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Diagnostic and Prognostic Value of Presepsin for Subclinical Chorioamnionitis in Pregnancies between 23-28 Week with Preterm Premature Rupture of the Membranes

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Background: Presepsin is an inflammatory marker released from monocytes and macrophages as an acute reaction to microbial infection. We hypothesized that it may be useful in pregnancies with preterm premature rupture of the membranes (PPROM) for early diagnosis of subclinical chorioamnionitis.

Aims: To determine whether the plasma presepsin level has any diagnostic or prognostic value for subclinical chorioamnionitis in pregnancies complicated with PPROM.

Study Design: Prospective cohort study.

Methods: Fifty-three singleton pregnancies between 23 and 28 weeks of gestation diagnosed with PPROM were prospectively included in the study. Venous blood samples were collected at admission, at the 48th hour of admission, and at the time of delivery to determine presepsin and C-reactive Protein (CRP) levels and white blood cell (WBC) counts. Chorioamnionitis was diagnosed by microscopic examination of the placenta and cords.

Results: Of the 53 PPROM cases included in the study, 41 (77.4%) had histologically confirmed chorioamnionitis. Neonatal sepsis developed in 24 (45.3%) of the newborns. The median presepsin level at admission was 135.0 pg/mL for pregnancies with subclinical chorioamnionitis and 113.5pg/mL for pregnancies without chorioamnionitis (p=0.573). There was also no significant difference between subclinical chorioamnionitis (+) and (−) cases in terms presepsin levels at the 48th hour and at delivery. However, chorioamnionitis (+) cases showed a significant decrease in both presepsin level and WBC count at the 48th hour after the administration of antibiotics, which increased significantly at delivery (p<0.001 and p=0.011, respectively).

Conclusion: The striking fluctuations in presepsin level after the diagnosis of PPROM can be used to predict subclinical chorioamnionitis and determine the optimal timing of delivery before the clinical signs of chorioamnionitis are established. However, presepsin level itself was neither diagnostic nor prognostic for neonatal sepsis.

Keywords: Premature rupture of the membranes, preterm, chorioamnionitis, neonatal sepsis

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Preterm premature rupture of the membranes (PPROM) is defined as rupture of the membranes before 37 weeks of gestation, prior to the onset of contractions. Approximately 30-40% of preterm deliveries are associated with PPROM (1-3). Prematurity is the major risk factor for neonatal mortality and morbidity in pregnancies with PPROM (3).

Acute inflammation of the placenta, termed chorioamnionitis, is also responsible for adverse neonatal outcomes in PPROM (1,4-8). Subclinical chorioamnionitis, which is defined as inflammation of the placenta without any clinical signs of chorioamnionitis [e.g., high fever, maternal or fetal tachycardia, elevated white blood cell (WBC) count or C-reactive protein (CRP) level, uterine tenderness, and foul odor of amniotic fluid] is seen in 40-70% of all PPROM cases (9,10). Subclinical chorioamnionitis is a major problem for pregnant women with PPROM. Newborns with PPROM have a high risk of sepsis and many other newborn infections that makes the prognosis even worse in premature newborns with PPROM (11). Thus, early and definitive diagnosis of subclinical chorioamnionitis, particularly in cases with PPROM, has crucial importance to prevent both maternal and neonatal mortality and morbidity. A biochemical biomarker, which has high diagnostic accuracy and can determine subclinical chorioamnionitis early, would be very useful in clinical practice.

Presepsin is an inflammatory marker released from monocytes and macrophages as an acute reaction to microbial infection (12). On the basis of its role as a biochemical marker for the early recognition of systemic infections, we hypothesized that it may be useful in pregnancies with PPROM for the early diagnosis of subclinical chorioamnionitis.

The aim of this study was to determine whether the plasma presepsin level has any diagnostic or prognostic value for subclinical chorioamnionitis in pregnancies complicated with PPROM.

