Original Article

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The Association Between C-Reactive Protein and the Duration of the Latent Phase of Labor in Women with Term Premature Rupture of Membranes

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ABSTRACT

Purpose: Intrauterine inflammation in the term period of pregnancy may be an important etiological factor in the occurrence of premature rupture of membranes. C-reactive protein (CRP) is one of the first mediators to rise in the inflammatory process. In this study, the association between CRP blood levels in women who gave birth at term on the duration of the latent phase of labor was investigated.

Methods: Fifty pregnant women who met the study criteria, were older than 18 years, had spontaneous rupture of membranes at 36 weeks and later, and had vaginal delivery were included. Records with missing data, patients who underwent cesarean section, those with non-spontaneous membrane rupture, patients showing signs of chorioamnionitis (fever >38 °C, leukocytes >15,000 mm^3, maternal tachycardia >100 bpm, fetal tachycardia >160 bpm, foul-smelling vaginal discharge, and/or uterine tenderness), and other causes that could elevate CRP were excluded. CRP was evaluated in those pregnancies that presented with spontaneous rupture of membranes at term. All patients were observed until birth by labor follow-up.

Results: There was no significant difference between the two groups in terms of active phase of labor, birth weight and 5' APGAR of the baby. The duration of the latent phase of labor was 661±298 minutes for group A and 347±219 minutes for group B (p=0.001).

Conclusion: In this study, the latent phase was found to be significantly shorter in the patient group with high CRP. CRP elevation may be a marker showing that the latent phase of labor is likely to be shorter and suggests a higher degree of inflammatory activity.

Keywords: Premature rupture of membranes, C-reactive protein, labor

INTRODUCTION

In 2-3% of pregnant women, the amniotic sac may rupture spontaneously before 37 weeks of gestation, which may occur because of infection or may cause infection in the mother and fetus afterwards. Premature rupture of membranes (PROM) occurs in 4.5-7.6% of all deliveries. PROM is a serious obstetric problem that may increase the risk of prematurity, cord prolapse, hypoxia, and infection that may affect the fetus, as well as risks that may concern the mother, such as increased cesarean section rate and choriodecidual infection.[1] Diagnosis of PROM may be made in 90% of cases by traditional methods, such as patient history, physical examination, nitrazine test, and fern test.[2,3] In cases where PROM is prolonged or amniotic fluid loss is intermittent, amniotic fluid flow and amniotic fluid pooling may not be observed in the vagina. In some cases, the liquid pooled in the vagina is contaminated with blood, urine, semen, meconium, vaginal discharge and vaginal douching. These can cause false positives and false negatives in test results. Currently, there is no defined gold standard test for the detection of PROM. Premature fetal membrane rupture, which occurs in 5-10% of all deliveries, has been associated

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with an increase in intrauterine infections, thus increasing both maternal and perinatal mortality and morbidity.

The number of leukocytes increases during pregnancy as well as during infection. Since the leukocyte count is also affected by some factors, such as stress and physical activity, it is not a reliable test for detecting infection in preterm labor. Fever, which is also a sign of infection, increases in the advanced stage of the infection. C-reactive protein (CRP) is a very sensitive acute phase reactant and can be used in the early investigation of inflammation due to its short half-life. CRP is primarily released from the liver as a result of cytokine action triggered by various infections. These cytokines include interleukin-1 (IL-1), IL-6, and tumor necrosis factor.[4] Due to its rapid synthesis and breakdown, it is a good indicator of the degree of inflammatory activity.[5] In human serum in the absence of inflammation, CRP is present at a low level of up to 0.5 mg/dL. Serum levels begin to rise as early as six hours after the onset of inflammation and can increase 24-fold within 24 hours. Even at very highest levels, CRP catabolism remains constant, meaning the only factor determining serum CRP levels is the rate of synthesis by hepatocytes. Due to its short half-life, CRP levels rapidly return to normal once inflammation subsides. Other advantages of CRP as an inflammatory marker include its ability to be measured in stored serum and its resistance to interference from serum proteins.[5] It has been suggested that CRP concentrations >1 mg/dL (10 mg/L) indicate clinically significant inflammation while concentrations between 0.3 and 1 mg/dL (3 and 10 mg/L) that is minor CRP elevation, indicate what is commonly referred to as low-grade inflammation.[6]

In the present study, we investigated the association between CRP levels and the latent phase of labor. Variables taken into account included demographic and clinical characteristics of the women including CRP level. We also investigated the relationship between outcomes, phases of labor and fetal effects on the newborn.

