ORIGINAL ARTICLE

CONTENTS

# Analysis of cases of premature rupture of membranes and preterm births to identify effective management measures to prevent them

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## ABSTRACT

**Aim:** Based on retrospective analysis recognize the key factors of development of premature childbirth and elaborate highly specific criteria for individual prognosis to improve perinatal outcomes.

**Materials and Methods:** A retrospective analysis of the birth histories of 250 women and their newborns with spontaneous preterm births at 22-36 weeks was conducted using archival data from the department for pregnant women with obstetric pathology of the State Institution "Institute of Pediatrics, Obstetrics and Gynecology named by academician OM Lukianova of the National Academy of Medical Sciences of Ukraine"

**Results:** Important risk factors for premature rupture of membranes (PROM) in preterm pregnancy include the presence of sexually transmitted diseases ($\chi2=31.188$, $p=0.001$), bacterial vaginosis ($\chi2=30.913$, $p=0.0001$), a history of abortion and/or preterm birth ($\chi2=16.62$, $p=0.0002$), SARS during pregnancy ($\chi2=16.444$, $p=0.0002$), chronic adnexitis in anamnesis ($\chi2=11.522$, $p=0.0031$), inflammatory cervical disease ($\chi2=11.437$, $p=0.0032$), anaemia ($\chi2=10.815$, $p=0.0044$), isthmic-cervical insufficiency (ICI) ($\chi2=10.345$, $p=0.0057$), chronic pyelonephritis with exacerbation ($\chi2=9.16$, $p=0.01$), smoking during pregnancy ($\chi2=10.815$, $p=0.0044$).

**Conclusions:** The results of a retrospective analysis of 250 cases of preterm birth at 22 to 36 weeks allowed us to identify ways to effectively use existing diagnostic measures to determine readiness for pregnancy and the possibility of prolonging pregnancy to the viability of the newborn. Ways to improve the prevention of preterm birth and the design of further research were identified.

**KEY WORDS:** pregnancy, spontaneous premature childbirth, premature rupture of membranes, vaginal microbiocenosis

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## INTRODUCTION

The problem of preterm birth in modern obstetrics and perinatology remains one of the most pressing, having not only a medical but also a social aspect, due to adverse perinatal outcomes for children [1, 2]. According to the World Health Organisation (WHO), 15 million children are born prematurely every year worldwide, which is an average of 7.5 % of births (6.2 – 11.9 %). 7.5 % of preterm births account for 69 – 83 % of perinatal losses. Every year, more than 1 million premature babies die worldwide. Those children who survive are 10 times more likely to suffer from illness and disability. In 50 – 70% of cases, perinatal mortality is caused by complications resulting from premature birth. The course of pregnancy reflects the health of the mother and the environment. Disorders of the neuroendocrine systems, peculiarities of immune reactions, the nature of bacterial and viral infection can cause premature water breakage, uterine infection, preterm birth and infant mortality [3, 4].

The morbidity and mortality rate of preterm infants is 40 times higher than that of full-term infants. Perinatal morbidity and mortality in preterm births depends on the gestational age and weight of the fetus, as well as the course of pregnancy and childbirth. A special place in the structure of perinatal morbidity and mortality in preterm infants is occupied by births with premature rupture of membranes [5-7]. Rupture of the membranes between 22 and 34 weeks of gestation is a complex, not fully resolved problem for obstetric practice. When prolonging a preterm pregnancy in the case of PROM, the most dangerous complication is the possibility of uterine infection, the development of chorioamnionitis, fetal and neonatal infection. The risk of infection is higher the lower the gestational age of the fetus [1, 8, 9].

Preterm newborns are at significant risk of developing respiratory distress syndrome, hypothermia, hypoglycaemia, hyperbilirubinemia, metabolic acidosis, haemorrhagic syndrome, necrotising enterocolitis, infectious diseases, intraventricular haemorrhage (IVH)

and the risk of early neonatal mortality. The choice of rational management of preterm pregnancy in the case of PROM is a complex problem, as it is necessary to take into account the ratio of the risk of infection during pregnancy prolongation and the risk and consequences of preterm birth [10-12].

Taking into account current views on PROM in preterm pregnancy, one of the main tasks of practical obstetrics is to identify early prognostically significant markers of intrauterine infection (IUI), choose the optimal time of delivery, and justify treatment tactics to improve perinatal outcomes.

Ukrainian scientific sources do not contain data on the association of a certain infectious factor in the mother with the implementation of uterine infection of the fetus and newborn. Safe latency periods for premature rupture of membranes in preterm birth have not been determined. There are no studies of the negative impact of environmental factors on the development of preterm birth and the formation of the period of early neonatal adaptation [13, 14].

Foreign scientific publications relate to the development and implementation of optimal schemes for the prevention of intrauterine infection in preterm pregnancy complicated by PROM, and the study of the long-term effects of antibiotics during pregnancy on child development [15, 16].

In recent years, antiphospholipid syndrome has been given a leading role among the autoimmune aspects of preterm birth and miscarriage. The etiological factors of this syndrome are not fully understood [17, 18].

At the current stage, the pathogenesis of preterm labour is not fully understood; the mechanism of labour initiation is explained by various theories: a decrease in progesterone levels, oxytocin stimulation and decidual activation [19].

The risk factors for perinatal morbidity and mortality in preterm birth are gestational age and fetal weight, and the characteristics of the course of preterm birth itself [20-22]. High perinatal morbidity and mortality are associated not only with prematurity, but also with the causes of preterm birth [23].

The issue of prediction and early warning of preterm birth needs to be improved. There is no consensus in the scientific literature on the obstetric tactics for managing women with PROM and no labour in preterm pregnancy. In such cases, doctors have to choose between the risk of giving birth to a preterm immature baby with immediate induction of labour and the risk of developing infectious complications in the pregnant woman and fetus with a wait-and-see approach [24].

