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The importance of C-reactive protein and procalcitonin in the diagnosis of chorioamnionitis in the cases with preterm premature rupture of membranes

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Abstract

Objective: Our aim is to compare the clinical biochemical markers of the cases who developed and did not develop clinical chorioamnionitis among those hospitalized in our clinic with the diagnosis of preterm premature rupture of membranes (PPROM). For that purpose, we investigated the significance levels of mean values, sensitivity and specificity levels of the infection markers and also their correlations with each other in the diagnosis of clinical chorioamnionitis.

Methods: Eighty-one cases with singleton pregnancy who were hospitalized with the pre-diagnosis of PPROM and followed up and treated in the Clinic of Gynecology and Obstetrics of the Faculty of Medicine at Mersin University were included in the study. The values of 48 cases who developed and did not develop clinical chorioamnionitis were compared.

Results: The mean WBC, CRP and procalcitonin values at labor and mean procalcitonin values at hospitalization were significantly higher in the cases diagnosed with chorioamnionitis than the cases without chorioamnionitis diagnosis.

Conclusion: We found out that the procalcitonin values at hospitalization and WBC, serum CRP and procalcitonin values at labor in the cases followed up with the diagnosis of PPROM were significant in clinical chorioamnionitis cases. We concluded in our study that these infection markers (procalcitonin in particular) can be used in the early diagnosis of chorioamnionitis by not checking at hospitalization only but also in the follow-ups of the patients regularly.

Keywords: Preterm premature rupture of membranes (PPROM), CRP, procalcitonin.

Özet: Preterm erken membran rüptürü olan olgularda koryoamniyonit tanısında C-reaktif protein ve prokalsitonin önemi

Amaç: Amacımız preterm erken membran rüptürü (PEMR) tanısı ile kliniğimize yatan hastalardan klinik koryoamniyonit gelişen ve gelişmeyen olguların klinik biyokimyasal belirteçlerini karşılaştırmaktır. Bu amaçla klinik koryoamniyonit tanısında enfeksiyon belirteçlerinin ortalama değerlerinin anlamlılık düzeyi, duyarlılık-özgüllükleri ve ayrıca bu belirteçlerin birbirleri ile olan korelasyonları araştırıldı.

Yöntem: Çalışmaya Mersin Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Kliniğine PEMR ön tanısı ile yatırılarak takip ve tedavi edilen 81 tekil gebeliği olan olgular alındı. Klinik koryoamniyonit gelişen olgular ve gelişmeyen 48 hastanın değerleri karşılaştırıldı.

Bulgular: Koryoamniyonit tanısı alan olguların doğum sırasındaki WBC, CRP ve prokalsitonin ortalaması ve yatış sırasındaki prokalsitonin ortalama değeri koryoamniyonit tanısı almayan gruptan anlamlı olarak daha yüksekti.

Sonuç: PEMR tanısı ile takip edilen olgularda hasta yatışındaki prokalsitonin ve doğum zamanındaki WBC, serum CRP ve prokalsitoninin klinik koryoamniyonit olgularında önemli olduğu görüldü. Çalışmamızdan bu enfeksiyon belirteçlerinin sadece hastanın yatışı sırasında değil hasta takibinde de düzenli aralıklarla bakılarak koryoamniyonitin erken tanısında kullanılabileceği (özellikle prokalsitonin) sonucuna varıldı.

Anahtar sözcükler: Preterm erken membran rüptürü (PEMR), CRP, prokalsitonin.

