

Preterm premature rupture of membranes at 32–34 weeks of gestation: duration of membrane rupture period and maternal blood indicators relation with congenital infection

Ieva Daunoravičienė^{1,2},

Rūta Lenkutienė³,

Audrė Musteikytė³,

Diana Ramašauskaitė⁴

¹ Clinic of Obstetrics and Gynecology, Faculty of Medicine, Vilnius University

² Clinic of Obstetrics and Gynecology, Vilnius City Clinical Hospital

³ Faculty of Medicine, Vilnius University

⁴ Center of Obstetrics and Gynecology, Vilnius University

Background. The study investigates the influence of the length of membrane rupture period among pregnant women with preterm premature rupture of membranes (PPROM) between the 32nd and 34th weeks of gestation on the development of chorioamnionitis and the congenital infection of a newborn. It seeks to ascertain the values of indicators in mother's blood that enable to predict chorioamnionitis and funisitis for mothers, and congenital infection for newborns.

Materials and methods. A retrospective study of case records of women with PPRM at 32 (32 w. + 0 d)–34 (33 w. + 6 d) weeks of gestation and their newborns was performed. Two comparative groups were made: 1) of women who had funisitis and / or chorioamnionitis with or without deciduitis and 2) of women having no proved inflammation (according to the results of histological examination of placenta). Analogically, comparative groups were made of their newborns: those who had diagnosis of congenital infection and those who had no infection. The duration of membrane rupture period and the blood markers were investigated in all the groups.

Results. The study included 135 women. Duration of the membrane rupture period lasted 85.17 ± 84.72 hrs in the group of women who had histological inflammation, and 40.06 ± 56.57 hrs in the group with no inflammation, $P = 0.01$, $AUC = 0.735$; the critical membrane rupture period value for developing intrauterine infection by the Youden index was 43.7 hrs. The corresponding maternal CRP values (mg/l) were 25.85 ± 40.27 vs. 5.23 ± 7.88 ($P = 0.01$, $AUC = 0.6$), the Youden index 4.6 mg/l. For the mothers of the newborns diagnosed with infection, the duration of the membrane rupture period was 55.95 ± 65.04 hrs, for the mothers of the newborns without congenital infection it was 40.25 ± 73.71 hours. Respectively, CRP values for the mothers of newborns averaged 12.25 ± 22.14 mg/l vs. 4.8 ± 4.82 mg/l ($P = 0.005$).

Conclusions. Longer membrane rupture period and higher maternal CRP are correlated with inflammatory changes in the placenta and umbilical cord, thus they can be used as the prognostic indicators of intrauterine infection. When the duration of the membrane rupture period lasts ≥ 44 hrs, the risk of chorioamnionitis and funisitis increases five times; when the maternal serum CRP is higher than 5 mg/l, funisitis / chorioamnionitis is twice more frequent than at lower than 5 mg/l CRP values.

Key words: preterm premature rupture of membranes (PPROM), chorioamnionitis

INTRODUCTION

Preterm premature rupture of membranes (PPROM) is the rupture of membranes during pregnancy before the 37th week of gestation (1). According to the literature, PPRM occurs in 3% of pregnancies and is responsible for, or associated with, approximately one-third of premature births (2). PPRM is strongly associated with increased neonatal morbidity and mortality (3–4).

The most common cause of PPRM before the 37th week of gestation is intrauterine infection (5). Infection occurs in 40–70% of premature deliveries. Recent evidence indicates that intrauterine infection is one of the main risk factors in newborn's inflammatory response syndrome, white matter lesions, cerebral palsy, chronic pulmonary illnesses and sepsis (5–9). Therefore accurate prediction of infection, including maternal chorioamnionitis and early-onset neonatal infection, remains a critical challenge for obstetrician management in these cases. Late diagnosis and delayed treatment enhance probability of poor long-term outcomes and handicap.

In the case of infection, microorganisms get into chorionic tissues and begin to produce endotoxins and exotoxins. The tissues respond producing cytokine. The numbers of inflammatory cytokines increase in mother's blood serum, amniotic fluid and fetus blood. Researchers have proved that interleukin-6 (IL-6) in mother's blood serum is significantly related with intrauterine infection and allows to identify the infection within 72 hours before parturition starts (10). However, the method of cytokine analysis is very expensive and rarely used in clinical practice. It is also established that IL-6 is the main trigger of the synthesis of C-reactive protein (CRP) (11). Therefore, not only the number of mother's white blood cells (WBC) but also the analysis of CRP in blood serum may indicate existing infection after PPRM (12). It is deemed that increased concentration of CRP in blood serum is one of the most accurate markers for early-onset neonatal infection prognosis. The sensitivity of this marker is of >90% (13), and it is the independent indicator of funisitis as well (14). These two laboratory markers are easily available in everyday clinical practice and help to distinguish between pregnant women who are in danger and must be treated immediately, and those who can continue their pregnancy (13).

In the case of PPRM, the way of treatment is one of the most discussed questions in perinatal medicine. These questions particularly concern the period between the 32nd and 34th gestational weeks. The issues related to the choice between expectant management and labour induction, tocolysis, the duration of administration of antibiotic prophylaxis, timing of administration of antenatal corticosteroids, and methods of testing for maternal / fetal infection are discussed every day. The majority of authors suggest expectant management until the 34th week of pregnancy. The main benefit of such management is the prolongation of pregnancy. Theoretically, it should reduce the neonatal morbidity caused by the prematurity. However, on the other side are risks of waiting – especially, the risk of intrauterine infection, which may determine poor perinatal outcomes.