The likelihood of spontaneous development of labour in PROM and preterm pregnancy depends on the gestational age – the shorter it is, the longer the latency period. Thus, within 24 hours, with an expected fetal weight of 500–1000 g, spontaneous labour begins in only 25 % of women [25]. According to the literature, different methods of delivery for women with PROM and preterm pregnancy show differences in the rates of perinatal morbidity of newborns: spontaneous induction of labour increases the incidence of respiratory disorders and congenital infections, while induction of labour with oxytocin increases the incidence of children with primary asphyxia, hypoxic-ischemic central nervous system (CNS) damage, intraventricular haemorrhage and severe conjugal jaundice [26-28].

Approaches to conservation therapy in women at risk of abortion need to be reviewed and supported by evidence. The danger of prolonging pregnancy in case of premature rupture of membranes has not been proven. The association between the duration of the latent period and inflammatory diseases in preterm infants needs to be studied; technologies for preventing preterm birth need to be improved; approaches to conservation therapy and pregravid preparation in women at risk of abortion need to be reviewed.

## AIM

Based on a retrospective analysis, identify the main factors in the development of preterm birth and develop highly specific criteria for individual prognosis to improve perinatal outcomes.

## MATERIALS AND METHODS

An analysis of the medical records of women with preterm births that occurred in the conditions of the State Institution "Institute of Pediatrics, Obstetrics and Gynecology named by academician OM Lukianova of the National Academy of Medical Sciences of Ukraine" for the period from 2010 to 2020 was carried out. To participate in the study, 250 pregnancy and childbirth histories of women who had preterm births at 22–36 weeks of gestation were selected, and the features of the course of pregnancy, childbirth and the health status of their newborns were studied. The main group included 250 pregnant women who gave birth at 22–36 weeks, including women with premature rupture of membranes, who underwent conventional examination and treatment according to the clinical protocol approved by the Order of the Ministry of Health of Ukraine No. 782 "Preterm Birth" of 29.12.05. The results of the analysis were compared with a group of women who gave birth at full term (37–40 weeks) – the control group, which consisted of 50 women.

In pregnant women with PROM in preterm pregnancy, monitoring was carried out in accordance with Ministry of Health of Ukraine Order No. 782; in case of choice of a wait-and-see tactic, dynamic monitoring of the pregnant woman and fetus was performed in an obstetric hospital with auscultation of the fetal heartbeat twice a day and, if necessary, recording cardiotocography at least once a day from the 32-nd week of pregnancy; ultrasound examination, including Doppler blood flow measurement from the 30-th week of pregnancy. Pregnant women performed the fetal movement test on their own. Clinical and laboratory monitoring was carried out to determine the number of leukocytes in the peripheral blood, depending on the clinical course, but at least once every three days; complete blood count once every 2–3 days (with blood formula); bacterioscopic examination of vaginal discharge once every three days (with counting the number of leukocytes in the smear). From the moment amniotic fluid leakage was registered, in the absence of signs of infection in the mother, prophylactic administration of semi-synthetic penicillins or second-generation cephalosporins at medium therapeutic doses was performed. In the case of a cervical suture or an obstetric unloading pessary, they were removed with the onset of labour. In the absence of labour, preservative therapy (progesterone, tocolysis, metabolic therapy, prophylaxis of respiratory distress syndrome within the recommended timeframe according to the Order of the Ministry of Health No. 782 "Preterm delivery" from the 24-th to the 34-th week of pregnancy) was performed.

The statistical processing of the results consisted in the use of parametric and non-parametric statistics. The evaluation of the obtained quantitative and qualitative indicators was carried out on an Intel Core i3 personal computer using the STATISTICA 8.0 software package (Statistica Inc., USA).

In the case of normal distribution in a sample of the same type of traits, the student's t-criterion was used to compare them. The difference was considered significant at $p < 0.05$.

We used the logistic regression method when there are binary outcomes (presence/absence of a symptom or subject) and a number of predictors of the disease; we estimated the Odds Ratio (OR). $\chi 2$ test (null hypothesis that the logistic regression coefficient is zero and alternative hypothesis that the odds ratio of "disease" associated with this variable is one) to determine whether each variable influences the presence or absence of disease (congenital infection) and to quantify the degree of this influence.

When interpreting the results, it is taken into account that if the Confidence Interval (CI) for the OR includes one, then the difference between the groups is statistically insignificant. If all CI values are greater than one, then the chance of having the trait is statistically significantly higher in the first group than in the second. If all CI values are less than one, the chance is higher in the second group.

The operational characteristics of diagnostic tests were determined by the following formulas:

Sensitivity = a / (a + c)

Specificity = d / (d + b)

Positive predictive value (PPV) = a / (a + b)

Negative predictive value (NPV) = d / (d + c),

Where:

a – true positive results;

b – false positive results;

c – false negative results;

d – true negative results.

## RESULTS

The average age of women in the study group was 31.34 ± 5.64 years and did not differ significantly from the control group, 30.54 ± 6.26 ($p > 0.05$). Among the women in the study group who gave birth prematurely, 137 (55 %) had their first birth, and 113 (45 %) had repeated births. 160 (64 %) of the women in the main group lived in urban areas, and 90 (36 %) in rural areas. Among the women in the main group, 99 (39.6 %) were single or in an unregistered marriage. Smoking during pregnancy was observed in 62 (24.8 %) pregnant women in the main group and in 4 (8.0 %) women in the control group ($p < 0.05$).

The threat of pregnancy termination, starting from the first trimester, occurred in 187 (74.8 %) women of the main group, in the second trimester – in 197 (78.8 %) patients. The anamnesis revealed that 170 (68.0 %) women in the main group had lost a pregnancy in the first trimester, including habitual miscarriage (2 to 9 abortions) in 112 (44.8 %) of the subjects. 13 (5.2 %) women had a history of ectopic pregnancy. With the help of modern assisted reproductive technologies, 26 (10.4 %) couples have repeatedly tried to get pregnant. In the past, 53 (21.2 %) women in the main group had experienced preterm births. In all cases of early preterm births, stillbirth was diagnosed; in late preterm births, babies were born alive, but with signs of prematurity, which required long-term rehabilitation. A retrospective analysis revealed that 11 (4.4 %) children with cerebral palsy grow up to be disabled from childhood.

