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Is Maternal Blood Procalcitonin Level a Reliable Predictor for Early Onset Neonatal Sepsis in Preterm Premature Rupture of Membranes?

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Key Words
Preterm premature rupture of membranes · Early onset neonatal sepsis · Procalcitonin · C-reactive protein · White blood cell count

Abstract
Background: This study is aimed at comparing the early diagnostic accuracy of maternal blood white blood cell (WBC) count, C-reactive protein (CRP) and procalcitonin in predicting early onset neonatal sepsis (EONS) among early preterm premature rupture of membrane (PPROM) pregnancies. ***Methods:*** A total of 57 consecutive pregnancies, complicated with PPROM, between 24 and 34 gestational weeks were recruited to the study at Suleymaniye Maternity Education and Research Hospital, Istanbul, Turkey between January 2012 and January 2013. All patients were hospitalized and followed up with expectant management. Maternal blood WBC count, CRP and procalcitonin levels were measured in the first 12 h of membrane rupture. EONS was diagnosed using clinical and laboratory findings, and obstetric and neonatal outcomes were noted. ***Results:*** The cutoff value for maternal blood CRP was ≥9.49 mg/dl. This value predicted EONS with 77.8% sensitivity, 80.0% specificity, 77.8% positive predictive value (PPV) and 80.0% negative predictive value (NPV). The cutoff value for maternal blood procalcitonin was 0.071 ng/ml. This value predicted EONS with 85.2% sensitivity, 86.7% specificity, 85.2% PPV and 86.7% NPV. ***Conclusion:*** Maternal blood procalcitonin levels were superior to maternal blood CRP and WBC count in predicting EONS. Consequently, the maternal blood procalcitonin level is a clinically useful, non-invasive and reliable biomarker in antenatal prediction of EONS.

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Introduction

Preterm premature rupture of membranes (PPROM) complicates almost 3% of all pregnancies and remains an important cause of neonatal morbidity and mortality worldwide [1]. PPROM is described as the rupture of amniotic membranes before the 37th week of gestation [2]. Chorioamnionitis (CA) is the inflammation of fetal membranes, amniotic fluid, placenta and/or decidua [3]. The incidence of CA increases up to 48% with PPROM [4]. There are conflicting results about the current treatment strategies in PPROM pregnancies [5].

The study was conducted in Suleymaniye Maternity Education and Research Hospital, Istanbul, Turkey between January 2012 and January 2013.

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The American Congress of Obstetricians and Gynecologists recommended that the expectant management should be preferred to reduce adverse neonatal outcomes due to prematurity in early PPROM pregnancies, in the absence of overt CA, abruption of placenta, fetal distress or active labor [6]. However, prolonged latency period may provoke CA, due to the inadequate intrauterine environment, which is associated with cerebral palsy, lung injury, necrotizing enterocolitis and early neonatal sepsis [7].

C-reactive protein (CRP), white blood cell (WBC) count, interleukin (IL)-6, IL-10, tumor necrosis factor-α and granulocyte colony stimulating factor are maternal biomarkers that were used to predict CA and neonatal infection in PPROM pregnancies. Despite several maternal early markers for subclinical intrauterine inflammation, the optimal timing of delivery is debatable, and the current management of PPROM is still based on the gestational age [8, 9]. A reliable, specific and non-invasive maternal test for the early diagnosis of subclinical intrauterine infection in PPROM can provide an indication to the obstetrician to go for an immediate delivery even before the presence of fetal inflammatory response syndrome and clinical CA.

Procalcitonin is a 116-amino-acid peptide precursor of calcitonin. It is an early and useful biomarker of bacterial infection in neonates and infants. The elevation of procalcitonin level is usually related to the severity of disease and mortality [10]. Procalcitonin concentrations increase more rapidly than CRP in blood [11]. In addition, recent studies have shown that procalcitonin is more sensitive and specific than CRP in the early detection of bacterial infection among infants and neonates. However, there are limited studies on the prediction of early onset neonatal sepsis (EONS) with maternal blood procalcitonin level [12]. It was hypothesized that maternal blood procalcitonin concentrations are upregulated in pregnancies complicated with PPROM before the occurrence of clinical CA and neonatal infection. The purpose of this study was to compare the early diagnostic accuracy of maternal blood WBC count, CRP and procalcitonin in predicting EONS among early PPROM pregnancies.