In publications, it is often mentioned that the gestational age of a newborn is one of the most important factors that determine the outcomes after PPRM. In the absence of additional complications, labour is usually induced in the 32nd–34th gestational weeks (14–15) due to the increased risk of neonatal infection in the prolonged membrane rupture period. However, some studies claim that longer duration of the membrane rupture period does not worsen outcomes in pregnancies that are complicated by PPRM (16).

The purpose of this study was to investigate the influence of the membrane rupture period duration on risks of developing chorioamnionitis and early-onset neonatal infection at the 32nd–34th gestational weeks after PPRM; and to determine the importance of mother's blood markers for the prediction of chorioamnionitis, funisitis and early-onset neonatal infection.

MATERIALS AND METHODS

The retrospective study was carried out in the Vilnius City Clinical Hospital analyzing the case records of women after PPRM, and of their newborns in the period of 1 January 2008 – 31 December 2013. Women were selected according to the gestation age at the moment of PPRM: between the 32nd week (32 weeks + 0 days) and 34th week (33 weeks + 6 days). Gestational age was determined according to the last menstrual period. If there was a difference of greater than 5 days between

the gestational age dated using the last menstrual period and the first trimester ultrasound or 10 days by the second trimester ultrasound scan, the estimated date of delivery and gestational age were adjusted as per the ultrasound data.

The selected pregnancies included only one-fetus pregnancies, fetuses without any congenital abnormalities. Only living newborns were selected. The case records of 135 women and newborns fulfilled the criteria of the study.

By the histological placental findings the women were divided into two groups: women with infection (funisitis and / or chorioamnionitis) and women with no infection. The groups were compared by the age of mother, gestational age at PPRM, administration of antibiotic prophylaxis before labour, timing of administration of antenatal corticosteroids, mother's and newborn's inflammatory markers (WBC count and CRP level in blood serum), duration of the membrane rupture period, the mode of delivery, weight of the newborn, the Apgar score rating scale by 1 + 5 minutes. The two groups of newborns were identified as well: newborns with congenital infection and newborns without congenital infection. We have compared these two groups of newborns in the same way as the groups of mothers. In order to find out the critical meaning of duration of the membrane rupture period and mother's CRP, we were looking for the relation between the duration of the membrane rupture period together with CRP in mother's blood serum, and placental funisitis and / or chorioamnionitis by drawing the ROC curve and counting the Youden index from it. We tried to find out whether the duration of the membrane rupture period influences the occurrence of intrauterine infection. We were looking for indicators of the highest predictive value for identifying congenital infection.

Statistic calculations were performed using the Statistical Package for the Social Sciences version 17.0 (SPSS Inc., Chicago, IL, USA). P-values <0.05, area under the ROC curve <0.5 were considered statistically significant.

RESULTS

From 135 maternal case records we have found that the average duration of the membrane rupture period is 51.88 ± 67.46 hours. The shortest duration of the membrane rupture period was 0.85 hour, the

longest duration was 336 hours. The median of the membrane rupture period is 29.53 hours.

According to the histological examination of the placentae, 95 (70%) patients had no infective changes, 11 (8%) patients had deciduitis, 29 (22%) patients were declared to have funisitis / chorioamnionitis with or without deciduitis (Fig. 1).

According to the literature (17), deciduitis, as such, is not obviously related with intrauterine infection, so in our study it was not considered as an inflammatory change of placenta.

In the group of women who had histologically confirmed infection of placenta, the CRP marker was statistically significant. The CRP levels in this group are considerably higher than the normal range and much higher than the CRP levels of women who did not have the infection of the placenta, respectively 25.85 ± 5.23 and 40.27 ± 7.88 , $P = 0.01$ (<0.05).

The other statistically significant indicator in this group is the duration of the membrane rupture period. The data shows that this period is considerably longer for women with chorioamnionitis / funisitis in comparison with women who had no infection according to histological examination of placenta (respectively 85.17 ± 84.72 and 40.06 ± 56.57 , $P = 0.01$ (<0.05)).

In the group of the women who had chorioamnionitis / funisitis, the newborns had congenital infection more often than the newborns of healthy mothers (respectively 86% and 67%, $P = 0.049$ (<0.05) – the statistically significant difference). Meanwhile, the white blood cells (WBC) count between these two groups had no statistically important difference (respectively 12.8 ± 3.27 and 12.33 ± 3.53 , $P > 0.05$).

Other factors, such as mother's age, parity, gestational age, duration of administration of antibiotic

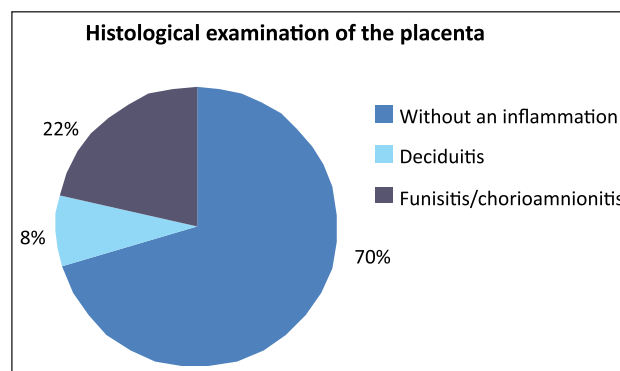


Fig. 1. Histological examination of the placenta

Table 1. Clinical characteristics of women with funisitis / chorioamnionitis and without infection