Hormonal imbalance in the hypothalamus-pituitary-ovarian system was detected in 189 (75.6 %) of the main group: ovarian-menstrual cycle (OMC) disorders, benign tumours of the uterus and append-

**Table 1.** Gynecological pathology in examined women (abs. number, %)

| Gynecological pathology | Main group (n = 250) | Control group (n = 50) |
|---|---|---|
| Inflammatory diseases of the cervix | 107 (42,8)* | 9 (18) |
| Chronic adnexitis | 85 (34,0)* | 6 (12) |
| Myoma of the uterus | 15 (6,0) | 2 (4) |
| Ovarian operations | 13 (5,2) | 1 (2) |
| Gynecological peritonitis | 2(0,8) | 0 |
| Infertility I and II | 15(6,0) | 2 (4) |
| Disorders of the menstrual cycle | 30 (12,0) | 5 (10) |
| Sexually transmitted diseases | 82 (32,0)* | 7(14) |
| Vaginitis | 52(20,8) | 5(10) |

* indicates the probability of differences compared to the control group, $p < 0,05$.

**Table 2.** Number of pregnant women by examination groups with extragenital pathology (abs. number, %)

| Extragenital pathology | Main group (n = 250) | Control group (n = 50) |
|---|---|---|
| Acute or gestational pyelonephritis | 25 (10,0) * | 2 (4) |
| Chronic pyelonephritis with exacerbation | 38 (15,2)* | 1 (2) |
| Chronic sinusitis and tonsillitis with exacerbation | 25 (10,0)* | 0 |
| Chronic bronchitis with exacerbation | 15 (6,0) * | 1 (2) |
| Bronchial asthma | 5 (2,0) | 0 |
| Acute respiratory viral infections | 22 (8,8)* | 2 (4) |
| Diseases of the cardiovascular system | 7 (2,8) * | 1 (2) |
| Diseases of the gastrointestinal tract | 8 (3,2) * | 1 (2) |
| Cholestatic hepatosis | 1 (0,4) | 0 |
| Anemia | 75 (30,0)* | 6 (12) |
| Disease of the thyroid gland | 8 (3,2) * | 1 (2) |
| Adiposity | 10 (4,0) | 2 (4) |
| Venous complications | 3 (1,2) | 0 |
| Varicose veins | 8 (3,2) * | 1 (2) |

* indicates the probability of differences compared to the control group, $p < 0,05$.

ages, endometrial pathology – 157 (62.8 %) cases, hyperandrogenism – 51 (20.4 %) observations, hyperprolactinemia – in 67 (26.8 %) women. In 108 (43.2 %) of the main group, hyperaggregation was detected, which was caused by antiphospholipid syndrome, mutation of coagulation factor V (G1691A), mutation of prothrombin (G20210A) and MTHFR (C677T), and hyperhomocysteinaemia. Hyperaggregation states (antiphospholipid syndrome, hyperfibrinogenemia, decreased Activated Partial Thromboplastin Time (APTT), increased Soluble Fibrin-monomer Complexes (SFMC), hyperhomocysteinemia) were observed in 180 (72.0 %) women. The anamnesis revealed that 101 (40.4 %) women in the main group had sexually transmitted diseases (STDs): chlamydia, ureaplasmosis, mycoplasmosis. Infection of the vagina and cervix (129 (51.6 %) cases) causes cervical dysplasia (68 (27.2 %) cases) and endometrial inflammation. Bacterial vaginosis was noted in 81 (32.4 %) women. Gynaecological pathology is presented in Table 1.

Therefore, a burdened obstetric and gynaecological history with predominantly inflammatory diseases in pregnant women in the main group makes urogenital infection a predictor of premature rupture of membranes in preterm pregnancy, along with hormonal disorders and hyperaggregation states. Concomitant extragenital pathology is important for pregnancy, the frequency of which in the study groups is shown in Table 2.

In the main group, concomitant extragenital pathology was present in 250 (100 %) cases, which is significantly more frequent compared to the control group – 18 (36.0 %), ($p < 0.05$). In women of the main group, a combination of several diseases was observed, and

**Table 3.** The course of pregnancy in examined women in groups (abs. number, %)

| Complications of pregnancy | Main group (n = 250) | Control group (n = 50) |
|---|---|---|
| The threat of abortion in the I and II trimesters | 105 (42,0)* | 9 (18,0) |
| Early gestosis | 33 (13,2) | 5 (10,0) |
| Late gestosis | 18 (7,2 ) | 3 (6,0) |
| Polyhydramnios | 20 (8,0) | 4 (8,0) |
| low tide | 45 (18,0) | 5 (10,0) |
| Isthmic-cervical insufficiency | 30 (12,0)* | 0 |
| Suture on the cervix | 13 (5,2 ) | 1 (2,0) |
| Fetal growth retardation I ст. | 35 (14,0) | 6 (12) |

* indicates the probability of differences compared to the control group, p < 0,05.