Materials and Methods

This study was conducted at Suleymaniye Maternity Education and Research Hospital, Istanbul, Turkey, between January 2012 and January 2013. Approval for the study was granted by the Local Ethics Committee. All subjects in the study (control and study groups) gave informed consent. Sixty-nine pregnancies, complicated with PPROM, between 24 and 34 gestational weeks were admitted to the obstetric clinic during the study period. The exclusion criteria were patients with multiple pregnancies, congenital abnormalities, hypertensive disorders, gestational diabetes mellitus and patients with active labor who had uterine contractions with cervical dilatation. Twelve patients were excluded from the study. Ten of them did not meet the inclusion criteria and 2 of them declined to participate in the study. Fifty-seven consecutive pregnancies, complicated by PPROM, were considered for the follow-up.

Rupture of membranes was diagnosed by the visualization of active fluid leakage from the cervical canal using dry speculum examination. Amnisure® test (AmniSure International LLC, Boston, Mass., USA) was used to confirm diagnosis, if necessary. Gestational age was determined by using last menstrual period and crown-rump length measurement in the first trimester. All patients were hospitalized and followed up with expectant management according to the clinical approach. From admission to delivery, all patients received prophylactic antibiotics (ampicillin 4 g/day) for 1 week and administered betamethasone therapy (two 12 mg at 12 h intervals for fetal lung maturation). Fetal surveillance was followed with fetal movement count and non-stress test daily. Uterine tenderness, purulent vaginal discharge, maternal fever, biomarkers of inflammation (maternal blood CRP, WBC count and procalcitonin) were studied during hospitalization for maternal monitoring. The latent period was defined as the time interval between membrane rupture and onset of delivery. The clinical CA was diagnosed in the presence of maternal fever ≥38°C, uterine tenderness, purulent vaginal discharge, leukocytosis (WBC >15,000 cells/mm^3), maternal tachycardia (>100/min), fetal tachycardia (>160/min) [13]. Expectant management was stopped in the presence of fetal distress, clinical CA, placental abruption, active labor and completion of 34 weeks of gestation. The diagnosis of EONS was performed by either the blood culture taken at birth found positive for bacteria (excluding *Staphylococcus epidermidis*) or two or more symptoms of infection (apnea, temperature instability, lethargy, feeding intolerance, respiratory distress, hemodynamic instability) within 72 h after birth, plus one of the following: (a) positive blood culture (culture proven sepsis); (b) CRP 20 mmol/l (suspicion of sepsis) and (c) positive surface cultures of a known virulent pathogen (suspicion of sepsis) [14]. Maternal blood WBC count, CRP and procalcitonin levels were measured in the peripheral venous blood sample without drug therapy for 6 h. All samples were obtained on admission to the hospital and prior to any drug treatment. Maternal venous blood samples were collected during the first 12 h of membrane rupture. Neonatal outcomes of the patients were noted after delivery.

WBC count was determined using Mindray BC 6800. CRP level was measured using Behring nephelometer II analyzer system. Procalcitonin level was measured with time resolved amplified cryptate emission technology (Brahms, Germany) on Cobas e601 analyzer (Roche, Hitachi, Japan).

Descriptive statistics for studied variables (characteristics) were presented as median, mean, SD and minimum–maximum values; continuous variables were compared among the 2 groups using Mann–Whitney U test. A chi-square test was used to examine the association between categorical variables. For discriminating EONS present and absent groups, cutoff values of CRP, WBC count and procalcitonin were determined by using ROC analysis. The sensitivity, specificity, positive, negative predictive values (NPVs) and likelihood ratios were calculated. Statistical signifi-