	Funisitis / chorioamnionitis		P
	Absent (n = 95)	Present (n = 29)	
Mother's age, years	29.84 ± 5.64	30.36 ± 5.74	0.68
Nulliparous	46 (48%)	12 (41%)	0.51
Gestational week after PPRM	32.78 ± 0.55	32.69 ± 0.54	0.44
Antibiotic prophylaxis (mother's)	88 (93%)	29 (100%)	0.13
Fetal lung maturation	72 (76%)	26 (90%)	0.11
Tocolysis	44 (46%)	14 (48%)	0.85
Mother's CRP levels, mg/l	5.23 ± 7.88	25.85 ± 40.27	0.01*
Mother's WBC count, ×10 ⁹ /l	12.33 ± 3.53	12.8 ± 3.27	0.52
Membrane rupture period duration, hours	40.06 ± 56.57	85.17 ± 84.72	0.01*
Caesarean section	27 (28%)	6 (21%)	0.41
Newborn's weight, kg	2.206 ± 0.32	2.129 ± 0.31	0.25
Apgar scale (1 + 5 min)	16.73 ± 1.31	16.52 ± 0.78	0.28
Newborn's CRP levels, mg/l	3.15 ± 10.42	5.98 ± 9.4	0.17
Newborn's WBC count, ×10 ⁹ /l	17.02 ± 6.37	16.77 ± 5.65	0.84
Newborn's infection	64 (67%)	25 (86%)	0.049*

* P < 0.05 means a statistically significant difference.

prophylaxis before labour, timing of administration of antenatal corticosteroids, tocolysis, newborn's weight, newborn's WBC count and CRP levels, the mode of delivery, Apgar score rating scale evaluation showed no significant difference in the comparative groups.

The duration of the membrane rupture period is related with the diagnosis of newborn's congenital infection: the newborns with the congenital infection experienced the membrane rupture period about 55.95 ± 65.04 hours, and the newborns without any infection experienced this period about 40.25 ± 73.71 hours.

There is a statistically significant link between the infection diagnosis of a newborn and CRP levels in mother's blood serum: mothers of the babies diagnosed with the infection had their CRP at 12.25 ± 22.14 mg/l and mothers of healthy babies had their CRP at 4.8 ± 4.82 mg/l (P = 0.005). However, there are no statistically reliable results to establish the relation between mother's WBC and newborn's infection: the WBC count for the mothers of infected babies was 12.76 ± 3.355 × 10⁹/l, and the WBC count for the mothers of healthy babies was 12.06 ± 2.820 × 10⁹/l.

The congenital infection and newborn's CRP levels are statistically significantly related: the newborns with the infection have CRP levels at 11.76 ± 5.58 mg/l, and the newborns without the infection have CRP levels at 0.44 ± 0.325 mg/l

(P = 0.000). There are no statistically reliable differences between the groups of newborns associating the infection and their WBC, respectively 16.30 ± 6.58 × 10⁹/l and 17.83 ± 6.06 × 10⁹/l (P > 0.05). Neonatal infection is significantly associated with the inflammatory changes in the placenta and umbilical cord. Among the newborns with the diagnosed infection, funisitis / chorioamnionitis was found in 23% of cases compared with only 9% (P = 0.004) in the newborns without diagnosed infection.

The diagnosis of infection is significantly related with the newborn's weight: the newborns with infection had lower weight: 2.133 ± 0.31 kg, and the newborns without infection had higher weight: 2.280 ± 0.327 kg (P = 0.018). The other data, such as mother's age, parity, gestational age, duration of administration of antibiotic prophylaxis before labour, timing of administration of antenatal corticosteroids, the mode of birth, and Apgar score rating scale, were not significantly different.

The duration of the membrane rupture period correlates with chorioamnionitis / funisitis. There are more cases of chorioamnionitis / funisitis when the duration of the membrane rupture period is longer. The area under the curve (AUC) is 0.735 (Fig. 2). According to the Youden index, the critical duration of the membrane rupture period is 43.7 hours. When the duration of the membrane rupture period was less than 44 hours, 9% of women had funisitis / chorioamnionitis; when the duration of

Table 2. Clinical characteristics of women and congenital infection of newborn

	Infection of newborn		P value
	Present (n = 100)	Absent (n = 35)	
Mother's age, years	30.16 ± 5.3	29.37 ± 6.3	0.474
Nulliparous	26 (26%)	11 (31%)	0.530
Gestational week after PPRM	32.68 ± 0.6	32.77 ± 0.4	0.338
Antibiotic prophylaxis (mother)	86 (85%)	28 (80%)	0.327
Fetal lung maturation	80 (80%)	26 (74%)	0.775
Mother's CRP levels, mg/l	12.25 ± 22.14	4.8 ± 4.82	0.005*
Mother's WBC count, ×10 ⁹ /l	12.76 ± 3.355	12.06 ± 2.820	0.317
Membrane rupture period duration, hours	55.95 ± 65.04	40.25 ± 73.71	0.297
Caesarean section	24 (24%)	13 (37%)	0.284
Newborn's weight, kg	2.133 ± 0.31	2.280 ± 0.33	0.018*
Apgar scale (1 + 5 min)	16.68 ± 1.34	16.43 ± 1.4	0.338
Newborn's CRP levels, mg/l	5.58 ± 11.76	0.44 ± 0.325	0.000*
Newborn's WBC count, ×10 ⁹ /l	16.30 ± 6.58	17.83 ± 6.06	0.227
Funisitis / chorioamnionitis	23 (23%)	3 (9%)	0.004*

* P < 0.05 is a statistically significant difference.

the membrane rupture period was 44 hours or longer, funisitis / chorioamnionitis was found in 44% of the investigated women (Table 3).