**Table 4.** Distribution of women with premature birth in different periods of pregnancy according to some clinical and paraclinical indicators (abs. number, %)

| Pregnancy period, weeks | The number of women with premature births (n) | The number of women with premature birth and long term PROM | Duration PROM, (год) (M±m) | Stillborn | Treat-ment in the Neonatal Intensive Care Unit | Died | Discharged home with the child |
|---|---|---|---|---|---|---|---|
| 22 – 27 | 27 | 18 (66,6) | 163,3 ± 58,2 | 25 (92,59) | 2 (7,4) | 1 (3,7) | 1 (3,7) |
| 28 – 31 | 31 | 26 (83,8) | 92,1 ± 44,3 | 7 (22,5) | 24 (77,4) | 3 (9,7) | 21 (67,7) |
| 32 - 34 | 52 | 34 (65,4) | 80,4 ± 39,9 | 0 | 52 (100) | 7 (13,5) | 45 (86,5) |
| 35-36 | 140 | 111 (79,3) | 30,6 ± 15,7 | 2 (1,4) | 31 (22,1) | 1 (0,7) | 137 (97,9) |
| In total | 250 | 189 (75,6) | 91,3 ± 34,9 | 34 (13,6) | 109 (43,6) | 12 (4,8) | 204 (81,6) |

**Table 5.** Distribution of women with premature birth in different periods of pregnancy according to the presence of obstetric complications (abs. number, %)

| Pregnan-cy period, weeks | Number of women from PROM more than 3 days | Premature detachment of the placenta | Prolapse of the umbilical cord | Compression of the umbilical cord |
|---|---|---|---|---|
| 22 – 27 | 8 (29,6) | - | - | - |
| 28 – 31 | 26 (83,8) | - | - | - |
| 32 - 34 | 34 (65,4) | - | - | - |
| 35-36 | 111 (79,3) | - | - | - |
| In total | 189 (75,6) | - | - | - |

**Table 6.** Distribution of premature newborns in different periods of pregnancy according to the presence of complications associated with prematurity and prematurity giving birth (abs. number, %)

| Pregnan-cy period, weeks | The number of premature newborns in in the Neonatal Intensive Care Unit | Lung hypoplasia | Deforma-tion of the skeleton | Respira-tory distress syndrome | Internally-ventricular hemorrhage |
|---|---|---|---|---|---|
| 22 – 27 | 2 | - | - | 2 (100) | 1 (50) |
| 28 – 31 | 24 | - | - | 9 (37,5) * | 4 (16,6)* |
| 32 – 34 | 52 | - | - | 1 (1,9) * | 3 (5,7)* |
| 35 – 36 | 31 | - | - | - | - |

* the probability of differences compared to the group of newborns at 22-27 weeks is marked,p < 0,05.

almost every second pregnant woman had a combination of extragenital pathology with the presence of an inflammatory component.

The duration of pregnancy in women in the main group with PROM had the following features: 105 (42.0 %) had a threat of miscarriage and/or preterm birth in the 1st and/or 2-nd trimester, which was significantly more frequent compared to the control group (p < 0.05). Early gestosis in women of the main group was observed in 33 (13.2 %) women, and late gestosis in 18 (7.2 %) pregnant women. Acute respiratory viral infection during pregnancy was experienced by 13 (13.0 %) of the study group. Preeclampsia was noted in 20 (8.0 %) pregnant women, preeclampsia in 45 (18.0 %) women, placental dysfunction and mild fetal growth retardation syndrome were observed in 35 (14.0 %). Isthmic-cervical

**Table 7.** The prognostic value of risk factors for predicting the realization of intrauterine infection in PROM in premature birth

| Indicator (risk factor) | Calculation index |
|---|---|
| Duration of the waterless period, (min) | 0,05 |
| Bacterial vaginosis | 3,05 |
| History of pregnancy losses (from 1 to 5) | 1,93 |
| Carriers of sexually transmitted infections | 1,68 |
| Acute Respiratory Diseases during pregnancy at any time | 1,07 |
| Herpes virus infections | 0,68 |
| Threat of abortion | 0,08 |
| Hyperaggregation state | 6,2 |

**Table 8.** The prognostic value of the combination of some non-parametric factors in determining the risk of premature birth at different times

| | Factor | Calculation index | P |
|---|---|---|---|
| Carriers of sexually transmitted infections | + Threat of termination of pregnancy at different times | 4,96 | 0,03 |
| | + Acute Respiratory Diseases during pregnancy at any time | 1,79 | 0,04 |
| | + History of pregnancy losses (from 1 to 5) | 2,13 | 0,24 |
| | + Lack of lactoflora | 1,82 | 0,54 |
| | + Hyperaggregation state | 1,98 | 0,99 |
| | + Progesterone deficiency | 1,64 | 0,69 |
| Herpes virus infection | + Threat of abortion at any time | 3,25 | 0,78 |
| | + Acute Respiratory Diseases during pregnancy at any time | 2,01 | 1,00 |
| | + History of pregnancy losses (from 1 to 5) | 207 | 1,00 |
| | + Lack of lactoflora | 1,01 | 1,00 |
| | + Progesterone deficiency | 2,90 | 1,00 |

**Table 9.** Chances and risk of intrauterine infection in pregnancy and premature pregnancy depending on the studied indicators

| Indicator | Statistical indicator | | | | | |
|---|---|---|---|---|---|---|
| | OR | 95 % CI | $\chi^2$ | p | OR | 95% CI |
| Violation blood flow in average cerebral arteries | 77,56 | 13,21 – 599,98 | 47,84 | 0,0006 | 25,50 | 6,77 – 153,48 |

**Table 10.** Results of the study of the influence of vaginal microflora on the risk of IUI implementation in premature newborns in premature pregnancies complicated by PROM

| Microflora | OR | 95% CI | $\chi^2$ | p | OR | 95% CI |
|---|---|---|---|---|---|---|
| *St. aureus* | 4,40 | 1,14 - 17,34 | 4,85 | 0,02 | 3,45 | 1,12 - 10,69 |
| *E. Coli* | 2,94 | 1,05 - 8,32 | 4,30 | 0,038 | 1,77 | 1,03 - 2,71 |
| *St. epidermidis* | 2,29 | 0,99 - 6,95 | 4,23 | 0,03 | 3,43 | 1,15 - 10,97 |
| *Enterococcus spp.* | 2,61 | 0,86 - 8,16 | 2,68 | 0,10 | 2,04 | 0,88 - 4,39 |
| *Klebsiella pneumoniae* | 3,45 | 0,76 - 15,6 | 2,29 | 0,12 | 2,96 | 0,78 - 11,06 |
| *Proteus vulgaris* | 3,33 | 0,62 - 17,79 | 1,57 | 0,20 | 2,96 | 0,64 - 13,39 |
| *Enterobacter chlochae* | 3,13 | 0,29 - 33,59 | 0,33 | 0,56 | 2,96 | 0,30 - 28,80 |
| *Proteus mirabilis* | 2,05 | 0,22 - 16,57 | 0,06 | 0,80 | 1,97 | 0,23–14,00 |
| *St. saprophiticus* | 1,89 | 0,97 - 5,55 | 0,19 | 0,65 | 1,42 | 0,89 - 4,13 |
| *St. haemoliticus* | 2,00 | 0,37 - 14,24 | 0,28 | 0,59 | 1,85 | 0,43 - 11,98 |
| *C. albicans* | 0,92 | 0,33 - 2,50 | 0,005 | 0,98 | 0,96 | 0,56 - 1,45 |