MATERIALS AND METHODS

Study design and patients

Fifty-three females with singleton pregnancies (mean age, 28.99±6.65 years) were enrolled in this prospective study between February 2014 and April 2015. Patients were admitted to the hospital with leakage of amniotic fluid between 23 and 28 weeks of gestation. The gestational age was determined by the first day of the last menstrual period and supported by first trimester obstetric ultrasonography. PPROM was diagnosed when amniotic leakage was seen from the cervical os in vaginal speculum examination. The exclusion criteria were the presence of uterine malformations, polyhydramnios, multiple pregnancies, diabetes, preeclampsia, immunological disorders, antepartum hemorrhage, any maternal systemic infection (pneumonia, urinary infection, etc.), and clinical chorioamnionitis (fever, uterine tenderness, vaginal discharge with foul odor).

The study was approved by the Institutional Ethics Committee (no. 37, date 02/21/2014). All patients were informed, and written consent was obtained before any study-related procedures were performed.

Study procedures

Patients were hospitalized after the diagnosis of PPROM and followed up for clinical signs of chorioamnionitis. Prophylactic antibiotics (ampicillin, ampisina 1 gr/ 1 flacon, Mustafa Nevzat Pharmaceuticals; İstanbul, Turkey) 4 g/day IV and azithromycin (Azomax 500 mg tb, Koçak Farma A.Ş.; İstanbul, Turkey) 1 g/day PO) and corticosteroids for lung maturation (betametazon 12 mg/day, IM for 2 days, Celeston amp., Merck-Sharp Dohme; İstanbul, Turkey) were administered. Maternal and fetal status was closely monitored, and the pregnancy was terminated when fetal distress, anhydramnios, or any clinical signs of chorioamnionitis were detected.

Venous blood samples were collected at admission before the administration of any medication, at the 48th hour of admission, and at the time of delivery in order to determine the presepsin and CRP levels as well as WBC counts. Placentas were collected from each patient after delivery for histological assessment of chorioamnionitis.

Analysis of blood sample

For the determination of presepsin and CRP levels and WBC counts, 1 mL blood samples were collected in ethylene diamine tetraacetic acid-containing tubes. For presepsin, plasma samples were centrifuged at 3000 rpm for 5 min and stored at −80°C before analysis. Presepsin was measured using the PATHFAST immunoanalyzer (Mitsubishi Chemical Medience Co.; Tokyo, Japan), which is a chemiluminescent enzyme immunoassay for the quantitative measurement of presepsin concentration. Monoclonal antibodies and polyclonal antibodies recognizing presepsin were used in the assay. Presepsin concentration can be determined by PATHFAST within 17 min.

CRP levels were measured by immunonephelometry on the BN ProSpec system (Dade Behring Inc.; Illinois, USA). WBC count was detected using the ABX Pentra DF 120 (Horiba Ltd., Kyoto, Japan).

Histological evaluation

Chorioamnionitis was diagnosed by microscopic examination of placenta and cords. All samples were examined by the same pathologist who was blinded to the patient's clinical course. On the basis of histological evaluation, cases were divided into two groups: chorioamnionitis (+) and chorioamnionitis (−).

For the diagnosis of histological chorioamnionitis, microscopic analysis of the placenta was performed at 400×, and previously described diagnostic criteria of chorioamnionitis (>10 polymorphonuclear leukocytes in 10 nonadjacent microscopic fields from the extraplacental membranes, chorionic plate, or umbilical cord blood vessels) were applied (7).

Criteria for neonatal sepsis

Neonatal sepsis was diagnosed according to the Töller scoring system (13). This scoring system includes clinical (hypotonia, bradycardia, apnea, respiratory stress, hepatomegaly, bad peripheral circulation, abdominal distension, and change in skin color) and laboratory (high leukocyte and low thrombocyte count, metabolic acidosis, and immature/total neutrophil ratio) parameters, each of which is given a score from 0 to 3. If the total score is over 10, clinical sepsis is diagnosed. On the basis of neonatal sepsis evaluation, cases were divided into two groups: sepsis (+) for those with clinical symptoms or strong clinical suspicions of sepsis [presence of symptoms, elevated CRP levels and/or affected WBC counts, positive blood culture between 4 and 120 days of life, bronchopulmonary dysplasia, pneumonia, or neonatal death] and sepsis (−) for those without any clinical symptom of sepsis.