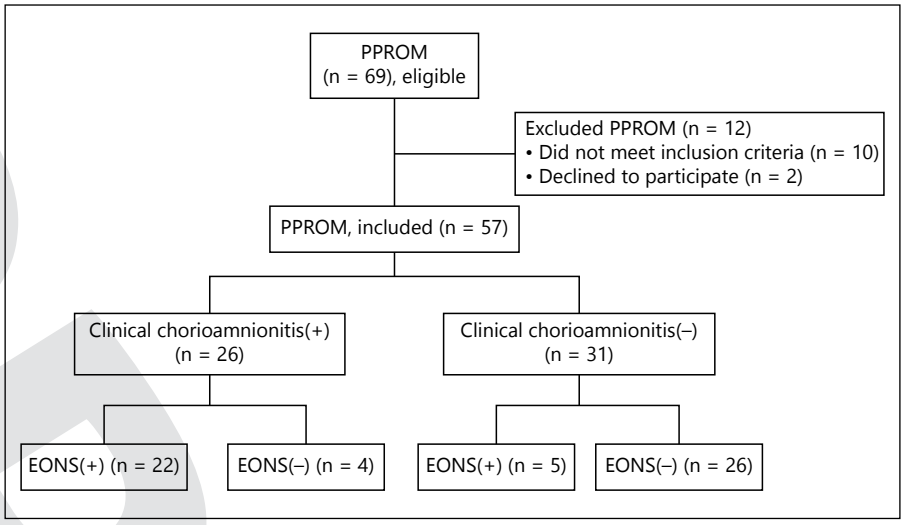

Fig. 1. The flowchart of the study population.

cance levels were considered as 0.05. Z ratio test was used to examine the association between categorical variables. Pearson correlation coefficient was used for comparing the maternal blood procalcitonin level and the latency period of patients. Linear discriminant analysis was used for evaluating the predictive ability of maternal blood WBC count, CRP and procalcitonin. The SPSS (IBM Corp., released 2013; IBM SPSS statistics for Windows, version 22.0; Armonk, N.Y., USA) statistical program was used for all statistical computations.

Results

Figure 1 shows the flowchart of the study design. The mean age of PPROM patients was 28.23 ± 6.30 years, 38.6% were primiparous and 7% had a previous history of PPROM. The mean gestational age at PPROM was 30.32 ± 2.99 years, and the mean gestational age at delivery was 31.60 ± 2.65 years. Nine (30%) of women in EONS present group and 13 (48.1%) in EONS absent group were primiparous. The mean latency period of all patients was 8.93 ± 6.06. Vaginal delivery rate was 22.8% and cesarean section rate was 77.2% in PPROM patients. The study population was divided into 2 groups according to the presence of EONS. Twenty-seven patients were in EONS present group and 30 patients were in EONS absent group. Among 27 patients with EONS, 21 patients were suspected of having neonatal sepsis which were diagnosed with 2 or more symptoms of infection and elevated CRP levels. And the remaining 6 patients were proved to have neonatal sepsis by the positive blood culture.

Cesarean section was more frequent in EONS present group (88.9%) compared to EONS absent group (66.7%). Table 1 shows the comparison of the clinical and obstetric outcomes between the 2 groups. Neonatal death rates were similar in the 2 groups (3.3, 7.4%, respectively; p = 0.492). Clinical CA was diagnosed in 26 (45.6%) women during expectant management, and 22 (84.6%) had neonates with EONS. Of the 31 women without clinical CA, 5 (16.1%) had neonates with EONS. The mean maternal blood WBC count, CRP and procalcitonin values were significantly higher in EONS present group than in EONS absent group (p = 0.001, p = 0.001 and p = 0.001, respectively). When analyzing the maternal blood procalcitonin and latency period with Pearson correlation test, it was observed that there was a significant positive correlation between them (r = 0.401; p = 0.002; n = 57).

The cutoff values for maternal blood WBC count, CRP and procalcitonin in predicting EONS were calculated as 12.25 c/mm^3 (area under curve (AUC) 0.798, 95% CI 0.68–0.91), 9.49 mg/dl (AUC 0.848, 95% CI 0.74–0.96) and 0.071 ng/ml (AUC 0.906, 95% CI 0.82–0.99), respectively by ROC curve analysis (fig. 2). The sensitivity, specificity, positive predictive value (PPV) and NPV of maternal blood WBC count, CRP and procalcitonin level in predicting EONS are shown in table 2.

When analyzing the performance of diagnostic tests in predicting EONS, the predictive values for maternal blood WBC count, CRP and procalcitonin levels for EONS were calculated as 70.2, 78.9 and 86.0%, respectively. The combination of maternal blood WBC count and CRP tests predicted EONS with 75.4%. Also, the combination of maternal blood WBC count, CRP and procalcitonin tests predicted EONS with 87.7%.