Increased CRP levels in mother's blood serum correlates with the increased probability of funisitis / chorioamnionitis. The area under the curve (AUC) is 0.6. According to the Youden index, the critical mother's CRP value is 4.6 mg/l (Fig. 3).

Table 3. The correlation between the duration of the membrane rupture period and funisitis / chorioamnionitis

	Funisitis / chorioamnionitis		P value
	Absent	Present	
<44 hours	82 (91.1%)	8 (8.9%)	0.000
≥44 hours	25 (55.6%)	20 (44.4%)	

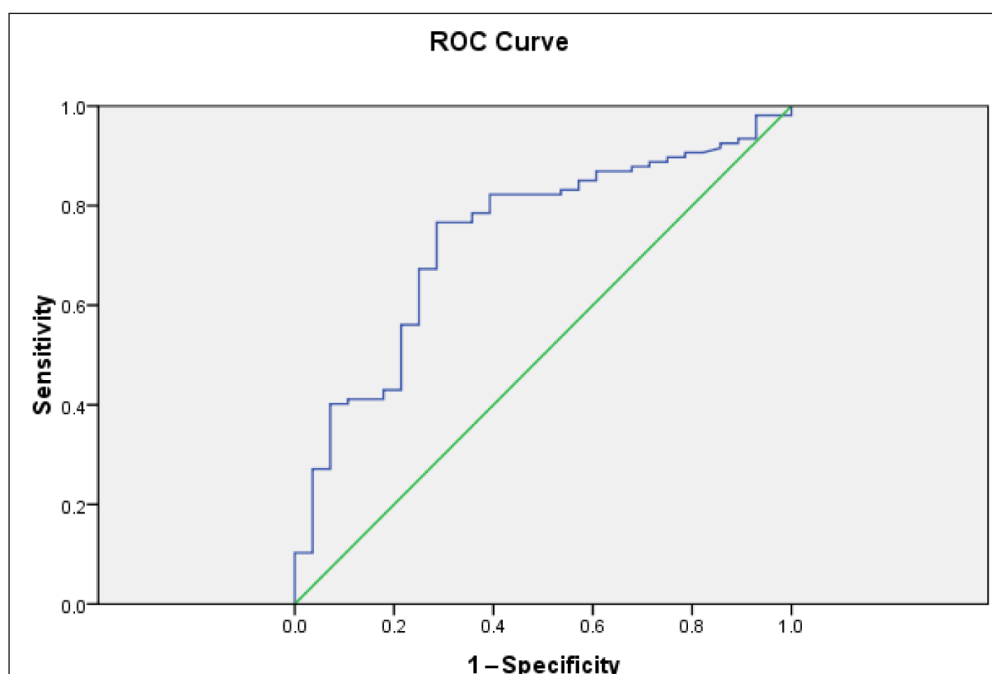
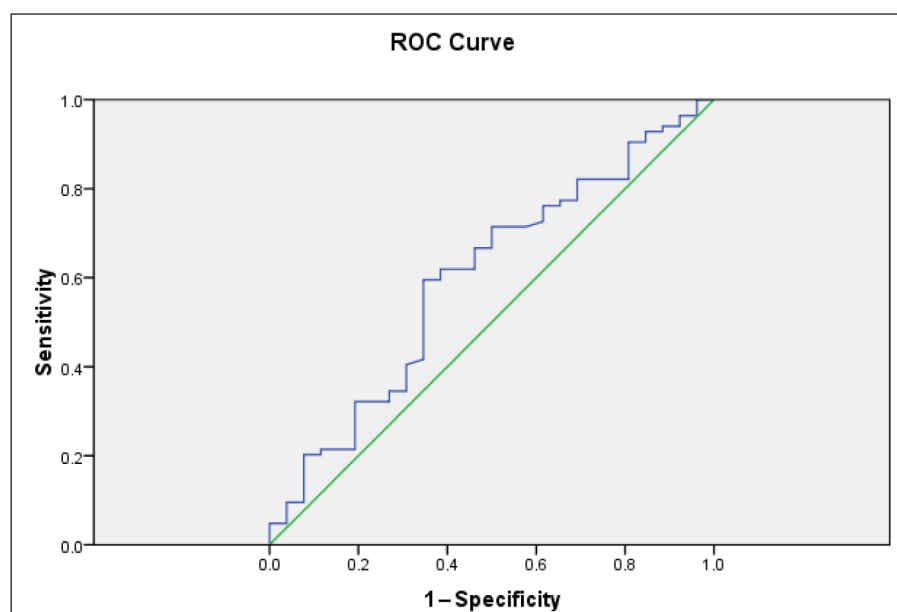
**Fig. 2.** The correlation between the duration of the membrane rupture period and funisitis / chorioamnionitis

Table 4. The relation between the CRP levels in mother's blood serum and funisitis / chorioamnionitis

