hyperplasia and hypoplasia of the thyroid gland – in one case ( $0.8 \pm 0.8\%$ ) (Fig. 1).

Analysis of gynecological history showed the presence of concomitant gynecological pathology in 16 ( $13.3 \pm 3.1\%$ ) women of the main group, namely uterine fibroids was observed in 11 ( $9.2 \pm 2.6\%$ ) patients, fibrocystic change of the breast – in 3 ( $2.5 \pm 1.4\%$ ), ovarian cyst, bicornuate uterus – one case each ( $0.8 \pm 0.8\%$ ).

In a study of the course of pregnancy (Fig. 2), it was found that pregnancies in women with pPROM were significantly more often accompanied by threatened abortion or preterm birth – in 50 ( $41.7 \pm 4.5\%$ ) pregnant women of the main group against 3 ( $15.0 \pm 8.0\%$ ) women of the control group ( $p < 0.05$ ). In particular, the threat of premature birth was observed in 29 ( $24.2 \pm 3.9\%$ ) and 1 ( $5.0 \pm 4.9\%$ ) pregnant women, respectively in study groups ( $p_{FET} = 0.075$ ). No statistically significant differences were found between the study groups in the incidence of anaemia during pregnancy ( $p > 0.05$ ). At the same time,



**Fig. 1.** Clinical and anamnestic characteristics of patients in the study groups.

Note: The relative value with standard error ( $F \pm m$ ) is shown; when calculating the error for  $F = 0\%$ , the Yates correction was used; significant differences between groups: \* -  $p < 0.05$

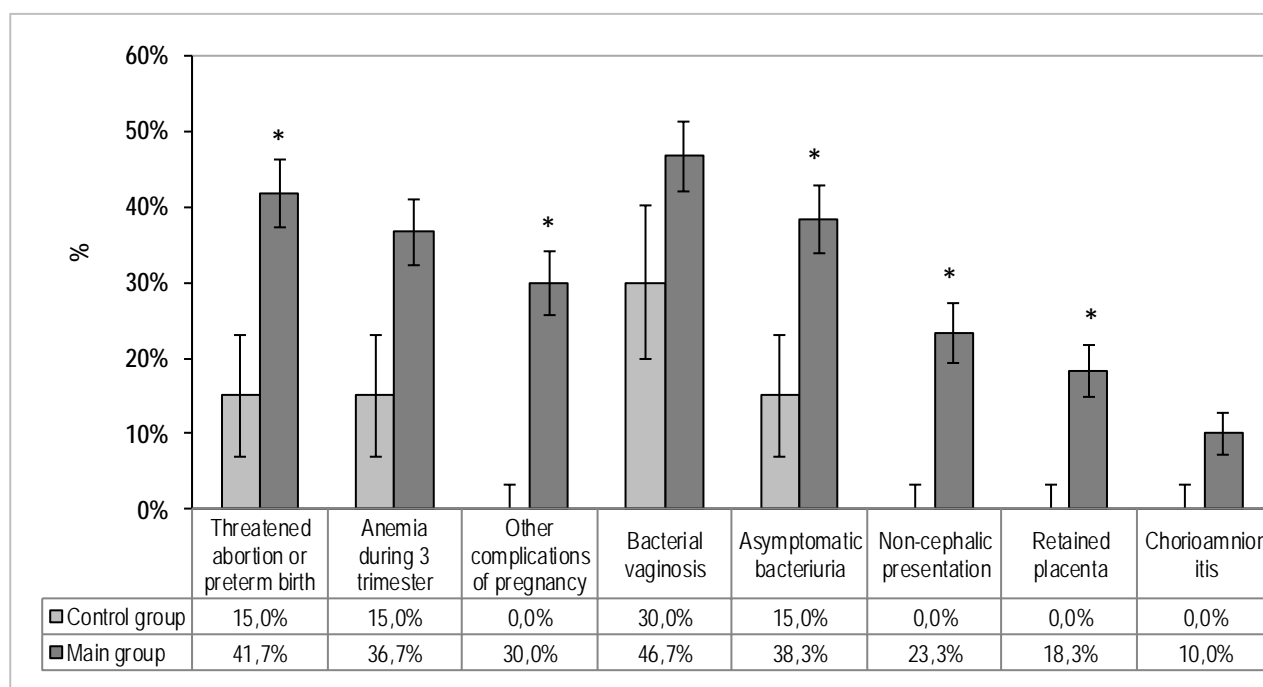
in the 3-rd trimester 44 (36.7±4.4%) pregnant of the main group (mild – 31, moderate – 13) and 3 (15.0±8.0%) pregnant of the control group (mild – 2, moderate – 1) had anaemia ( $p_{FET} = 0.074$ ). At the time of hospitalization of pregnant, anaemia was also significantly more common in women with pPROM – 54 (45.0±4.5%) against 4 (20.0±8.9%) cases in the control group ( $p < 0.05$ ).