**Table 11.** Chances and risk of congenital pneumonia depending on the spectrum of the microflora of the birth canal

| indicator | Statistical indicator | | | | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | $\chi^2$ | p | OR | 95% CI |
| Mycoplasmagenytalium | 17,56 | 4,64 - 71,01 | 26,12 | 0,0005 | 8,28 | 3,20 - 23,72 |
| Trichomonasvaginalis | 15,77 | 3,39 - 83,64 | 18,13 | 0,0005 | 9,86 | 2,78 - 43,41 |
| Chlamydiatrachomatis | 8,34 | 2,72 - 26,29 | 17,27 | 0,0006 | 3,64 | 1,93 - 6,31 |
| Gardnerellavaginalis | 5,90 | 2,00 - 17,79 | 12,14 | 0,0012 | 2,96 | 1,58 - 5,07 |
| Ureaplasmaurealyticum | 2,44 | 0,85 - 7,03 | 2,60 | 0,10 | 1,80 | 0,89 - 3,33 |

insufficiency was observed in 30 (12.0 %) women, and cervical suture in 13 (5.2 %) pregnant women in the main group. Data on the course of pregnancy in the examined women in the groups are presented in Table 3.

Overall, the incidence of complicated pregnancy in women with premature rupture of membranes was observed in 119 (100 %) cases, which is an unfavourable prognostic risk factor for pregnancy and also indicates a fairly frequent combination of several complications of pregnancy in women with premature rupture of membranes in preterm pregnancy.

The microbiocenosis of the genital tract is of great prognostic importance for pregnancy. Among the isolated microflora of the vagina and cervical canal in pregnant women of the examined groups, opportunistic gram-negative microflora prevailed in 182 (72.8 %) cases in the main group and in 8 (16.0 %) cases in patients of the control group ($p < 0.05$), namely *Esch. Coli* – 70 (28 %) and 2 (4.0 %) respectively, *Enterococcus. spp.* – 62 (24.8 %) and 1 (2.0 %), *Klebsiella pneumoniae* – 12 (4.8 %) and 1 (2.0 %), *Proteus vulgaris* – 13 (5.2 %) and 1 (2.0 %), *Enterobacter chloacae* – 7 (2.8 %) and 1 (2.0 %), *Proteus mirabilis* – 5 (2 %) and 2 (4.0 %). *Providencia alcalifac* and *Enterobacter aerogenes* were found in 5 (2.0 %) and 8 (3.2 %) women of the main group and were absent in the control group.

Gram-positive flora occurred in 231 cases (92.40 %) in the main group and in 6 (12.0 %) cases in the control group ($p < 0.05$), namely: *St. epidermidis, St. saprophyticus, St. aureus* were found only in women of the main group. *Candida albicans* was found in 178 cases (71.2 %) in the main group and in 7 (14.0 %) in the control group ($p < 0.05$), *Gardnerella vaginalis* – in 82 (32.8 %) in the main group and in 2 (4.0 %) women in the control group ($p < 0.05$), which indicates the combination of several types of microorganisms in the microbiocenosis of the genital tract of pregnant women. It is known that a high concentration of microorganisms leads to upward infection of the amniotic membranes, which is the main cause of their premature rupture. Thus, in the quantitative analysis in our study, the conditionally pathogenic microflora was in a concentration of 106-7 colony-forming units per 1 ml of fluid (CFU/ml) in the main group and 103-4 CFU/ml in the control group ($p < 0.05$). Thus, a high concentration of microorganisms in the genital tract of pregnant women leads to ascending infection of the membranes, their premature rupture, infection of the fetus and newborn, and necessitates the prophylactic administration of antibiotic therapy in prolonged pregnancy complicated by PROM.

The duration of pregnancy in the main group of women had the following features: abnormalities of labour (weakness of labour, discoordinated labour) were observed in 25 women (10.0 %), incorrect fetal position, pathological presentation at the time of the onset of labour – in 47 women (18.8 %) of the main group and 4 (8.0 %) of the control group ($p < 0.05$). Fetal distress was diagnosed in 30 women of the main group (12.0 %) and 2 (4.0 %) women of the control group ($p < 0.05$), chorionamnionitis clinic was not noted in any of the subjects of the main and control groups ($p < 0.05$).

According to the analysis of the course of labour in the study groups, the third period was complicated by a defect in the placenta, partial tight attachment of the placenta with manual separation and discharge of the placenta in 27 women (10.8 %) of the main group and was not observed in women of the control group ($p < 0.05$). Premature placental abruption was observed in 5 women (2.0 %) in the intervention group and 1 woman in the control group (2.0 %) ($p > 0.05$). Surgical delivery was performed in 47 women in the intervention group (18.8 %). In the control group, 5 women underwent caesarean section (10.0 %). Indications for surgical delivery were premature placental abruption, fetal malposition, uterine scarring, and fetal distress.

In a retrospective analysis of uteroplacental and fetal-placental blood flow disorders (assessment of

blood flow velocity curves in the uterine arteries and umbilical cord arteries), Doppler (comparison of vascular resistance indices, diastolic component of blood flow) made it possible to establish parameters in which it was inappropriate to prolong pregnancy, which led to an urgent delivery regardless of gestational age in 98 (39.2 %). The distribution of women with preterm births at different gestational ages is shown in Table 4.