CRP levels, mg/l	Funisitis / chorioamnionitis		Sensitivity	Specificity	P value
	Absent	Present			
<5	51 (83.6%)	10 (16.4%)	61.1%	61.5%	0.046
≥5	33 (67.3%)	16 (32.7%)			
<10	67 (78.8%)	18 (21.2%)	80%	30.8%	0.263
≥10	17 (68%)	8 (32%)			
<15	76 (78.4%)	21 (21.6%)	90.5%	18.9%	0.180
≥15	8 (61.5%)	5 (38.5%)			
<20	78 (78%)	22 (22%)	91.2%	15.4%	0.201
≥20	6 (60%)	4 (40%)			

**Fig. 3.** The relation between the CRP levels in mother's blood serum and funisitis / chorioamnionitis

DISCUSSION

Many studies show that histologically confirmed funisitis / chorioamnionitis is an integral indicator of lower newborn's viability and life prognosis (18–20). It is also proved that funisitis / chorioamnionitis is associated with a higher risk of neonatal sepsis (21–22). However, some researchers claim that the histological diagnosis of chorioamnionitis is not important in the prediction of newborn's further quality of life, especially if these newborns get adequate treatment and care (23–24).

Our study has shown the association between the increased CRP levels in mother's blood serum and histologically confirmed intrauterine infection, as well as congenital infection. The CRP concentration greater than 5 mg/l was the main indicator of mother's funisitis / chorioamnionitis and the reading re-

flecting the newborn's infection. The WBC count did not have any prognostic meaning neither for mother's intrauterine infection nor for newborn's congenital infection in our study.

Various similar studies were carried out for a long time, but their results differ. A retrospective study of 90 women with PPRM between the 23rd and 41st gestational weeks by Yoon and colleagues showed that neither CRP levels nor WBC count had any influence on histological appearance of chorioamnionitis (25). Also, Smith and colleagues conducted a retrospective study with 73 pregnant women and did not find any significant influence of CRP on the diagnosis of chorioamnionitis (26). Meanwhile Popowski et al. carried out a retrospective study of 399 pregnant women at or after 34 weeks of gestation. In their study, the CRP levels in blood serum were the most accurate marker that showed infection (13).

The importance of CRP levels in serum for the diagnosis of funisitis / chorioamnionitis (27–30), for the determination of neonatal sepsis (31) and the association between neonatal infection and funisitis / chorioamnionitis are discussed in many works of various authors (32–33). For example, van de Laar made a very important review of scientific works. The review included 5 studies, 381 patients, from which 227 had a histological diagnosis of chorioamnionitis, correlating with increased readings of CRP levels (34). Meanwhile, another systematic review of scientific work including 8 studies and 610 patients claims that there is no clear correlation between increased CRP levels and early diagnosis of chorioamnionitis. It is due to the fact that critical CRP values vary greatly from 5 to 40 mg/l (35). A study by Perrone et al. did not prove any significant prognostic value of the WBC count, the same as our study (30).

Based on these and other studies, Lee et al. suggest that in practice it is worth using the CRP value as an indicator of early-onset neonatal sepsis and a prognostic test of funisitis rather than a diagnostic indicator. It can help to classify women into two groups of those who run high risk (have high CRP levels) and those who are in low risk (have low CRP levels) (32).

Another important prognostic indicator of possible appearance of infection is the duration of the membrane rupture period. Our study has found that longer duration of the membrane rupture period is associated with histologically confirmed chorioamnionitis / funisitis and is more frequent in congenital infection; the critical value of the duration of membrane rupture period is 44 hours. It is important to mention a retrospective study by Ekin et al. It included 3 257 patients and their data. The study shows that longer duration of the membrane rupture period has significant influence (OR = 2.23, 95 % CI = 1.48–3.14; $p = 0.002$) on the development of chorioamnionitis (36). Similar results that a prolonged duration of membrane rupture of more than 48–168 hours has significant influence on the development of chorioamnionitis were found by other researchers as well (37–38). There were certain studies suggesting that prolonged duration of the membrane rupture period is associated with decreasing risk of newborn's illnesses and the duration of the membrane rupture period is decreasing when there is an increase of gestational age (39–40).

Unspecified neonatal infection is the condition when a newborn is prescribed to take antibiotics as there is a risk of having infection in the organism (41). There are not many accurate epidemiologic data about neonatal infection rate in Lithuania (42). According to our study data, 74% ($n = 100$) of newborns had the diagnosis of congenital infection. The most common was the unspecified congenital infection. Pneumonia and / or sepsis were diagnosed in 24% of cases ($n = 24$, respectively, 23 cases of pneumonia and 1 case of sepsis). According to Tamelienė, there is a possibility that such low indicator of early-onset sepsis relates to the fact that sepsis is hidden under early unspecified neonatal infection diagnosis. The illness of this name is not mentioned in scientific articles. The condition when there are clinical symptoms and two or more laboratory study markers of the infection should be identified as the early neonatal sepsis (43). Tamelienė believes that an early unspecified diagnosis could hide other illnesses, which are typical for early neonatal period, such as intracranial haemorrhage and neonatal respiratory distress syndrome. So Tamelienė claims that the congenital infection hyper diagnostics should not be rejected (41).

In the process of the study we confronted several limitations. First of all, this study is retrospective because pregnant women with cases of our interest are rare, but all the data was carefully collected from patients' archives and checked. Secondly, we were trying to evaluate blood markers of women and their newborns, and to find the correlating risk of the infection. We compared the results with healthy women and their newborns. We believe that our study results remain valid, whereas significantly higher CRP levels in maternal serum are observed in the group of women with histologically confirmed placental and umbilical cord inflammatory changes and the group of newborns with congenital infection. Longer duration of the membrane rupture period distinctly correlates with neonatal infection and mother's chorioamnionitis / funisitis.