Table 1. Baseline and clinical characteristics of patients

	Neonatal sepsis(–) (n = 30)	Neonatal sepsis(+) (n = 27)	p value
Age, years	27.80±6.21	28.70±6.48	0.548*
Gravida, median (min–max)	2 (1–6)	2 (1–5)	0.707*
Parity, median (min–max)	1 (0–4)	1 (0–3)	0.838*
History of chronic disease, n (%)	3 (10)	4 (14.8)	0.580#
History of PPROM, n (%)	2 (6.7)	2 (7.4)	0.913#
Gestational age at PPROM	31.13±2.91	29.41±2.86	0.020*
Latency period, days	5.90±5.1	12.30±5.26	0.001*
Gestational age at delivery	31.93±2.64	31.22±2.67	0.252*
Cesarean section, n (%)	20 (66.7)	24 (88.9)	0.046#
Neonatal death, n (%)	1 (3.3)	2 (7.4)	0.492#
WBC count, c/mm^3	11.06±2.61	15.53±4.62	0.001*
<12.25 c/mm^3, n (%)	21 (70)	8 (29.6)	0.001ɣ
≥12.25 c/mm^3, n (%)	9 (30)	19 (70.4)	0.001ɣ
CRP, mg/dl	7.58±7.34	32.30±42.17	0.001*
<9.49 mg/dl, n (%)	24 (80)	9 (22.2)	0.001ɣ
≥9.49 mg/dl, n (%)	6 (20)	21 (77.8)	0.001ɣ
Procalcitonin, ng/ml	0.062±0.11	0.33±0.21	0.001*
<0.071 ng/ml, n (%)	26 (86.7)	4 (14.8)	0.001ɣ
≥0.071 ng/ml, n (%)	4 (13.3)	23 (85.2)	0.001ɣ

Chi-square test was used to compare categorical variables.
* p < 0.05, Mann–Whitney U test was used to compare continuous variables.
ɣ Z ratio test was used to examine the association between categorical variables.

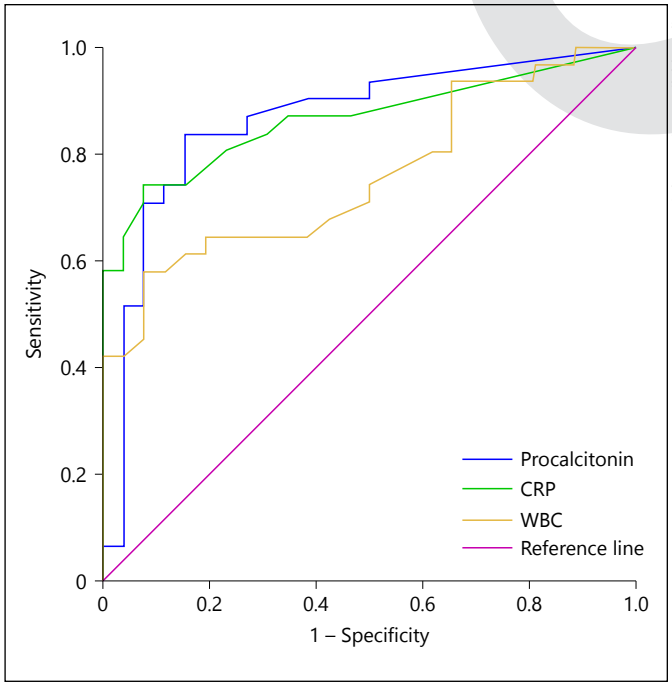

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Fig. 2. The ROC curve of maternal blood WBC count, CRP and procalcitonin for the prediction of EONS.

Table 2. Prognostic value of maternal blood WBC count, CRP and procalcitonin for predicting EONS

	Prediction of EONS
WBC count ≥12.25 c/mm^3, %	
Sensitivity	67.9
Specificity	72.4
PPV	70.4
NPV	70.0
Likelihood ratio	9.534
CRP ≥9.49 mg/dl, %	
Sensitivity	77.8
Specificity	80.0
PPV	77.8
NPV	80.0
Likelihood ratio	20.233
Procalcitonin ≥0.071 ng/ml, %	
Sensitivity	85.2
Specificity	86.7
PPV	85.2
NPV	86.7
Likelihood ratio	32.648

PROOF

Discussion

In this study, the maternal blood procalcitonin level was found to be significantly elevated in early PPROM patients with EONS. Maternal blood procalcitonin cutoff level of 0.071 ng/ml predicted EONS with 85.2% sensitivity and 86.7% specificity. The sensitivity, specificity, PPV and NPV of maternal blood procalcitonin for predicting EONS were higher than those of maternal CRP and WBC count.