No significant differences were found between the study groups in the frequency of respiratory and gynecological infections ( $p > 0.05$ ). Bacterial vaginosis was present in 56 (46.7±4.6%) and 6 (30.0±10.2%) pregnant women, respectively ( $p > 0.05$ ). However, asymptomatic bacteriuria was significantly more common in pregnant women with pPROM than in women in the control group – 38.3±4.4% vs. 15.0±8.0% of cases ( $p < 0.05$ ).

One-third (30.0±4.2%) of the women in the main group had such complications of the gestational period as premature placental abruption (8.3±2.5% of patients), fetal distress (8.3±2.5%), gestational diabetes (9.2±2.6%), preeclampsia (5.0±2.0%), cervical insufficiency (10.0±2.7%), which were absent in women of the control group ( $p < 0,01$ ) (Fig.

2). Almost a quarter of cases of pPROM – 28 (23.3±3.9%) recorded the non-cephalic presentation and abnormal position of the foetus, including breech presentation – 26 (21.7±3.8%) and transverse foetal position – 2 (1.6±1.2%), while as in pregnant women of the control group, such cases were not recorded ( $p < 0.05$ ).

The gestational age at delivery in women in the main group averaged 31.4±3.8 weeks, of which the period from 23 to 25 weeks was in 11 (9.1±2.6%) women, from 26 to 34 weeks – in 80 (66.7±4.3%), from 35 to 36 weeks – in 29 (24.2±3.9%). The duration of the latency in the expectant tactics of pPROM in premature birth by informed consent of the woman ranged from 2.5 to 1400 hours, with a median of 93.1 (26,1; 252.8) hours. At 24-34 weeks gestation, 84 (70.0±4.2%) women in the main group received prophylaxis for neonatal respiratory distress syndrome, of whom 57 (47.5±4.6%) received dexamethasone and 27 (22.5±3.8%) received betamethasone in appropriate doses 24 mg. Nifedipine tocolysis was performed in 69 (57.5±4.5%) cases and 118 (98.3±1.2%) pregnant women received antibacterial therapy.



**Fig. 2.** Characteristics of pregnancy and delivery in patients of the study groups

*Note: The relative value with standard error ( $F \pm m$ ) is shown; when calculating the error for  $F = 0\%$ , the Yates correction was used; significant differences between groups: \* -  $p < 0.05$*

Vaginal delivery occurred in 85 (70.8±4.1%) women of the main group, in 35 (29.2±4.1%) cases caesarean section was performed ( $p<0.01$  between study groups). Chorioamnionitis occurred in 12 (10.0±2.7%) pregnant women, with a higher incidence in women who became pregnant using assisted reproductive technology – 3 out of 8 cases (37.5±17.1%) against 9 out of 112 cases (8.0±2.6%) ( $p<0.05$ ).

We did not find significant differences between the overall frequency of complications of labour and the postpartum period in the study groups, which were observed in 30 (25.0±3.9%) women in the main group and 3 (15.0±8.0%) patients in the control group ( $p>0.05$ ). However, the most common complication of pPROM was retained placenta – 22 (18.3±3.5%) cases, which was not recorded in patients of the control group ( $p<0.05$ ). Among other complications of labor in patients of the main group there was perineal tear of the 2<sup>nd</sup> and 3<sup>rd</sup> degree – in 6 (5.0±2.0%), rupture of the cervix – in 1 (0.8±0.8%) patient.

Analysis of peripheral blood parameters in the examined patients showed a significantly reduced level of red blood cells – 3.79±0.09 E12/L vs. 4.05±0.10 E12/L ( $p<0.05$ ), hematocrit – 33.9±0.8% vs. 38.6±0.7% ( $p<0.001$ ), the relative content of monocytes – 4.82±0.25% vs. 5.94±0.44% ( $p<0.05$ ) and increased ESR – 35.0±1.2 mm/h vs. 27.8±3.8 mm/h ( $p<0.05$ ) in the blood of pregnant women of the main group in comparison with the control group. However, these differences did not have a significant effect on the course of labor and the postpartum, except for significantly increased ESR, which was closely associated with the development of chorioam-

nionitis ( $r=0.277$ ,  $p=0.002$ ).

In order to find new diagnostic and prognostic markers of pPROM and the complications of pregnancy, labour and the postpartum in such women, we examined the serum levels of 25-OH vitamin D and the expression of antimicrobial peptides ( $\beta$ -2-defensins) in the study groups. There was a significant decrease ( $p<0.001$ ) in these parameters in the examined pregnant women of the main group compared to control group (table 1). Thus, the average content of 25-OH vitamin D in the blood of pregnant women with pPROM was reduced 2 times, and the expression level of  $\beta$ -2-defensins – 1.4 times compared with the control group.