CONCLUSIONS

22% of women from our study had chorioamnionitis / funisitis and 86% of newborns had congenital infection. According to the results, the duration of

the membrane rupture period is 2.1 times longer for the women with histologically confirmed chorioamnionitis / funisitis in comparison with the women who had no histological infection. The most important blood marker in predicting intrauterine infection is CRP levels in maternal blood serum. It was almost 5 times higher in the histologically confirmed infected women as compared with the women with no confirmed infection.

When the duration of the membrane rupture period increases, the congenital neonatal infection is diagnosed more often. Newborns with diagnosed congenital infection had the duration of the membrane rupture period 2 times longer than newborns without infection. Elevated CRP levels in maternal blood serum show a higher risk of congenital infection in the newborn. The mothers of newborns with congenital infection had 2.6 times higher CRP levels in comparison with the women who gave birth to healthy babies.

The duration of the membrane rupture period and CRP levels in mother's blood serum correlate with chorioamnionitis / funisitis and could be used as prognostic indicators. When the duration of the membrane rupture period is longer than 44 hours, the risk of chorioamnionitis / funisitis becomes five times higher. There was found a reliable correlation between CRP levels and histologically confirmed intrauterine infection. At a lower than 5 mg/l CRP value the occurrence of chorioamnionitis / funisitis was twice less than in the cases when the CRP level reaches or is greater than 5 mg/l (16.4% and 32.7%, respectively).

Received 22 January 2015

Accepted 13 February 2015

References

1. Medina TM, Hill DA. Preterm premature rupture of membranes: diagnosis and management. *Am Fam Physician*. 2006 Feb 15; 73(4): 659–64.
2. Lee T, Silver H. Etiology and epidemiology of PPRM. *Clin. Perinatol*. 2001; 28: 721–34.
3. Pilypienė I. Vaisiaus uždegiminio atsako sindromo įtaka neišnešiotu naujagimio sveikatai ir psichomotorinei raidai [daktaro disertacija]. 2012.
4. Pasquier JC, Picaudic JC, Rabilloudd M, Claris O, Ecochard R, Moret S, Mellier G. Neonatal outcomes after elective delivery management of preterm premature rupture of the membranes before 34 weeks' gestation (DOMINOS study). *Eu J Obstet Gynecol*. 2009; 143: 18–23.
5. Romero R, Gotsch F, Pineless B, Kusanovic JP. Inflammation in pregnancy: its roles in reproductive physiology, obstetrical complications, and fetal injury. *Nutr Rev*. 2007 Dec; 65(12 Pt 2): S194–202.
6. Romero R, Gomez R, Ghezzi F, Yoon BH, Mazor M, Edwin SS, Berry SM. A fetal systematic inflammatory response is followed by the spontaneous onset of preterm parturition. *Am J Obstet Gynecol*. 1998; 179: 186–93.
7. Yoon BH, Romero R, Kim KS, Park JS, Ki SH, Kim BI, Jun JK. A systemic fetal inflammatory response and the development of bronchopulmonary dysplasia. *Am J Obstet Gynecol*. 1999; 181: 773–9.
8. Yoon BH, Romero R, Park JS, Kim CJ, Kim SH, Choi JH, Han TR. Fetal exposure to intra-amniotic inflammation and the development of cerebral palsy at the age of three years. *Am J Obstet Gynecol*. 2000; 182: 675–81.
9. Pacora P, Chaiworapongsa T, Maymon E, Kim YM, Gomez R, Yoon BH, et al. Funisitis and chorionic vasculitis: the histological counterpart of the fetal inflammatory response syndrome. *J Matern Fetal Neonatal Med*. 2002; 11: 18–25.
10. Murtha AP, Sinclair T, Hauser ER, Swamy GK, Herbert WN, Heine RP. Maternal serum cytokines in preterm premature rupture of membranes. *Obstet Gynecol*. 2007; 109: 121–7.
11. Castell JV, Gomez-Lechon MJ, David M, Fabra R, Trullenque R, Heinrich PC. Acute-phase response of human hepatocytes: regulation of acute phase protein synthesis by interleukin-6. *Hepatology*. 1990; 12: 1179–86.
12. Park KH, Kim SN, Oh KJ, Lee SY, Jeong EH, Ryu A. Noninvasive prediction of intra-amniotic infection and / or inflammation in preterm premature rupture of membranes. 2012 Jun; 19(6): 658–65.
13. Popowski T, Goffinet F, Maillard F, Schmitz T, Leroy S, Kayem G. Maternal markers for detecting early-onset neonatal infection and chorioamnionitis in cases of premature rupture of membranes at or after 34 weeks of gestation: a two-center prospective study. *BMC Pregnancy Childbirth*. 2011; 11: 26.
14. Pasquier JC, Rabilloud M, Picaud JC, Ecochard R, Claris O, Gaucherand P, et al. A prospective population based study of 598 cases of PPRM between