Statistical analysis

The study data were investigated using visual (histogram, probability plots) and analytical methods (Shapiro-Wilk test) to determine whether or not they were normally distributed. Descriptive analyses included mean and standard deviation for normally distributed data and the median and interquartile range (IQR) for the non-normally distributed variables. The mean differences between the groups were evaluated by Student's *t*-test for normally distributed variables and Mann-Whitney U test for non-normally distributed variables. Categorical variables were analyzed by chi-square test with Fisher's exact test for groups with less than five subjects expected in a cell. Because the changes in the distribution of CRP and presepsin levels and WBC counts over a period of time did not comply with the parametric test assumptions, Friedman test was performed to test whether there was a significant change over time in presepsin and CRP levels and WBC counts in chorioamnionitis and sepsis cases. The Wilcoxon test adjusted with Bonferroni correction for multiple comparisons was performed to test the significance of pairwise differences.

All of the analyses were performed using the Statistical Package of Social Science (version 11.5, SPSS Inc.; Chicago, IL, USA). A p value less than 0.05 was considered to be statistically significant. Bonferroni correction was used to adjust p value for post-hoc multiple comparisons (p=0.05/number of comparisons).

RESULTS

Of the 53 PPROM cases included in the study, 41 (77.4%) had histologically confirmed chorioamnionitis, whereas the remaining 12 (22.6%) had no evidence of chorioamnionitis. Neonatal sepsis developed in 24 (45.3%) newborns from 53 PPROM pregnancies. There were no statistically significant differences between patients with and without chorioamnionitis in terms of maternal age, gravidity, parity, gestational weeks at admission, birth weight, and hospitalization duration (Table 1). Although cesarean section rate was lower in pregnancies with chorioamnionitis than in those without, the

TABLE 1. Demographic and obstetrics characteristics of cases with respect to presence of chorioamnionitis or neonatal sepsis

	Chorioamnionitis			Neonatal sepsis		
	Chorioamnionitis (+) (n=41)	Chorioamnionitis (-) (n=12)	p	Sepsis (+) (n=24)	Sepsis (-) (n=29)	p
Age (years)	28.3±6.1	29.7±7.2	0.520	29.2±5.7	28.2±6.9	0.573
Gravidity	2.0 (1.0-3.0)	2.5 (1.3-4.0)	0.191	3 (1.3-4)	2 (1-2.5)	0.01
Parity	1.0 (0-2.0)	1.0 (0.3-3.0)	0.161	1.5 (0.3-2)	1 (0-1)	0.027
Gestational week at admission	25 (23-27)	25.5 (24-27.8)	0.682	25 (24-27)	26 (23.5-27.5)	0.745
Birth weight (gram)	997.4±454.7	1067.92±385.57	0.628	968±323	1050±516	0.480
Hospitalization duration (days)	3.5 (1.0-7.0)	2.5 (1.0-17.8)	0.871	3 (1-11)	3 (1-7)	0.851
Primary caesarean section rate	15 (36.6%)	8 (66.7%)	0.064	-	-	-

Data are given as mean±standard deviation (SD), median (Interquartile range((IQR)), or number (n) (%).

TABLE 2. Serum presepsin, CRP, WBC levels during study period with respect to presence of chorioamnionitis or neonatal sepsis