Neonatal sepsis, which occurs in the first 28 days of life, is the most common cause of morbidity and mortality in neonates. It is categorized into 2 groups as: early onset (≤72 h of life) and late onset (≥72 h of life) neonatal sepsis [15]. EONS remains an important complication for preterm infants and presents as a bacterial infection that is transmitted from the mother to the fetus vertically before or during labor [16]. Prolonged rupture of membranes disrupts the environment of amniotic cavity and also contributes to the high rates of CA following neonatal infection. Likewise, intraamniotic infection is intimately correlated with EONS [17].

In this study, EONS rate was found to be 47.4% among early PPROM patients. This rate was higher than the previous studies. Mercer et al. [18] reported this rate as 5.4%, Khashoggi [19] reported 7.7% in Saudi Arabia and Noor et al. [20] reported 28.2% in Pakistan. Prematurity was the most important factor associated with EONS [21]. The study population consisted of early PPROM patients (gestational age between 24 and 34 weeks), hence a higher rate of EONS than previous studies was found, and the proven EONS rate was 10.5% (6/57) which was comparable to the previous studies. It was seen that more attention has been focused on postnatal clinical examinations and blood tests to predict EONS in neonatal period. This study targeted the prediction of EONS prenatally among early PPROM patients with evaluation of maternal blood procalcitonin level.

Maternal WBC count was an old parameter used for predicting intraamniotic infection. Maternal WBC count increases physiologically at the end of gestation, due to the inflammatory alterations and elevated cortisol secretion [22]. Hence, it could not be a specific and reliable predictor for inflammatory conditions during pregnancy [12]. In consistent with published reports, the predictive values of maternal WBC count for EONS were found to be lowest compared to maternal blood CRP and procalcitonin levels.

Many researches were conducted to identify whether maternal CRP, procalcitonin and IL-6 can be used as non-invasive predictors of subclinical intraamniotic infection and EONS or not [12–31]. Kayem et al. [23] reported that >20 mg/dl of CRP level predicted neonatal infection with 21% sensitivity, 95% specificity, 50% PPV and 84% NPV. Torbe [24] found the CRP level cutoff to be ≥10 mg/dl with 52% sensitivity, 76% specificity, 52% PPV and 76% NPV in predicting EONS. In this study, the cutoff value for CRP was ≥9.49 mg/dl and this value predicted EONS with 77.8% sensitivity, 80.0% specificity, 77.8% PPV and 80.0% NPV. Thyroid's para follicular cells (C cells), lung neuroendocrine cells and intestine synthesizes procalcitonin, and recent studies have shown that it was a relatively specific biomarker of bacterial infection [25, 26]. Oludag et al. [12] reported 0.054 ng/ml cutoff value for maternal blood procalcitonin for predicting histologic CA and neonatal infection. They stated that maternal procalcitonin level was more useful than CRP in predicting histologic CA. On the contrary, maternal CRP level was more beneficial than procalcitonin in determining neonatal infection. Kopyra et al. [27] represented high predictive values of procalcitonin compared to CRP and IL-6 for predicting intraamniotic infection. Torbe [28] reported 1.9 ng/ml cutoff value for maternal serum procalcitonin in predicting histologic CA with 75% sensitivity and 45% specificity. Greksova et al. [29] also suggested that a combination of maternal serum and cord blood levels of CRP, procalcitonin and neopterin highly predicted perinatal infection. However, there are conflicting results in the published reports. Thornburg et al. [30] concluded that the maternal serum procalcitonin level did not predict pathological CA, funisitis and neonatal sepsis. Also, Torbe and Czajka [31] did not find any correlation between cervicovaginal fluid procalcitonin levels and subclinical intraamniotic infection in PPROM patients.

As can be seen from the reported data, there is a lack of evidence on predicting EONS. In this study, the optimal cutoff value for maternal blood procalcitonin was 0.071 ng/ml. In addition, this value predicted EONS with 85.2% sensitivity, 86.7% specificity, 85.2% PPV and 86.7% NPV. This study shows that maternal blood procalcitonin levels were superior to maternal blood CRP and WBC count in predicting EONS. Furthermore, the highest predictive values of maternal procalcitonin were found in the published reports for diagnosing EONS among early PPROM patients.