- 24 and 34 weeks' gestation: description, management, and mortality (DOMINOS cohort). *Eur J Obstet Gynecol.* 2005; 121: 164–70.
15. Cox SM, Leveno KJ. Intentional delivery versus expectant management with preterm rupture of membranes at 30–34 weeks' gestation. *Obstet Gynecol.* 1995; 86: 875–9.
 16. Manuck TA, Maclean CC, Silver RM, Varner MW. Preterm premature rupture of membranes: does the duration of latency influence perinatal outcomes? *Am J Obstet Gynecol.* 2009; 201: 414–6.
 17. Roescher AM, Timmer A, Erwich JJHM, Bos AF. Placental pathology, perinatal death, neonatal outcome, and neurological development: a systematic review. *PLoS One.* 2014; 9(2): e89419.
 18. Thomas W, Speer CP. Chorioamnionitis: important risk factor or innocent bystander for neonatal outcome? *Neonatology.* 2011; 99: 177–87.
 19. Bersani I, Thomas W, Speer CP. Chorioamnionitis – the good or the evil for neonatal outcome? *J Matern Fetal Neonatal Med.* 2012 Apr; 25 Suppl 1: 12–6.
 20. Aziz N, Cheng YW, Caughey AB. Neonatal outcomes in the setting of preterm premature rupture of membranes complicated by chorioamnionitis. *J Matern Fetal Neonatal Med.* 2009 Sep; 22(9): 780–4.
 21. Jenster M, Bonifacio SL, Ruel T, Rogers EE, Tam EW, Partridge JC, et al. Maternal or neonatal infection: association with neonatal encephalopathy outcomes. *Pediatr Res.* 2014 Jul; 76(1): 93–9.
 22. Ahn HM, Park EA, Cho SJ, Kim YJ, Park HS. The association of histological chorioamnionitis and antenatal steroids on neonatal outcome in preterm infants born at less than thirty-four weeks' gestation. *Neonatology.* 2012; 102(4): 259–64.
 23. Henderson L, Russell L, Robertson CM, Liang Y, Chen Y, Abdalla A, Lacaze-Masmonteil T. Neonatal and neurodevelopmental outcomes of very low birth weight infants with histologic chorioamnionitis. *J Pediatr.* 2011 Mar; 158(3): 397–402.
 24. Kiser C, Nawab U, McKenna K, Aghai ZH. Role of guidelines on length of therapy in chorioamnionitis and neonatal sepsis. *Pediatrics.* 2014 Jun; 133(6): 992–8.
 25. Yoon BH, Jun JK, Park KH, Syn HC, Gomez R, Romero R. Serum C-reactive protein, white blood cell count, and amniotic fluid white blood cell count in women with preterm premature rupture of membranes. *Obstet Gynecol.* 1996; 88(6): 1034–40.
 26. Smith EJ, Muller CL, Sartorius JA, White DR, Maslow AS. C-reactive protein as a predictor of chorioamnionitis. *J Am Osteopath Assoc.* 2012 Oct; 122(10): 660–4.
 27. Popowski T, Goffinet F, Batteux F, Maillard F, Kayem G. Prediction of maternofetal infection in preterm premature rupture of membranes: serum maternal markers. *Gynecol Obstet Fertil.* 2011 May; 39(5): 302–8.
 28. Lee SY, Leung CW. Histological chorioamnionitis – implication for bacterial colonization, laboratory markers of infection, and early onset sepsis in very-low-birth-weight neonates. *J Matern Fetal Neonatal Med.* 2012 Apr; 25(4): 364–8.
 29. Howman RA, Charles AK, Jacques A, Doherty DA, Simmer K, Strunk T, et al. Inflammatory and haematological markers in the maternal, umbilical cord and infant circulation in histological chorioamnionitis. *PLoS One.* 2012; 7(12): e51836.
 30. Perrone G, Anceschi MM, Capri O, Galoppi P, Pizzulo S, Buccheri M, et al. Maternal C-reactive protein at hospital admission is a simple predictor of funisitis in preterm premature rupture of membranes. *Gynecol Obstet Invest.* 2012; 74(2): 95–9.
 31. Jeon JH, Namgung R, Park MS, Park KI, Lee C. Positive maternal C-reactive protein predicts neonatal sepsis. *Yonsei Med J.* 2014 Jan; 55(1): 113–7.
 32. Lee SY, Park KH, Jeong EH, Oh KJ, Ryu A, Park KU. Relationship between maternal serum C-reactive protein, funisitis and early-onset neonatal sepsis. *J Korean Med Sci.* Jun. 2012; 27(6): 674–80.
 33. Park CW, Yoon BH, Park JS, Jun JK. An elevated maternal serum C-reactive protein in the context of intra-amniotic inflammation is an indicator that the development of amnionitis, an intense fetal and AF inflammatory response are likely in patients with preterm labor: clinical implications. *Matern Fetal Neonatal Med.* 2013 Jun; 26(9): 847–53.
 34. Van de Laar R, van der Ham DP, Oei SG, Willekes C, Weiner CP, Mol BWJ. Accuracy of C-reactive protein determination in predicting chorioamnionitis and neonatal infection in pregnant women with premature rupture of membranes: a systematic review. *Eur J Obstet Gynecol Reprod Biol.* 2009 Dec 12; 147(2): 124–9.
 35. Trochez-Martinez RD, Smith P, Lamont RF. Use of C-reactive protein as a predictor of chorioamnionitis in preterm prelabour rupture of membranes: a systematic review. *BJOG.* 2007 Jul; 114(7): 796–801.
 36. Ekin A, Gezer C, Taner CE, Ozeren M, Uyar I, Gulhan I. Risk factors and perinatal outcomes associated with latency in preterm premature rupture of