METHODS

This study was carried out in University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Obstetrics and Gynecology between 2013 and 2014. The University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee approval was obtained for the study (approval number: 319, date: 22.04.2014).

Inclusion criteria were over the age of 18 years, pregnant women who completed the 36th gestational week according to the last menstrual date or first trimester ultrasound measurements, the delivery was terminated vaginally with spontaneous PROM, and the files were complete.

Exclusion criteria were having incomplete records, patients terminated with caesarean section, and non-spontaneous rupture of membranes. In addition any patient with evidence of other causes of inflammation, such as showing signs of chorioamnionitis, which included fever >38 °C, leukocytes >15,000 mm^3, maternal tachycardia (>100 bpm), fetal tachycardia (>160 bpm), foul-smelling vaginal discharge, and/or uterine tenderness, and other causes that could elevate CRP were excluded from the study.

Patients who met the inclusion criteria and whose consented were selected from the patient files. The patient's information from these files, and hemogram (HMG), hematocrit (HCT), white blood cell count (WBC) and CRP level results from laboratory tests were recorded. In addition, information such as the patient's gravitational status, body mass index, any comorbidities, and cigarette and/or alcohol use were recorded. Information such as the birth weight, 5' APGAR score, and active phase and latent phase of labor durations were recorded. The latent phase was defined as the period until the cervical dilation was 4 cm and the effacement was 80%,[7] when labor contractions were detected in pregnant women above 36 weeks of age who were admitted to our hospital with the diagnosis of PROM. The period from cervical dilation to 4 cm and effacement 80% to delivery was defined and measured as the active phase. Those with a CRP of 5 mg/L or below were defined as group A, and those with a CRP above 5 mg/L were defined as group B.

Statistical Analysis

SPSS, version 17.0 was used for statistical calculations (IBM Inc., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to evaluate the normal distribution of continuous variables. The analysis of normally distributed data was performed with the independent t-test, and analysis of non-normally distributed data was performed with the Mann-Whitney U test. Chi-square was used to compare categorical variables and Fisher's exact test was used for appropriate data. P-values <0.05 were considered statistically significant.

RESULTS

In this study, 50 patients diagnosed with PROM between 2013 and 2014 were evaluated. There were 23 patients in group A with a CRP higher than 5 mg/L, and 27 patients in group B with a CRP lower than 5 mg/L. The clinical features of the two groups are compared in Table 1. No significant differences were found between the groups for demographic, pregnancy history or for hematology parameters (HMG, HCT and WBC).

In Table 2, the comparison of birth phases, birth weight and 5' APGAR are shown. There was no significant difference between the two groups in terms of duration of active phase of labor, birth weight and 5' APGAR of the baby. The duration of the latent phase of labor was 661±298 minutes for group A and 347±219 minutes for group B (p=0.001). The latent phase duration was significantly shorter in patients in group B.

DISCUSSION

In many studies, the role of intrauterine inflammation and infection in preterm labor and last trimester pregnancy with PROM has been investigated. However, recently, there has been increased evidence that subclinical intrauterine inflammatory cytokine response may be very important in early pregnancy as well.[8] It is hypothesized that in intrauterine inflammation in the very early period of pregnancy, the fetus exacerbates the

Table 1. Comparison of clinical features of group A and group B

	Group A CRP >5 mg/L (n=23)	Group B CRP <5 mg/L (n=27)	p	RR (95% CI)
Age	26.1±4.8	28.4±6.6	0.161	
Gravidity	1.7±1.1	2.6±2.2	0.084	
Parity	0.6±1.1	1.6±1.3	0.142	
Gestational age	37.1±0.7	37.7±0.8	0.698	
BMI	27.5±3.5	22.1±2.8	0.496	
Smoking	2 (0.7)	3 (11.1)	0.777	0.7 (0.1-5.0)
Alcohol	1 (4.3)	1 (3.7)	0.98	1.1 (0.1-17.7)
Comorbidities	3 (13.6)	4 (14.8)	0.407	0.9 (0.2-3.6)
HMG	11.3±1.4	11.6±0.9	0.394	
HCT	33.9±4.1	35.1±2.8	0.238	
WBC	10.4±2.0	12.1±3.1	0.123	

Data are shown as mean ± standard deviation or n (%). BMI: Body mass index, HMG: Hemogram, HCT: Hematocrit, WBC: White blood cell, CRP: C-reactive protein, CI: Confidence interval, RR: Relative risk

Table 2. Comparison of duration of latent and active phases of labor and fetal outcomes between groups A and B