The differences revealed by means of the comparative analysis between study groups of pregnant women with pPROM and control group allowed to outline the factors which can serve as predictors of pPROM and premature birth. The risk of pPROM was found to increase significantly with an increase in the number of abortions ( $r=0.196$ ;  $p=0.021$ ), complications of pregnancy ( $r=0.240$ ;  $p=0.004$ ), including the threatened abortion ( $r=0.192$ ;  $p=0.023$ ), in the presence of extra-genital pathology ( $r=0.214$ ;  $p=0.011$ ), especially chronic pyelonephritis ( $r=0.171$ ;  $p=0.043$ ), asymptomatic bacteriuria ( $r=0.171$ ;  $p=0.043$ ), with non-cephalic presentation of the fetus ( $r=0.204$ ;  $p=0.016$ ), decreased levels of 25-OH vitamin D ( $r= -0.592$ ;  $p<0.001$ ) and  $\beta$ -2-defensins ( $r= -0.584$ ;  $p<0.001$ ). The trend toward increased probability of pPROM is observed with increasing number of pregnancies ( $r=0.140$ ;  $p=0.098$ ), the presence in the 3<sup>rd</sup> trimester of pregnancy of threatened preterm birth ( $r=0.163$ ;  $p=0.053$ ) and anaemia ( $r=0.161$ ;  $p=0.058$ ).

**Table 1.** Indicators of vitamin D levels of 25-OH and expression of antimicrobial peptides ( $\beta$ -2-defensins) in patients of study groups

Indicator		Control group (n=20)	Main group (n=120)
25-OH Vitamine D, pg/ml	Min-Max	39.86 – 73.50	1.82 – 41.12
	M±m	52.90 ± 2.37 *	26.32 ± 0.87 *
$\beta$ -2-defensins, pg/ml	Min-Max	91.15 – 132.45	4.36 – 104.44
	M±m	107.42 ± 2.56 *	78.03 ± 1.74 *

**Note.** Significant differences between groups: \* -  $p < 0.001$  according to the criteria of Student and Mann-Whitney

## Conclusions

1. Preterm premature rupture of membranes is a serious problem of modern obstetrics and requires a comprehensive approach to this complication;

2. pPROM is significantly ( $p < 0.05$ ) more common in the presence of such risk factors as: 2 or more abortions in the anamnesis, chronic pyelonephritis, asymptomatic bacteriuria, complicated pregnancy with the threatened abortion and the development of other serious complications (cervical insufficiency, premature placental abruption, fetal distress, gestational diabetes, preeclampsia), non-cephalic presentation of the fetus;

3. The average content of 25-OH vitamin D in the blood of pregnant women with

pPROM was reduced 2 times, and the expression of  $\beta$ -2-defensins - 1.4 times compared with pregnant women of the control group ( $p < 0.001$ );

4. The established clinical, anamnestic and laboratory features of pregnancy and labor in pregnant women with pPROM may become the basis for the creation of algorithms for early diagnosis and prediction of pPROM and premature birth.

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**Conflicts of interest:** authors have no conflict of interest to declare.

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## КЛИНИКО-АНАМНЕСТИЧЕСКИЕ И ЛАБОРАТОРНЫЕ ПРЕДИКТОРЫ ПРЕЖДЕВРЕМЕННОГО РАЗРЫВА ПЛОДНЫХ ОБОЛОЧЕК У БЕРЕМЕННЫХ

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**Резюме.** Проведено исследование с целью оценки клинического статуса беременных с преждевременным разрывом плодных оболочек (ПРПО) и определения роли показателей 25-ОН витамина D и уровня экспрессии антимикробных пептидов ( $\beta$ -2-дефензины) как прогностических маркеров ПРПО.

В результате исследования двух групп женщин [с ПРПО на 23-36 неделе гестации (основная группа) и с интактными плодными оболочками и нормальными вагинальными родами (контрольная группа)] установлено, что ПРПО достоверно ( $p < 0,05$ ) чаще встречается при наличии таких факторов риска как: 2 и более аборт в анамнезе, хронический пиелонефрит, бессимптомная бактериурия, угроза прерывания беременности. Наиболее частым осложнением ПРПО была задержка частей плаценты при вагинальных родах. Среднее содержание 25-ОН витамина D в крови беременных с ПРПО составило  $26,32 \pm 0,87$  нг/мл против  $52,9 \pm 2,37$  нг/мл в контрольной группе, а уровень экспрессии  $\beta$ -2-дефензинов –  $78,03 \pm 1,74$  нг/мл против  $107,42 \pm 2,56$  нг/мл, соответственно ( $p < 0,001$ ).

По мнению авторов, клинико-анамнестические и лабораторные особенности течения беременности и родов у беременных с ПРПО могут стать основанием для создания алгоритмов ранней диагностики и прогнозирования ПРПО и преждевременных родов.

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