Introduction

The preterm premature rupture of membranes (PPROM) is the rupture of amniotic membrane without the development of uterine contraction before 37 weeks of gestation. PPROM is one of the most common severe gestational complications and it is seen in about 3% of all pregnancies.[1] The primary goal in its management is to prevent preterm labor and to reduce complications that

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will develop during follow-up. Extending the week of gestation by preventing preterm labor is the basic method of reducing prematurity-related complications.[2,3] While about 15–25% of the pregnant women with PPROM have infection symptoms at prepartum period, about 15–20% of them have clinical infection symptoms at postpartum period.[4,5] The patients with PPROM are followed up until 34 weeks of gestation or displaying clinical symptoms.[6] Any delay in the diagnosis and treatment of chorioamnionitis during patient follow-up leads to the development of infection which then results in the maternal and neonatal inflammatory response, fetal hypoxia and increased cerebral palsy risk.[7] Therefore, it is very important to detect the presence of chorioamnionitis early in pregnancies complicated with PPROM in order to manage pregnancy follow-up and prevent developing complications.

Today, there is no test that can diagnose chorioamnionitis accurately. The clinical infection indications such as tachycardia, increased body temperature and fundal sensitivity in chorioamnionitis patients are not specific to this disease.[8] Although some indications were investigated in previous studies, none of them were shown to be accurate enough.[9,10] The parameters studies the most for the prediction of chorioamnionitis in the patients with PPROM are white blood cells (WBC), glucose in the amniotic fluid, maternal serum C-reactive protein (CRP), interleukin-6 (IL-6) and procalcitonin.[11,12] Due to being non-specific and the changes in gestational physiology, these parameters have limited potential in the diagnosis of chorioamnionitis.

Our aim in this study is to compare the clinical biochemical markers of the cases who developed and did not develop clinical chorioamnionitis among those hospitalized in our clinic with the diagnosis of preterm premature rupture of membranes. For that purpose, we investigated the significance levels of mean values, sensitivity and specificity levels of the infection markers and also their correlations with each other in the diagnosis of clinical chorioamnionitis.

Methods

Eighty-one cases with singleton pregnancy who were followed up and treated by hospitalizing with the prediagnosis of PPROM at the Clinic of Gynecology and Obstetrics, Faculty of Medicine, Mersin University between January 1, 2010 and December 31, 2019 were included in our study. Written approval was obtained for the study from the Medical Ethics Committee of the Faculty of Medicine, Mersin University (22.01.2020, no: 11664). The weeks of gestation of the cases determined by their last menstrual period or first-trimester ultrasound examination varied between 24 and 34. The patients who had fetal anomaly, risk factors for preterm labor (twin pregnancies, preterm labor or cerclage history etc.), gestational diabetes mellitus, gestational hypertension, heart disease, ablatio placentae or placenta previa in their current pregnancy were excluded from the study. Blood biochemistry, hemogram, full urine analysis, urine culture and cervical culture by sterile speculum examination were taken from the patients. For beta-group streptococcus prophylaxis, all cases were administered 2 g ampicillin (IV) every 6 hours for 48 hours, 1 g (PO) azithromycin once, and 500 mg amoxicillin (PO) every 8 hours for the following 5 days. The cases were also administered betamethasone for fetal lung maturation and magnesium sulphate infusion for neuroprotective purposes under 32 weeks. The cases were checked for their body temperature, pulse and blood pressure four times a day during the follow-up. In addition, their daily WBC levels, maternal serum CRP with 3-day intervals and weekly procalcitonin levels were checked (during follow-up, clinical or laboratory values were checked more frequently in suspicious conditions in terms of chorioamnionitis). Thirty-three cases who were found to have fever (>37.8 °C), vaginal discharge, maternal tachycardia (>100 beat/min) and fetal tachycardia (>160 beat/min), abdominal pain, uterine sensitivity and leukocytosis in the follow-up were diagnosed with clinical chorioamnionitis, and included in “Group 1”. Forty-eight cases who did not develop clinical chorioamnionitis and delivered after 34 weeks of gestation were included in “Group 2”. The data of all groups were analyzed by using SPSS version 18.0 (IBM, Armonk, NY, USA). All data were presented as mean±SD or number (percentage). Student’s t-test, Mann-Whitney U test and ROC test were used to compare the mean±SD, frequency and prediction values of the data of both groups. Two-way $p<0.05$ value was considered statistically significant.