		Chorioamnionitis					Neonatal sepsis				
		Chorioamnionitis (+) (n=41)		Chorioamnionitis (-) (n=12)			Sepsis (+) (n=24)		Sepsis (-) (n=29)		
		n	Median (IQR)	n	Median (IQR)	p	n	Median (IQR)	n	Median (IQR)	p
Presepsin (pg/mL)	Admission	41	135.0 (98.1-182.0)	12	113.5 (106.7-151.8)	0.573	24	124.5 (109-184.5)	29	135 (93.3-162.5)	0.886
	48th hour	25	106.0 (78.5-123.5)	7	120.0 (71.8-167.0)	0.732	15	114 (72.3-167)	17	96.4 (81.5-128)	0.763
	Delivery	41	172.0 (138.5-254.0)	12	135.5 (97.5-186.3)	0.145	24	197.5 (146.75-296.5)	29	155 (118.5-210.5)	0.256
CRP (mg/dL)	Admission	41	1.40 (0.45-2.30)	12	0.95 (0.35-2.18)	0.496	24	1.5 (0.55-3.30)	29	1.2 (0.3-1.95)	0.133
	48th hour	25	0.45 (0.20-1.20)	7	0.40 (0.20-1.30)	0.947	15	0.65 (0.25-1.75)	17	0.3 (0.5-0.8)	0.079
	Delivery	41	1.90 (0.70-5.05)	12	0.85 (0.43-1.35)	0.57	24	2.05 (1.03-5.2)	29	1.1 (0.25-2.5)	0.04
WBC count (10^3/mm^3)	Admission	41	14.7 (11.1-16.6)	12	13.3 (12.0-14.9)	0.260	24	14.8 (12-16.5)	29	14.1 (9.8-16.3)	0.526
	48th hour	25	13.5 (10.6-15.7)	7	12.6 (10.1-16.4)	0.809	15	13.5 (10.9-14.6)	17	13.4 (9.8-16.6)	0.801
	Delivery	41	16.0 (14.5-20.6)	12	14.0 (12.1-17.5)	0.145	24	16.9 (14-18.5)	29	15.5 (12.1-19.9)	0.317

IQR: interquartile range; CRP: C-reactive protein; WBC: white blood cell

difference did not reach the level of statistical significance (36.6% vs. 66.7%, respectively; p=0.064). Both gravidity and parity were significantly higher in cases with neonatal sepsis (p=0.01 and p=0.027, respectively; Table 1). Other clinical characteristics and maternal age were similar between pregnancies with and without neonatal sepsis (Table 1).

Serum presepsin and CRP levels and WBC counts

Serum presepsin and CRP levels and WBC counts were measured for all patients at admission and delivery. However, because 21 out of 53 patients (39.6%) gave birth in the first 48 hours, serum presepsin and CRP levels and WBC counts could only be obtained for 32 patients at the 48th hour of admission. The median presepsin level was 135.0 pg/mL (IQR, 98.1-182.0 pg/mL) for pregnancies with chorioamnionitis and 113.5 pg/mL (106.7-151.8 pg/mL) for pregnancies without chorioamnionitis (p=0.573). There was also no significant difference between chorioamnionitis (+) and (−) cases in terms of presepsin levels at the 48th hour and at delivery (Table 2). Similarly, neither CRP level nor WBC count showed any significant difference between chorioamnionitis (+) and (−) cases in any of the three timepoints (Table 2).

Cases with and without neonatal sepsis had no significant difference in any of the presepsin and CRP levels and WBC counts at admission, in the 48th hour, and at delivery, except for significantly higher CRP levels at delivery in cases with neonatal sepsis (2.05 mg/dL vs. 1.1 mg/dL; p=0.04) (Table 2).

When only cases in which the serum presepsin and CRP levels and WBC counts at all three timepoints were evaluated, chorioamnionitis (+) cases showed a significant decrease in both presepsin level and WBC count in the 48th hour, which increased at delivery (p=0.0001 and p=0.011, respectively). Changes in serum presepsin and CRP levels and WBC counts over time were not significant for chorioamnionitis (−) cases (Figure 1-3). There was no significant change in presepsin and CRP levels and WBC counts over time in sepsis (+) and sepsis (−) cases, except for WBC count, which significantly decreased in the 48th hour and increased at delivery in sepsis (+) cases (p=0.013) (Figure 1-3).

There were no statistically significant differences in neonatal mortality, sepsis, and neonatal infection between chorioamnionitis (+) and (−) cases (Table 3).

DISCUSSION

Management of PPROM is still a great challenge for obstetrics. Extreme and very preterm deliveries with PPROM are associated with high perinatal death, severe neonatal morbidities, and long-term sequelae (14). Therefore, these patients are advised to be conservatively managed until 34 weeks of gestation and followed up for clinical signs of infection, fetal well-being, and signs of active labor.