	Group A CRP >5 mg/L (n=23)	Group B CRP <5 mg/L (n=27)	p
Latent phase (min)	661±298	347±219	**0.001**
Active phase (min)	460±335	401±287	0.904
Birth weight (g)	3200±485	3212±378	0.926
5' APGAR	8.8±0.2	8.9±0.5	0.45

CRP: C-reactive protein, min.: Minute

event by increasing the subclinical inflammatory response. In a study, it was suggested that with high CRP value (>110 ng/mL) detected during genetic amniocentesis (at 16-20 weeks of gestation), increased the probability of delivery before 34 weeks of gestation with a sensitivity of 80.8% and a specificity of 69.5%.[9] Ozer et al.[10] reported that when the CRP value in the amniotic fluid was above the cut-off value of 0.65 mg/L, its sensitivity in predicting delivery before 37 weeks of gestation was 92.9% and specificity was 78.7%. However, Tarim et al.[11] in a larger cohort showed that the amniotic fluid CRP value was not significantly different between groups with term and preterm birth in pregnant women (9.3% and 9.9%) whose preterm birth frequency was similar to the previous study. In one study, a correlation was found between a CRP level higher than 1.5 mg/dL and a short latent period in PPROM.[12] In the present study, the latent phase duration was significantly shorter in the group with high CRP. In a study conducted in patients with CRP >1.5 mg/dL, high maternal blood levels of CRP were found to be associated with triggering of preterm birth.

It has been reported that patients with a threat of premature birth with high CRP levels did not respond to tocolytic therapy, and patients with a threat of premature birth with normal CRP levels responded well to tocolytic therapy.[13]

There is no standard CRP value that can be considered normal. However, individuals with CRP levels <1 mg/L are thought to be at the lowest risk of some form of inflammation.[14] The detection limit of traditional assays developed to aid in the diagnosis of infectious or inflammatory diseases ranges from 3 to 5 mg/L. Several publications support or conclude that CRP is an indicator of preterm labor and chorioamnionitis.[15-18]

Recent studies support the role of infection in the etiology of PROM. The cause-effect relationship between PROM and infection is intertwined. So, while choriodecidual infection is shown as the most important cause in the etiology of PROM. However, if delivery does not occur after a certain period, PROM itself may result in choriodecidual infection. The longer the latent period in PROM, the higher the risk of this infection.[19] PROM remains one of the most troubling issues in obstetrics, as it increases maternal and fetal morbidity and mortality. Many studies have been conducted into optimal clinical management in PROM, and it is generally accepted that the gestational week is a major determinant of type of management, together with whether the fetus has reached the viability limit, and the maternal and fetal obstetric balance. The most important parameter determining perinatal complications in these cases is the week of gestation. Tocolysis is not indicated in pregnancies that have completed the 34th

gestational week, and when there is thought to be sufficient fetal lung development for the fetus to survive in the external environment. There are always some exceptions to this, such as if cervical dilation has started above 36 weeks of gestation, immediate delivery of the fetus is the recommended approach. In other cases, a period of waiting may be appropriate, but this waiting period is limited to 12 hours in many centers. It has been proven that obstetric balance is negatively impaired in prolongation of PROM, that is, maternal and fetal complication rates increase.[20] Induction of labor is recommended in cases where spontaneous labor or uterine contractions do not start after 12 hours.

The purpose of induction is to deliver vaginally whenever possible and to avoid caesarean delivery. Although oxytocin infusion is the most used approach for induction, there are reports that using oxytocin without cervical softening increases caesarean rates in cases with inappropriate cervix. In such cases, preinduction to prepare the cervix for delivery shortens the delivery time and increases the success of vaginal delivery.

Study Limitations

The limitations of our study were that it was conducted retrospectively with a small number of cases and the evaluation of a single mediator, CRP, with only two groups. The results should be validated with prospective studies with a larger number of cases, more careful division of cases by CRP level grouping, for example <3, 3-10 and >10 mg/dL and evaluating more parameters.

CONCLUSION

In this study, it was shown that CRP levels above 5 mg/dL were associated with significant shortening of the latent phase of labor. In clinical practice, measuring blood CRP may help in predicting premature birth, considering its effect on the duration of birth.

Ethics

Ethics Committee Approval: The University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee approval was obtained for the study (approval number: 319, date: 22.04.2014).

Informed Consent: Retrospective study.