Results

A total of 81 cases diagnosed with PPROM were included in our study. The clinical chorioamnionitis developed

in 33 (40.7%) of the cases during follow-up. The characteristics of 33 cases diagnosed with clinical chorioamnionitis (Group 1) and 48 cases not diagnosed with clinical chorioamnionitis (Group 2) are shown in **Table 1**.

The ages and weeks of gestation of the cases in both groups were similar (p values were 0.88 and 0.88, respectively). The mean procalcitonin values of the cases in Group 1 with chorioamnionitis diagnosis at hospitalization were significantly higher than the group not diagnosed with chorioamnionitis. Although WBC, neutrophil, lymphocyte count and maternal serum CRP values of the cases in Group 1 at hospitalization were higher than the cases in Group 2, the difference was not statistically significant. The mean WBC, CRP and procalcitonin values at labor in the group diagnosed with chorioamnionitis were higher than the other group. There was no significantly difference between the groups in terms of fetal serum CRP and fetal WBC values.

Sensitivity and specificity of the infection markers in cases diagnosed with chorioamnionitis are shown in **Table 2**. The marker with the highest sensitivity for chorioamnionitis diagnosis was the maternal serum CRP at hospitalization and procalcitonin level at labor (69%) and the marker with the highest specificity for chorioamnionitis diagnosis was procalcitonin level at labor (84%) while the parameter with the highest negative predictive value was maternal serum CRP value at hospitalization (92%).

Discussion

Although the early diagnosis criteria of chorioamnionitis in PPROM cases is a controversial topic, establishing the diagnosis of chorioamnionitis early and to initiate the treatment early are very important in terms of reducing maternal and fetal complications. PPROM is responsible for 30% of preterm labors and is the most common reason of hospitalization at newborn intensive care unit.[13] Long-term rupture of membranes in these labors also results in the higher incidence of postpartum endometritis.[14] Increased mortality and morbidity rates related with respiratory distress syndrome, intraamniotic infection and intraventricular hemorrhage are also seen more

Table 1. The characteristics of patients diagnosed and not diagnosed with clinical chorioamnionitis.*

	Group 1 (Chorioamnionitis +) n=33 Mean±SD	Group 2 (Chorioamnionitis -) n=48 Mean±SD	p-value
Age (year)	30.5±7.1	30.8±5.1	0.88
Labor week	29.8±4.2	29.6±4.8	0.88
WBC at hospitalization	13.414±5947	12.914±4161	0.96
WBC at labor	13.844±6173	11.145±3154	**0.03**
Neutrophil count	11.045±8364	10.465±4375	0.79
Lymphocyte count	1719±711	1700±541	0.96
Thrombocyte count (million)	241±60	242±94	0.78
CRP at hospitalization	19±14.7	21.8±33	0.36
CRP at labor	40.8±56	13.6±16	**0.01**
Procalcitonin at hospitalization	0.35±0.31	0.22±0.55	**0.04**
Procalcitonin at labor	0.28±0.19	0.06±0.05	**0.001**
Fetal weight (gram)	1639±806	1500±877	0.48
1-minute Apgar score	6±2	5±2	0.16
5-minute Apgar score	7±3	6±3	0.11
Fetus serum CRP	1.12±1.6	0.89±1.8	0.60
Fetus WBC	3781±988	3397±650	0.55

*Independent Student's t-test and Mann-Whitney U test were used.