From the data presented, it can be argued that the greatest obstetric losses are associated with the gestational age of the newborn. That is, the very fact of preterm birth, rather than the duration of the latent period, is a factor in the development of postnatal complications. Therefore, the main task of obstetricians and gynaecologists is to effectively prevent early preterm birth or to delay delivery as much as possible. The distribution of women with preterm births at different gestational ages according to the presence of certain obstetric complications is shown in Table 5.

The analysis of the postpartum period showed that there were no cases of postpartum endometritis in both the main and control groups, and uterine subinvolution occurred in 30 women (12.0 %) in the main group and 3 (6.0 %) in the control group.

The clinical parameters of 109 newborns born prematurely and treated in the neonatal intensive care unit (NICU) were analysed. The gestational age of children treated in the NICU was as follows: 22–27 weeks – 2 (10.5 %) children, 28–31 weeks – 24 (22.01 %), 32–34 weeks – 52 (47.7 %), 35–36 weeks – 31 (28.5 %) children.

There were 42 (38.53 %) children on artificial lung ventilation (ALV). The average length of stay for a newborn on mechanical ventilation was 7–10 days. There were 21 (19.3 %) children on SiPAP. Kurasuf was administered to 46 (42.2 %) newborns. After birth, 12 preterm infants died on days 3–12: 3 (25 %) due to congenital pneumonia, 8 (66.7 %) from hypoxic-ischemic CNS damage.

The distribution of preterm infants by weight is as follows: from 500 g to 999 g – 2 (1.83 %) infants, from 1000 g to 1499 g – 24 (22.01 %), from 500 g to 1999 g – 52 (47.7 %), from 2000 g to 2499 g – 31 (28.4 %) infants.

The distribution of women with preterm births at different stages of pregnancy by the presence of complications in the newborn is shown in Table 6

Hypoxic-ischemic damage to the central nervous system (in the form of depression syndrome) and respiratory distress syndrome were present in 100 % of infants born prematurely before 29–30 weeks of gestation; intrauterine infection in the form of congenital bilateral pneumonia, rhinitis, conjunctivitis, omphalitis – 87 (79.81 %) of newborns; intraventricular hemorrhage of the P-S degree – 45 (41.3 %) of babies in the main group.

We conducted a regression analysis to determine the role of some factors in the development of preterm birth. Thus, smoking can be considered a risk factor for PROM in preterm pregnancy ($\chi 2=10.815$, $p=0.0044$). Factors were selected to predict the occurrence of uterine infection in preterm birth using statistically significant predictors (Table 7).

As the data show, the duration of the waterless period has the least impact on the development of uterine infection in preterm birth. Thus, the calculated index of the impact of a history of pregnancy loss increases the likelihood of this event by 39 times compared to a long latency period under conditions of waiting tactics.

We also determined the prognostic value of the combination of some non-parametric factors in determining the risk of preterm birth at different times (Table 8).

No significant difference was found between the weights of the born and deceased children in the respective age categories ($p > 0.05$).

The influence (increased chances of developing an event) of some laboratory and clinical parameters on the risk of developing PROM in preterm pregnancy was analysed. For C-reactive protein in pregnant women's serum +++ (OR 110.07, 95 % CI 18.63 – 865.36), amniotic fluid index < 3 cm according to ultrasound (OR 55.20, 95 % CI 12.50 – 276.57), placental hypoplasia (corresponding to gestational age 5 mm) (OR 7.07, 95 % CI 3.68 – 18, 36) can be considered reliable prognostic criteria for the occurrence of intrauterine infection in a preterm newborn in preterm pregnancy with PROM and recommend determining the prognosis of the risks of delivery or prolongation of the latent period.

We also analysed the prognostic significance of Doppler in the middle cerebral artery for the risk of antenatal infection. The results of the distribution of prognostic indicators are presented in Table 9.

At the antenatal phase, Doppler ultrasound in the fetal middle cerebral artery (OR 77.56, 95 % CI 13.21 – 599.98) can be used to predict the realisation of IUI in a preterm infant and timely delivery in combination with the above methods based on the determination of C-reactive protein in pregnant women's serum and amniotic fluid index. An early sign of fetal distress should be considered a decrease in the S/D ratio.

The prognostic significance of the data of bacteriological examination of vaginal contents was studied. The role of certain pathogens of urogenital infections in the development of intrauterine infection in preterm birth and PROM was investigated using polymerase chain reaction (PCR). An analysis of the results of the study of the impact of vaginal microflora on the risk of VUI in preterm infants with preterm pregnancy complicated by PROM is presented in Table 10.

The presence of *St. aureus* (OR 4.40, 95 % CI 1.14 – 17.34) and *E. Coli* (OR 2.94, 95 % CI 1.05 – 8.23) in high concentrations in the birth canal of a pregnant woman at the time of PROM significantly increases the risk of congenital infection in a preterm infant and justifies the prophylactic use of antibiotics. At the same time, *St. epidermidis*, according to our study, reduces the risk of congenital infection in preterm pregnancy (OR 0.29, 95 % CI 0.08 – 0.95).

We investigated the impact of certain pathogens of urogenital infections and TORCH infections on the risk of congenital infection in preterm pregnancy against the background of PROM. The results are shown in Table 11. In the examination for TORCH infections, according to the retrospective analysis, it was found that 41 (20.7 %) had Ig M, and exacerbation of herpes virus infection (high Ig G titres) was detected in 138 (69.7 %) pregnant women.

Thus, the presence of markers of urogenital infection in the labour tract of pregnant women, namely *Mycoplasma genytalium* (OR 17.56, 95 % CI 4.64 – 71.01), *Trichomonas vaginalis* (OR 15.77, 95% CI 3.39 – 83.64), *Chlamydia trachomatis* (OR 8.34, 95 % CI 2.72 – 26.29), *Gardnerella vaginalis* (OR 5.90, 95 % CI 2.00 – 17.79), significantly increases the risk of having a child with congenital infection in PROM and preterm pregnancy.