Authorship Contributions

Concept: R.A., Design: R.A., Data Collection or Processing: O.A., Analysis or Interpretation: F.Ş., İ.Ö., Literature Search: R.A., F.Ş., Writing: S.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Garg A, Jaiswal A. Evaluation and management of premature rupture of membranes: a review article. Cureus. 2023;15(3):e36615.
2. Naylor CS, Gregory K, Hobel C. Premature rupture of the membranes: an evidence-based approach to clinical care. Am J Perinatol. 2001;18(7):397-413.
3. Berger R, Abele H, Bahlmann F, et al. Prevention and therapy of preterm birth. Guideline of the DGGG, OEGGG and SGGG (S2k Level, AWMF Registry Number 015/025, February 2019) - Part 2 with recommendations on the tertiary prevention of preterm birth and the management of preterm premature rupture of membranes. Geburtshilfe Frauenheilkd. 2019;79(8):813-833.
4. Hofmeyr GJ, Gülmezoglu AM. Vaginal misoprostol for cervical ripening and induction of labour. Cochrane Database Syst Rev. 2003:CD000941.
5. Watts DH, Krohn MA, Hillier SL, Wener MH, Kiviat NB, Eschenbach DA. Characteristics of women in preterm labor associated with elevated C-reactive protein levels. Obstet Gynecol. 1993;82(4 Pt 1):509-514.
6. Kushner I, Antonelli MJ. What should we regard as an "elevated" C-reactive protein level? Ann Intern Med. 2015;163(4):326.
7. Friedman EA. An objective approach to the diagnosis and management of abnormal labor. Bull N Y Acad Med. 1972;48(6):842-858.
8. Liu X, Wang Y, Zhang F, et al. Double- versus single-balloon catheters for labour induction and cervical ripening: a meta-analysis. BMC Pregnancy Childbirth. 2019;19(1):358.
9. Sciscione A, Larkin M, O'Shea A, Pollock M, Hoffman M, Colmorgen G. Preinduction cervical ripening with the Foley catheter and the risk of subsequent preterm birth. Am J Obstet Gynecol. 2004;190(3):751-754.
10. Ozer KT, Kavak ZN, Gökaslan H, Elter K, Pekin T. Predictive power of maternal serum and amniotic fluid CRP and PAPP-A concentrations at the time of genetic amniocentesis for the preterm delivery. Eur J Obstet Gynecol Reprod Biol. 2005;122(2):187-190.
11. Tarim E, Bağiş T, Kiliçdağ EB, Sezgin N, Yanik F. Are amniotic fluid C-reactive protein and glucose levels, and white blood cell counts at the time of genetic amniocentesis related with preterm delivery? J Perinat Med. 2005;33(6):524-529.
12. Zhang S, Wang R, Wang J, et al. Differentiate preterm and term infant brains and characterize the corresponding biomarkers via DICCCOL-based multi-modality graph neural networks. Front Neurosci. 2022;16:951508.
13. Park JH, Bae JG, Chang YS. Neonatal outcomes according to the latent period from membrane rupture to delivery among extremely preterm infants exposed to preterm premature rupture of membrane: a nationwide cohort study. J Korean Med Sci. 2021;36(14):e93.
14. Wilson PW, Pencina M, Jacques P, Selhub J, D'Agostino R Sr, O'Donnell CJ. C-reactive protein and reclassification of cardiovascular risk in the framingham heart study. Circ Cardiovasc Qual Outcomes. 2008;1(2):92-97.
15. 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 Gynaecol. 2018;38(5):622-628.
16. Musilova I, Kacerovsky M, Stepan M, et al. Maternal serum C-reactive protein concentration and intra-amniotic inflammation in women with preterm prelabor rupture of membranes. PLoS One. 2017;12(8):e0182731.
17. Asadi N, Faraji A, Keshavarzi A, Akbarzadeh-Jahromi M, Yoosefi S. Predictive value of procalcitonin, C-reactive protein, and white blood

cells for chorioamnionitis among women with preterm premature rupture of membranes. Int J Gynaecol Obstet. 2019;147(1):83-88.

18. Sun S, Serrano MG, Fettweis JM, et al. Race, the vaginal microbiome, and spontaneous preterm birth. mSystems. 2022;7(3):e0001722.
19. Vogel I, Goepfert AR, Thorsen P, et al. Early second-trimester inflammatory markers and short cervical length and the risk of recurrent preterm birth. J Reprod Immunol. 2007;75(2):133-140.
20. Everest NJ, Jacobs SE, Davis PG, Begg L, Rogerson S. Outcomes following prolonged preterm premature rupture of the membranes. Arch Dis Child Fetal Neonatal Ed. 2008;93(3):F207-F211.