in the newborns of mothers with PPROM.[14] There are many studies conducted so far for the early diagnosis of PPROM. These studies investigated the markers such as WBC, maternal serum CRP, glucose in the amniotic fluid and procalcitonin, but none of these markers can establish the diagnosis of chorioamnionitis accurately. Having a limited capability in diagnosis may result from the marker itself or gestational physiology. The increase of WBC during pregnancy physiologically and after steroid administration limits its value during the follow-up of patients with PPROM. Similarly, physiological changes seen in the late period of pregnancy limit the efficacy of maternal serum CRP. The blood concentration of maternal serum CRP value vary between 5 and 10 mg/L in healthy individuals. On the other hand, it may reach up to 10–40 mg/L in the infections in pregnant women caused by slight inflammation and viruses. Moderate to severe inflammation reaches above 40 mg/L in pregnant women in cases such as bacterial infection.[15] Normal serum concentration of procalcitonin which is another infection marker is below 0.01 mg/mL.[16] The results of the studies investigating the role of procalcitonin in predicting chorioamnionitis in patients with PPROM are controversial.[12,17,18]

Thornburg et al. found in their study that procalcitonin and maternal CRP values at labor are high in the patients who developed clinical chorioamnionitis.[12] Torbé showed in their study that maternal plasma procalcitonin value increased both in PPROM and mature ruptures of membranes.[19,20] Sreepapong et al. reported a weak correlation between chorioamnionitis and maternal serum CRP, WBC and neutrophil count.[21] In our study, we found that procalcitonin value at first hospitalization and WBC, maternal serum CRP and procalcitonin values at labor were higher in the cases who developed chorioamnionitis (**Table 1**). Our results were similar with other studies conducted previously. In our study, we could not find a significant correlation with neutrophil count similar to the other studies although neutrophil count was high in the chorioamnionitis cases. Procalcitonin value at labor in particular was significantly higher than the others.

Infection and inflammation is limited with chorionic and amniotic membranes in the early stages of chorioamnionitis and IL-6 release starts in these sites. IL-6 which increases in maternal blood over time also increases CRP levels in the maternal circulation. As a result, a natural systemic response is created in the body against the infection. The inflammation and acute phase reactants increase defense cells and these cells increase infection markers in return. In cases of infection, procalcitonin and CRP increase as a response to the infection but their responses are different from each other. Serum CRP reaches its highest level about 4–6 hours later as a result of the inflammation in the body,[27] and its half-life is about 19 hours.[29] Although procalcitonin also reaches its peak level in 4–6 hours, it has a long half-life about 25–30 hours.[24] Fast induction and having a better half-life makes CRP important in patient follow-up, and this makes maternal serum CRP superior to procalcitonin in the diagnosis and follow-up of the patients with PPROM. In addition to this disadvantage, evaluation by immunoassay is another disadvantage of procalcitonin.[19] In their study, Simon et al. reported that procalcitonin is a better marker than CRP for bacterial infections.[22] In another study, the authors concluded that procalcitonin is a better marker specific to bacterial infections although maternal serum CRP is more sensitive marker than procalcitonin in bacterial infection and inflammation cases.[19] In our study, we found that maternal serum

Table 2. Sensitivity and specificity values of markers associated with clinical chorioamnionitis.

	Cut-off	Sensitivity	Specificity	PPD	NPD
WBC at hospitalization	12.000	36	39	12	72
WBC at labor	11.845	36	35	12	70
CRP at hospitalization	12.45	69	68	27	92
CRP at labor	11.94	57	58	30	82
Procalcitonin at hospitalization	0.29	60	62	31	84
Procalcitonin at labor	0.115	69	84	33	87

NPD: negative predictive value; **PPD:** positive predictive value.

CRP at hospitalization had higher sensitivity and specificity than other markers in the chorioamnionitis group (**Table 2**). This results from the early induction of CRP in case of inflammation. We found in our study that the negative predictive value of CRP which has high sensitivity in this period and which can be used in the prediction of chorioamnionitis was 92%, which was higher than other markers (**Table 2**). Clinical chorioamnionitis indications (such as fever, maternal tachycardia, fetal tachycardia etc.) results from the systemic response of body to the infection agency. This response also results in the increase of infection markers. This infection (mainly bacterial) causes WBC, CRP and procalcitonin to increase in the maternal blood. Although this bacterial infection increases CRP in the maternal blood, procalcitonin is more sensitive to bacterial infection. As it can be seen in **Table 1**, procalcitonin was the marker with the highest sensitivity and specificity to detect our cases with clinical chorioamnionitis. These results of procalcitonin are also consistent with other studies.