In the present study, we studied pregnant females at 23-28 weeks of gestation, who were extreme preterm patients, in

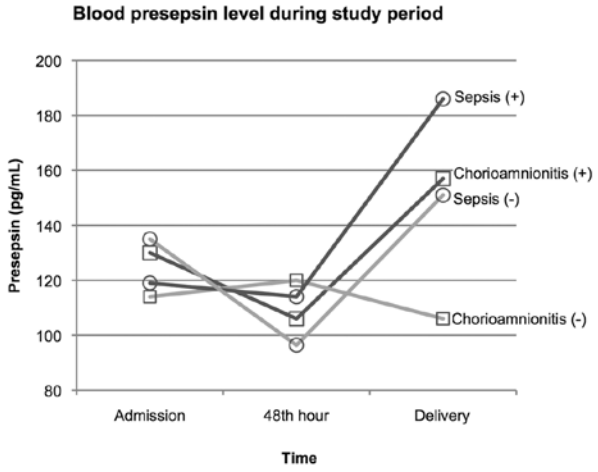

FIG. 1. The change in serum presepsin level over time with respect to the presence of chorioamnionitis or neonatal sepsis. Only cases with blood measurements for all three timepoints were evaluated (n=32). Change over time in serum presepsin level was significant only for chorioamnionitis (+) cases (p<0.001). Pairwise comparison revealed that p=0.014 for presepsin level at admission vs. that at the 48th hour, p=0.170 for that at admission vs. that at delivery, and p=0.001 for that at the 48th hour vs. that at delivery (adjusted level of p value was 0.017 for pairwise comparisons).

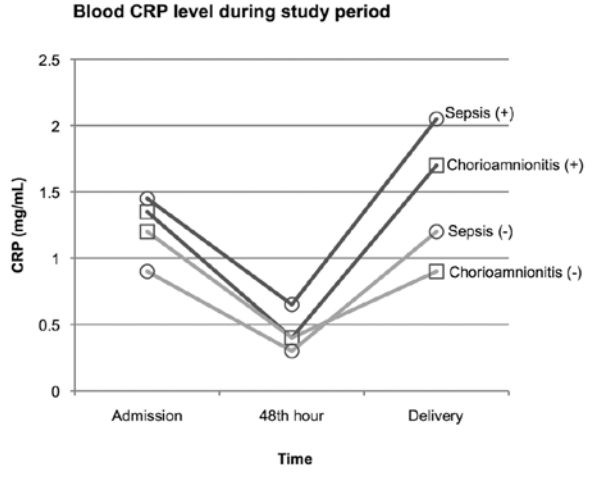

FIG. 2. The change in serum CRP level over time with respect to the presence of chorioamnionitis or neonatal sepsis. Only cases with blood measurements for all three timepoints were evaluated (n=32). The change in serum CRP levels over time was not statistically significant in any of the groups.

order to maximize survival and reduce neonatal morbidity. It is known that a gain of 2-3 days in these weeks is associated with a 1-5% increase in survival (15). However, it is a critical decision to take considering the risks and benefits of delaying labor in these patients. Before 26 weeks of gestation, only 17.8% of neonates were discharged from the hospital without any morbidity (16). Histological and

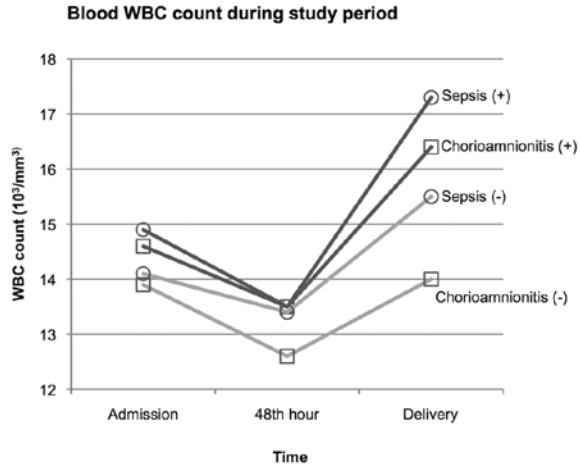

FIG. 3. The change in blood WBC counts over time with respect to the presence of chorioamnionitis or neonatal sepsis. Only cases with blood measurements for all three timepoints were evaluated (n=32). Change over time in blood WBC count was significant only for chorioamnionitis (+) and sepsis (+) cases (p=0.011 and p=0.013, respectively). For chorioamnionitis (+) cases, pairwise comparison revealed that p=0.3 for blood WBC count at admission vs. that at the 48th hour, p=0.001 for that at admission vs. that at delivery, and p=0.037 for that at the 48th hour vs. that at delivery (adjusted level of p value was 0.017 for pairwise comparisons).