The limitations of this study include the number of cases and the absence of pathological examination of placenta for confirming histological CA. Also, the effect of betamethasone which was used for fetal lung maturation

before 34 weeks of gestation on maternal blood procalcitonin concentrations could not be excluded.

In spite of significant efforts, there was no maternal serum marker alone or in combination to propose reasonable sensitivity and specificity for predicting EONS in PPROM pregnancies. The results of this study suggested that maternal blood procalcitonin level is a clinically useful, non-invasive and reliable biomarker in antenatal prediction of EONS. The combination of maternal blood procalcitonin, CRP and WBC count increases the early diagnostic accuracy of EONS. In clinical practice of early PPROM, high level of maternal blood procalcitonin may alert the obstetrician for possible neonatal infection. Moreover, obstetricians may include maternal blood procalcitonin level in their decision for women complicated with PPROM to either immediate delivery (active management) or prolongation of pregnancy (expectant management). Further large and prospective studies are needed to define the best cutoff value for maternal blood procalcitonin for predicting EONS.

Disclosure Statement

The authors declare that they have no conflict of interest. The authors indicated that there was no financial relationship with the organization that sponsored the research. The authors had full control of all primary data and agreed to allow the journal to review their data if requested.

References

1 Mercer BM: Preterm premature rupture of the membranes. Obstet Gynecol 2003;101:178–193.
2 Stringer M, Miesnik SR, Brown L, Martz AH, Macones G: Nursing care of the patient with preterm premature rupture of membranes. MCN Am J Matern Child Nurs 2004;29:144–150.
3 Goldenberg RL, Culhane JF, Iams JD, Romero R: Epidemiology and causes of preterm birth. Lancet 2008;371:75–84.
4 Hillier SL, Witkin SS, Krohn MA, Watts DH, Kiviat NB, Eschenbach DA: The relationship of amniotic fluid cytokines and preterm delivery, amniotic fluid infection, histologic chorioamnionitis, and chorioamnion infection. Obstet Gynecol 1993;81:941–948.
5 Ramsey PS, Nuthalapaty FS, Lu G, Ramin S, Nuthalapaty ES, Ramin KD: Contemporary management of preterm premature rupture of membranes (PPROM): a survey of maternal-fetal medicine providers. Am J Obstet Gynecol 2004;191:1497–1502.
6 Practice bulletins No. 139: premature rupture of membranes. Obstet Gynecol 2013;122:918–930.
7 Yoon BH, Romero R, Park JS, Kim CJ, Kim SH, Choi JH, Han TR: Fetal exposure to an intraamniotic inflammation and the development of cerebral palsy at the age of three years. Am J Obstet Gynecol 2000;182:675–681.
8 Delanghe JR, Speeckaert MM: Translational research and biomarkers in neonatal sepsis. Clin Chim Acta 2015;451(pt A):46–64.
9 Cetin O, Dokurel Cetin I, Uludag S, Sen C, Verit FF, Guralp O: Serial ultrasonographic examination of the fetal thymus in the prediction of early neonatal sepsis in preterm premature rupture of membranes. Gynecol Obstet Invest 2014;78:201–207.
10 van Rossum AM, Wulkan RW, Oudesluys-Murphy AM: Procalcitonin as an early marker of infection in neonates and children. Lancet Infect Dis 2004;4:620–630.
11 Dandona P, Nix D, Wilson MF, Aljada A, Love J, Assicot M, Bohuon C: Procalcitonin increase after endotoxin injection in normal subjects. J Clin Endocrinol Metab 1998;83:3296–3301.
12 Oludag T, Gode F, Caglayan E, Saatli B, Okyay RE, Altunyurt S: Value of maternal procalcitonin levels for predicting subclinical intraamniotic infection in preterm premature rupture of membranes. J Obstet Gynaecol Res 2014;4:954–960.
13 Newton ER: Chorioamnionitis and intraamniotic infection. Clin Obstet Gynecol 1993;36:795–808.