- membranes between 24 and 34 weeks of gestation. Arch Gynecol Obstet. 2014 Sep; 290(3): 449–55.
37. Test G, Levy A, Wiznitzer A, Mazor M, Holcberg G, Zlotnik A, Sheiner E. Factors affecting the latency period in patients with preterm premature rupture of membranes. Arch Gynecol Obstet. 2011 Apr; 283(4): 707–10.
 38. Xie AL, DI XD, Chen XM, Hu YC, Wang YH. Factors and neonatal outcomes associated with histologic chorioamnionitis after premature rupture of membranes in the preterms. Zhonghua Fu Chan Ke Za Zhi. 2012 Feb; 47(2): 105–9.
 39. Nayot D, Penava D, Da Silva O, Richardson BS, de Vrijer B. Neonatal outcomes are associated with latency after preterm premature rupture of membranes. J Perinatol. 2012 Dec; 32(12): 970–7.
 40. Dagklis T, Petousis S, Margioulas-Siarkou C, Mavromatidis G, Kalogiannidis I, Prapas N, Mampoulous A, Rousso D. Parameters affecting latency period in PPROM cases: a 10-year experience of a single institution. J Matern Fetal Neonatal Med. 2013 Sep; 26(14): 1455–8.
 41. Tamelienė R, Markūnienė E, Stonienė D, Drazdienė N, Vezbergienė N, Chijenas V, et al. Ankstyvoji naujagimių infekcija Lietuvoje. Lietuvos akušerija ir ginekologija. 2009 kovas; 12(1): 8–16.
 42. Ramašauskaitė D, Skrebieienė A, Laužikienė D, Drąsutienė SG, Drejerienė V, Klimienė R. Nėštumo ir gimdymo veiksnių ryšys su neišnešiotų naujagimių ankstyva infekcija. Medicinos teorija ir praktika. 2011; 4: 487–94.
 43. Haque K. Definitions of bloodstream infection in the newborn. Pediatr Crit Care Med. 2005; 6(3 Suppl): 45–9.

**Ieva Daunoravičienė, Rūta Lenkutienė,
Aubrė Musteikytė, Diana Ramašauskaitė**

**PRIEŠLAIKINIS VAISIAUS VANDENŲ
NUTEKĖJIMAS 32–34 NĖŠTUMO SAVAITE –
BEVANDENIO LAIKOTARPIO IR MOTINOS
KRAUJO RODIKLIŲ RYŠYS SU ĮGIMTA
INFEKCIJA**

Santrauka

Tikslas. Ištirti bevandenio laikotarpio trukmės, esant PVVN 32–34 nėštumo savaitei, įtaką chorioamnionito ir naujagimio įgimtos infekcijos išsivystymui. Nustatyti motinos kraujo rodiklių reikšmę numatant chorioamnionitą, funizitą ir naujagimio įgimtą infekciją.

Metodika. Retrospektyvinė analizė atlikta esant PVVN 32 (32 sav. + 0 d.) – 34 (33 sav. + 6 d.) nėštumo savaitei analizuojant gimdyvių ir jų naujagimių istorijas. Tiriamosios grupės sudarytos remiantis placentos histologinio tyrimo rezultatais: I grupė – moterys, kurioms nustatytas funizitas ir / ar chorioamnionitas su ar be deciduito; II grupė – moterys, kurioms uždegimas nebuvo patvirtintas. Analogiškai lyginti naujagimiai, kuriems buvo ir nebuvo nustatyta įgimta infekcija. Tiriamosiose grupėse analizuota bevandenio periodo trukmė ir motinos kraujo rodmenų duomenys.

Rezultatai. Tyrimo kriterijus atitiko 135 moterys. Bevandenio laikotarpio trukmė moterų, kurių placentose nustatytas uždegimas, – $85,17 \pm 84,72$ val., moterų, neturėjusių uždegimo placentoje, – $40,06 \pm 56,57$ val. ($P = 0,01$, plotas po ROC kreive (AUC) – 0,735), kritinė bevandenio laikotarpio trukmė intrauterinei infekcijai pasireikšti pagal Youden indeksą – 43,7 val. Analogiškai motinos CRB reikšmės (mg/l) $25,85 \pm 40,27$ ir $5,23 \pm 7,88$ ($P = 0,01$, AUC – 0,6), Youden indeksas – 4,6 mg/l. Gimdyvių, kurių naujagimiams buvo nustatyta įgimta infekcija, bevandenio laikotarpis truko $55,95 \pm 65,04$ val., kuriems įgimtos infekcijos nebuvo, – $40,25 \pm 73,71$ val. Atitinkamai naujagimių motinų CRB reikšmės vidutiniškai siekė $12,25 \pm 22,14$ mg/l ir $4,8 \pm 4,82$ mg/l ($P = 0,005$).

Išvados. Ilgesnė bevandenio laikotarpio trukmė ir aukštesnis motinos CRB koreliuoja su uždegiminiais placentos ir virkštelės pokyčiais ir gali būti naudojami kaip intrauterinės infekcijos prognostiniai rodikliai. Esant ilgesniam nei ≥ 44 val. bevandeniui laikotarpiui chorioamnionito ir funizito rizika padidėja penkis kartus; esant motinos CRB < 5 mg/l, funizito / chorioamnionito atvejų buvo dvigubai mažiau nei CRB ≥ 5 mg/l.

Raktažodžiai: priešlaikinis vaisiaus vandenų nutekėjimas (PVVN), chorioamnionitas