WBC, which is another infection marker, increases in the maternal blood with the response to infection just like CRP and procalcitonin. Some other studies reported that WBC increased in cases with clinical chorioamnionitis similar to maternal serum CRP.[25] The same study found that maternal serum CRP was more sensitive than WBC. In another study, the authors reported that both maternal serum CRP and WBC increased in case of inflammation in the body of pregnant women, and maternal serum CRP was a more specific marker than WBC in the diagnosis of acute chorioamnionitis.[26] We observed in our study that the sensitivity and specificity of CRP were higher than WBC in the cases with clinical chorioamnionitis (**Table 2**).

Conclusion

We found out that the procalcitonin values at hospitalization and WBC, serum CRP and procalcitonin values at labor in the cases followed up with the diagnosis of PPROM were significant in clinical chorioamnionitis cases. We concluded in our study that these infection markers (procalcitonin in particular) can be used in the early diagnosis of chorioamnionitis by not checking at hospitalization only but also in the follow-ups of the patients regularly.

Making a timely decision for the labor of the patients hospitalized with PPROM diagnosis is important. In case of preterm labor, PPROM causes fetal prematurity and increased morbidity in the newborn as a result. In case of post-term labor, chorioamnionitis develops and it results with increased maternal and fetal mortality and morbidity. In order to establish this balance, close follow-up of the infection markers of patients hospitalized with PPROM diagnosis is important. There is no full consensus about when and which of these markers are more important. We found out in our study that procalcitonin level at hospitalization in cases followed up with PPROM diagnosis and WBC, serum CRP and procalcitonin values at labor are important in clinical chorioamnionitis cases. We concluded in our study that these infection markers (procalcitonin in particular) can be used in the early diagnosis of chorioamnionitis by not checking at hospitalization only but also in the follow-ups of the patients regularly.

Conflicts of Interest: No conflicts declared.

References

1. Mercer BM. Preterm premature rupture of the membranes: current approaches to evaluation and management. Obstet Gynecol Clin North Am 2005;32:411–28. [PubMed] [CrossRef]
2. Tsakiridis I, Mamopoulos A, Chalkia-Prapa EM, Athanasiadis A, DagklisT. Preterm premature rupture of membranes: a review of 3 national guidelines. Obstet Gynecol Surv 2018;73: 368–75. [PubMed] [CrossRef]
3. Committee on Practice Bulletins-Obstetrics. ACOG practice bulletin no. 188: Pre labor rupture of membranes. Obstet Gynecol 2018;131:e1–e14. [PubMed] [CrossRef]
4. Kenyon S, Boulvain M, Neilson JP. Antibiotics for preterm rupture of membranes. Cochrane Database Syst Rev 2013;(12):CD001058. [PubMed] [CrossRef]
5. Seliem W, Sultan AM. Presepsin as a predictor of early onset neonatal sepsis in the umbilical cord blood of premature infants with premature rupture of membranes. Pediatr Int 2018;60: 428–32. [PubMed] [CrossRef]
6. Tita AT, Andrews WW. Diagnosis and management of clinical chorioamnionitis. Clin Perinatol 2010;37:339–54. [PubMed] [CrossRef]
7. Yoon BH, Romero R, Park JS, Kim CJ, Kim SH, Choi JH, et al. Fetal exposure to an intra-amniotic inflammation and the development of cerebral palsy at the age of three years. Am J Obstet Gynecol 2000;182:675–81. [PubMed] [CrossRef]
8. Newton ER. Chorioamnionitis and intraamniotic infection. Clin Obstet Gynecol 1993;36:795–808. [PubMed] [CrossRef]
9. Czikk MJ, McCarthy FP, Murphy KE. Chorioamnionitis: from pathogenesis to treatment. Clin Microbiol Infect 2011; 17:1304–11. [PubMed] [CrossRef]
10. Practice Bulletins No. 139: Premature rupture of membranes. Obstet Gynecol 2013;122:918–30. [PubMed] [CrossRef]