14 van der Ham DP, van der Heyden JL, Opmeer BC, Mulder AL, Moonen RM, van Beek JH, et al: Management of late-preterm premature rupture of membranes: the PPROMEXIL-2 trial. Am J Obstet Gynecol 2012;207:276.e1–e10.
15 Edwards MS, Baker CJ: Krugman's infectious diseases of children; in Gershon AA, Hotez PJ, Katz SL (eds): Sepsis in the Newborn. Philadelphia, Mosby, 2004, pp 545–561.
16 Hornik CP, Fort P, Clark RH, Watt K, Benjamin DK Jr, Smith PB, Manzoni P, Jacqz-Aigrain E, Kaguelidou F, Cohen-Wolkowiez M: Early and late onset sepsis in very-low-birthweight infants from a large group of neonatal intensive care units. Early Hum Dev 2012;88(suppl 2):S69–S74.
17 Lau J, Magee F, Qiu Z, Hoube J, Von Dadelszen P, Lee SK: Chorioamnionitis with a fetal inflammatory response is associated with higher neonatal mortality, morbidity, and resource use than chorioamnionitis displaying a maternal inflammatory response only. Am J Obstet Gynecol 2005;193(3 pt 1):708–713.
18 Mercer BM, Miodovnik M, Thurnau GR, Goldenberg RL, Das AF, Ramsey RD, et al: Antibiotic therapy for reduction of infant morbidity after preterm premature rupture of the membranes. A randomized controlled trial. National Institute of child health and human development maternal-fetal medicine units network. J AMA 1997;278:989–995.
19 Khashoggi TY: Outcome of pregnancies with preterm premature rupture of membranes. Saudi Med J 2004;25:1957–1961.
20 Noor S, Nazar AF, Bashir R, Sultana R: Prevalance of PPROM and its outcome. J Ayub Med Coll Abbottabad 2007;19:14–17.
21 Benitz WE, Gould JB, Druzin ML: Risk factors for early-onset group B streptococcal sepsis: estimation of odds ratios by critical literature review. Pediatrics 1999;103:e77.
22 Rizzo G, Capponi A, Vlachopoulou A, Angelini E, Grassi C, Romanini C: Interleukin-6 concentrations in cervical secretions in the prediction of intrauterine infection in preterm premature rupture of the membranes. Gynecol Obstet Invest 1998;46:91–95.
23 Kayem G, Goffinet F, Batteux F, Jarreau PH, Weill B, Cabrol D: Detection of interleukin-6 in vaginal secretions of women with preterm premature rupture of membranes and its association with neonatal infection: a rapid immunochromatographic test. Am J Obstet Gynecol 2005;192:140–145.
24 Torbe A: Evaluation of cytokines and procalcitonin concentrations in cervico-vaginal secretion, in plasma blood and in amniotic fluid in pregnancy complicated by preterm labor. Habilitation thesis. Ann Acad Med Stetin 2003:92.
25 Müller B, White JC, Nylén ES, Snider RH, Becker KL, Habener JF: Ubiquitous expression of the calcitonin-I gene in multiple tissues in response to sepsis. J Clin Endocrinol Metab 2001;86:396–404.

26 Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J: Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis 2004;39:206–217.
27 Kopyra P, Seremak-Mrozikiewicz A, Drews K: Usefulness of PCT, IL-6, CRP measurement in the prediction of intraamniotic infection and newborn status in pregnant women with premature rupture of membranes. Ginekol Pol 2010;81:336–341.
28 Torbe A: Maternal plasma procalcitonin concentrations in pregnancy complicated by preterm premature rupture of membranes. Mediators Inflamm 2007;2007:35782.
29 Greksova K, Parrak V, Chovancova D, Stencl P, Oravec J, Marsik L, Sysak R, Fuchs D, Peskova Z, Borovsky M: Procalcitonin, neopterin and C-reactive protein in diagnostics of intrauterine infection and preterm delivery. Bratisl Lek Listy 2009;110:623–626.
30 Thornburg LL, Queenan R, Brandt-Griffith B, Pressman EK: Procalcitonin for prediction of chorioamnionitis in preterm premature rupture of membranes. J Matern Fetal Neonatal Med 2016;29:2056–2061.
31 Torbe A, Czajka R: Are vaginal fluid procalcitonin levels useful for the prediction of subclinial infection in patients with preterm premature rupture of membranes? J Obstet Gynecol Res 2005;31:464–470.

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