## DISCUSSION

The risk factors for perinatal morbidity and mortality in preterm birth are gestational age and fetal weight, and the characteristics of the course of preterm birth itself [20, 21]. High perinatal morbidity and mortality are associated not only with prematurity, but also with the causes of preterm birth [22].

The issue of prediction and early warning of preterm birth needs to be improved. There is no consensus in the scientific literature on the obstetric tactics for managing women with PROM and no labour in preterm pregnancy. In such cases, doctors have to choose between the risk of giving birth to a preterm immature baby with immediate induction of labour and the risk of developing infectious complications in the pregnant woman and fetus with a wait-and-see approach [23].

The likelihood of spontaneous development of labour in PROM and preterm pregnancy depends on the gestational age – the shorter it is, the longer the latency period. Thus, within 24 hours, with an expected fetal weight of 500–1000 g, spontaneous labour begins in only 25 % of women [5, 7, 24]. According to the literature, different methods of delivery for women with PROM and preterm pregnancy show differences in the rates of perinatal morbidity of newborns: spontaneous induction of labour increases the incidence of respiratory disorders and congenital infections, while induction of labour with oxytocin increases the incidence of children with primary asphyxia, hypoxic-ischemic central nervous system (CNS) damage, intraventricular haemorrhage and severe conjugal jaundice [13, 18, 24].

A detailed analysis of the effect of the duration of the water-free interval on the incidence of clinical symptoms of chorionamnionitis depending on the gestational age suggests the need to find more sensitive and early markers of intrauterine infection than clinical signs of chorionamnionitis in order to prevent severe forms of congenital infection and improve perinatal outcomes [8, 16, 25].

Thus, in the case of PROM, the timing of pregnancy prolongation should depend on the gestational age, expected weight of the newborn, clinical condition of the mother and fetus, and the onset of infection symptoms. Thus, a complicated obstetric and gynaecological history (even with one fetal loss in the history) with the presence of predominantly inflammatory diseases in pregnant women of the main group, the presence of acute respiratory disease in the 1-st and 2-nd trimester, hyperaggregation and hormonal dysfunction are key risk factors for premature rupture of membranes in preterm pregnancy [11, 12, 26].

Prolongation of pregnancy with PROM from the 28-th week of pregnancy significantly reduces the incidence of type I respiratory distress syndrome in preterm infants, thus reducing the need for mechanical ventilation and exogenous surfactant, the average duration of mechanical ventilation and the length of stay in the intensive care unit [26,27].

Approaches to conservation therapy in women at risk of abortion need to be reviewed and supported by evidence. The danger of prolonging pregnancy in case of premature rupture of membranes has not been proven. The association between the duration of the latent period and inflammatory diseases in preterm infants needs to be studied; technologies for preventing preterm birth need to be improved; approaches to conservation therapy and pregravid preparation in women at risk of abortion need to be reviewed.

## CONCLUSIONS

1. Important risk factors for premature rupture of membranes in preterm pregnancy include the presence of sexually transmitted diseases ($\chi2=31.188$, $p=0.001$), bacterial vaginosis ($\chi2=30.913$, $p=0.0001$), a history of abortion and/or preterm birth ($\chi2=16.62$, $p=0.0002$), SARS during pregnancy ($\chi2=16.444$, $p=0.0002$), chronic adnexitis in anamnesis ($\chi2=11.522$, $p=0.0031$), inflammatory cervical disease ($\chi2=11.437$, $p=0.0032$), anaemia

($\chi2=10.815$, p=0.0044), isthmic-cervical insufficiency ($\chi2=10.345$, p=0.0057), chronic pyelonephritis with exacerbation ($\chi2=9.16$, p=0.01), smoking during pregnancy ($\chi2=10.815$, p=0.0044).

2. The highest infant mortality and stillbirth rates are associated with gestational age of less than 34 weeks, which requires an effective system of prevention of very early preterm birth and methods of its prediction.
3. In the case of premature rupture of membranes up to 32–33 weeks of gestation, prolongation of pregnancy should be ensured to the maximum extent possible to increase the viability of the newborn. Prolongation of pregnancy in this period should be confirmed by the absence of threatening signs of septic complications in the mother and fetus.
4. Depending on the gestational age, concomitant pathology, obstetric situation, obstetric and gynaecological history, an individual tactic for the management of preterm pregnancy against the background of premature rupture of membranes is chosen.