11. Çakar E, Çakar ŞE, Taşan HA, Karçaaltıncaba D, Şentürk MB, Koç N, et al. Diagnostic and prognostic value of presepsin for subclinical chorioamnionitis in pregnancies between 23–28 week with preterm premature rupture of the membranes. Balkan Med J 2016;33:668–74. [PubMed] [CrossRef]
12. 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;29:2056–61. [PubMed] [CrossRef]
13. Arias R, Tomich P. Etiology and outcome of low birth weight and preterm infants. Obstet Gynecol 1982;60:277–81. [PubMed]
14. ACOG Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 80: premature rupture of the membranes. Clinical management guidelines for obstetrician-gynecologists. Obstet Gynecol 2007;109:1007–19. [PubMed] [CrossRef]
15. Chew KS. What's new in emergencies trauma and shock? C-reactive protein as a potential clinical biomarker for influenza infection: more questions than answers. J Emerg Trauma Shock 2012;5:115–7. [PubMed] [CrossRef]
16. Assumma M, Signore F, Pacifico L, Rossi N, Osborn JF, Chiesa C. Serum procalcitonin concentrations in term delivering mothers and their healthy offspring: a longitudinal study. Clin Chem 2000;46:1583–7. [PubMed] [CrossRef]
17. Cetin O, Aydın ZD, Verit FF, Zebitay AG, Karaman E, Elasan S, et al. Is maternal blood procalcitonin level a reliable predictor for early onset neonatal sepsis in preterm premature rupture of membranes? Gynecol Obstet Invest 2017;82:163–9. [PubMed] [CrossRef]
18. Oludag T, Gode F, Caglayan E, Saatli B, Okyay RE, Altunyurt S. Value of maternal procalcitonin levels for predicting subclinical intra-amniotic infection in preterm premature rupture of membranes. J Obstet Gynecol Res 2014;40:954–60. [PubMed] [CrossRef]
19. Samsudin I, Vasikaran SD. Clinical utility and measurement of procalcitonin. Clin Biochem Rev 2017;38:59–68. [PubMed]
20. Torbé A. Maternal plasma procalcitonin concentrations in pregnancy complicated by preterm premature rupture of membranes. Mediators Inflamm 2007;2007:35782. [PubMed] [CrossRef]
21. Sereepapong W, Limpongsanurak S, Triratanachat S, Wannakrairot P, Charuruks N, Krailadsiri P. The role of maternal serum C-reactive protein and white blood cell count in the prediction of chorioamnionitis in women with premature rupture of membranes. J Med Assoc Thai 2001;84(Suppl 1):S360–S6. [PubMed]
22. 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;39:206–17. [PubMed] [CrossRef]
23. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest 2003;111:1805–12. [PubMed] [CrossRef]
24. Oberhoffer M, Vogelsang H, Meier-Hellmann A, Jäger L, Reinhart K. Anti-katacalcin-antibody reaction in different types of human leukocytes indicates procalcitonin content: 487. Shock 1997;7(Suppl 1):123.
25. Aggarwal A, Pahwa S. Evaluation of the role of CRP as an early predictor of chorioamnionitis in PPROM. Int J Reprod Contracept Obstet Gynecol 2018;7:1351–6. [CrossRef]
26. Rewatkar M, Jain S, Jain M, Mohod K. C-reactive protein and white blood cell count as predictors of maternal and neonatal infections in prelabour rupture of membranes between 34 and 41 weeks of gestation. J Obstet Gynecol 2018;38:622–8. [PubMed] [CrossRef]

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