## REFERENCES


1. Kim CJ, Romero R, Chaemsaithong P et al. Acute chorioamnionitis and funisitis: definition, pathologic features, and clinical significance. Am. J. Obstet. Gynecol. 2015;213(4):29-52. doi:10.1016/j.ajog.2015.08.040. DOI
2. Gorbenko NI, Borikov OYu, Ivanova OV et al. The effect of quercetin on oxidative stress markers and mitochondrial permeability transition in the heart of rats with type 2 diabetes. Ukr. Biochem. J. 2019;91(5):46-54. doi:10.15407/ubj91.05.046. DOI
3. Vitale SG, Marilli I, Rapisarda AM et al. Cellular and biochemical mechanisms, risk factors and management of preterm birth: state of the art. Minerva Ginecol. 2014;66(6):589-595.
4. Chaemsaithong P, Romero R, Korzeniewski SJ et al. A point of care test for interleukin–6 in amniotic fluid in preterm prelabor rupture of membranes: a step toward the early treatment of acute intra–amniotic inflammation/infection. J. Matern. Fetal Neonatal Med. 2016;29(3):360-367. doi: 10.3109/14767058.2015.1006621. DOI
5. Areia AL, Moura P, Mota-Pinto A. The role of innate immunity in spontaneous preterm labor: A systematic review. J. Reprod. Immunol. 2019;136:102-616. doi: 10.1016/j.jri.2019.102616. DOI
6. Weiner E, Barrett J, Zaltz A et al. Amniotic fluid volume at presentation with early preterm prelabor rupture of membranes and association with severe neonatal respiratory morbidity. Ultrasound Obstet Gynecol. 2019;54(6):767-773. doi: 10.1002/uog.20257. DOI
7. Asgharnia M, Mirblouk F, Salamat F et. al. Predictive value of aspartate aminotransferase and alanine aminotransferase levels in vaginal fluid for the diagnosis of premature rupture of membranes. Iran J Reprod Med. 2014;12(4):269-274.
8. He XG, Xu FD, Li GF et al. Effect of different antibiotic use strategies on infection in neonates with premature rupture of membranes and high-risk factors for neonatal infection. Zhongguo Dang Dai Er Ke Za Zhi. 2020;22(4):310-315. doi: 10.7499/j.issn.1008-8830.1910170. DOI
9. Cetin O, Dokurel Cetin I, Uludag S et al. Serial ultrasonographic examination of the fetal thymus in the prediction of early neonatal sepsis in preterm premature rupture of membranes. Gynecol Obstet Invest. 2014;78(3):201– 207. doi: 10.1159/000364871. DOI
10. Cobo T, Jacobsson B, Kacerovsky M et al. Systemic and local inflammatory response in women with preterm prelabor rupture of membranes. PLoS One. 2014;9(1):852-77. doi: 10.1371/journal.pone.0085277. DOI
11. Dars S, Malik S, Samreen I et al. Maternal morbidity and perinatal outcome in preterm premature rupture of membranes before 37 weeks gestation. Pak. J. Med. Sci. 2014;30 (3):626-629. doi: 10.12669/pjms.303.4853. DOI
12. Ecevit A, Anuk-İnce D, Yapakçı E et al. Association of respiratory distress syndrome and perinatal hypoxia with histologic chorioamnionitis in preterm infants. Turk. J. Pediatr. 2014;56 (1):56-61.
13. Prelabor Rupture of Membranes. ACOG Practice Bulletin, Number 217 Practice Guideline. Obstet. Gynecol. 2020;135(3):80-97. doi: 10.1097/AOG.0000000000003700. DOI
14. Ekin A, Gezer C, Taner CE et al. Perinatal outcomes in pregnancies with oligohydramnios after preterm premature rupture of membranes. Matern. . Fetal. Neonatal. Med. 2014;28(16):1-5. doi: 10.3109/14767058.2014.972927. DOI
15. Vouga M, Greub G, Prod'hom G et al. Treatment of genital mycoplasma in colonized pregnant women in late pregnancy is associated with a lower rate of premature labour and neonatal complications. Clin. Microbiol. Infect. 2014;20(10):1074-9. doi: 10.1111/1469-0691.12686. DOI
16. Eleje GU, Adinma JI, Ghasi S et al. Antibiotic susceptibility pattern of genital tract bacteria in pregnant women with preterm premature rupture of membranes in a resource-limited setting. Int J Gynaecol Obstet. 2014;127(1):10-4. doi: 10.1016/j.ijgo.2014.04.016. DOI
17. Tajik P, Van der Ham DP, Zafarmand MH et al. Using vaginal Group B Streptococcus colonisation in women with preterm premature rupture of membranes to guide the decision for immediate delivery: a secondary analysis of the PPROMEXIL trials. BJOG. 2014;121(10):1263-73. doi: 10.1111/1471-0528.12889. DOI
18. Herevych NV, Nochvina OA, Nikitina IM. Fetal infections optimization of pregnancy and delivery introduction. Wiad Lek. 2021;74(1):28-34.

19. Romero R, Gomez-Lopez N, Winters AD et al. Evidence that intra-amniotic infections are often the result of an ascending invasion a molecular microbiological study. Perinat Med. 2019;47(9):915-931. doi: 10.1515/jpm-2019-0297. DOI
20. Palacio M, Kühnert M, Berger R et al. Meta-analysis of studies on biochemical marker tests for the diagnosis of premature rupture of membranes: comparison of performance indexes. BMC Pregnancy Childbirth. 2014;14:183. doi: 10.1186/1471-2393-14-183. DOI
21. Higgins RD, Saade G, Polin RA et al. Evaluation and Management of Women and Newborns With a Maternal Diagnosis of Chorioamnionitis: Summary of a Workshop. Obstet Gynecol. 2016;127(3):426-436. doi: 10.1097/AOG.0000000000001246. DOI
22. Brown RG, Al-Memar M, Marchesi JR et al. Establishment of vaginal microbiota composition in early pregnancy and its association with subsequent preterm prelabor rupture of the fetal membranes. Transl. Res. 2019;207:30-43. doi: 10.1016/j.trsl.2018.12.005. DOI
23. Patriota AF, Guerra GV, Souza AS. Premature rupture of the membranes before the 35th week: perinatal outcomes [Article in Portuguese]. Rev Bras Ginecol Obstet. 2014;36(7):296-302. doi: 10.1590/so100-720320140004958. DOI
24. Carrapato MRG, Pereira T, Silva C et al. Late preterms: are they all the same? J. Matern. Fetal. Neonatal. Med. 2020;33(10):1780-1785. doi: 10.1080/14767058.2018.1527897. DOI
25. Bartkevicie D, Pilypiene I, Ramasauskaite D et al. Significance of C-reactive protein in predicting fetal inflammatory response syndrome. Ginekol. Pol. 2015;86(12):926-931.
26. Sim WH, H. Ng, Sheehan P. Maternal and neonatal outcomes following expectant management of preterm prelabor rupture of membranes before viability. J. Matern. Fetal. Neonatal. Med. 2020;33(4):533-541. doi: 10.1080/147677058.2018.1495706. DOI
27. Boiko VI, Nikitina IM, Babar TV, Boiko AV. The problem of miscarriage in multiple pregnancy. Wiad Lek. 2018;71(7):1195-1199.

## CONFLICT OF INTEREST

The Authors declare no conflict of interest

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