TABLE 3. Neonatal outcomes with respect to presence of chorioamnionitis

	Chorioamnionitis		
	Chorioamnionitis (+) (n=41)	Chorioamnionitis (-) (n=12)	p
Mortality	22 (53.7)	3 (25)	0.08
Sepsis	17 (41.5)	7 (58.3)	0.302
Infection	9 (22)	6 (50)	0.076

subclinical chorioamnionitis and lower gestational week at delivery were significantly associated with early-onset neonatal sepsis (17,18). The rate of chorioamnionitis was reported to be 47.3% in mothers who delivered before 32 weeks of gestation and 83.3% in those who delivered before 30 weeks (18). In cases with PPROM, chorioamnionitis rate was 86.7% at 28-29 weeks of gestation, decreasing to 70.1% at 30-31 weeks of gestation (19). Between 22-28 weeks of gestation, chorioamnionitis was determined in 90% of cases (15). We determined chorioamnionitis rate to be 77%, which was similar to those reported in literature. Neonatal morbidity was high in newborns with histologic chorioamnionitis (18). In order to improve neonatal and maternal outcomes in PPROM patients, we need accurate and early diagnostic inflammatory markers to diagnose chorioamnionitis before the clinical signs are established.

Presepsin, a soluble CD14-subtype, is a new biochemical marker for the early recognition of systemic infections, par-

ticularly, sepsis and septic shock (12). According to manufacturer studies, the mean presepsin level in health individuals was determined to be 160 pg/mL (95% confidence interval, 148-171 pg/mL). Receiver operating curve analyses revealed a cut-off value of 337 pg/mL for discrimination between healthy normal individuals and patients with sepsis (20). However, because of individual differences in immune response and different clinical situations, varying elevations in the literature, cut-off levels for sepsis were determined to range from 317 pg/mL to 600 pg/mL (21-23). The median presepsin levels in both patients with and without chorioamnionitis at admission, 48th hour, and delivery were lower than the levels in manufacturer studies. This is the first study measuring presepsin levels in pregnant women. Differences in the immune system during pregnancy might affect the presepsin level.

In our study, mean presepsin levels were similar between patients. Presepsin concentrations may occur in those with and without chorioamnionitis at admission, 48th hour, and delivery; therefore, we could not calculate a cut-off value for presepsin to determine chorioamnionitis at any time during the clinical follow-up. There was also no difference in the presepsin levels between patients with and without neonatal sepsis. Thus, presepsin levels were neither diagnostic nor prognostic for chorioamnionitis and neonatal sepsis.

This prospective study indicates that in PPROM pregnancies with chorioamnionitis, serum presepsin levels decrease at the 48th hour after admission to hospital with antibiotic use and then show a marked elevation at delivery. Because PPROM is associated with infection, particularly in preterm deliveries of 30 weeks or earlier, we suggest that antibiotic usage keeps infection-induced high presepsin levels under control to some extent, but shows a rapid increase later, suggesting chorioamnionitis. However, in patients without chorioamnionitis, serum presepsin levels did not show a remarkable change from the time of admission to delivery. We think that striking fluctuations in presepsin level after the diagnosis of PPROM can be used to predict subclinical chorioamnionitis. Thus, we suggest that changes in the presepsin levels can be used to predict chorioamnionitis and terminate the pregnancy before the clinical signs of chorioamnionitis are established. This is a preliminary study. With increasing sample size, we believe that the cut-off point for presepsin can be determined to diagnose subclinical chorioamnionitis.

Topcuoglu et al. (24) showed that presepsin level could be used as a reliable biomarker for late onset sepsis and treatment response in preterm infants. We could not find any value of maternal presepsin levels or changes in these levels over time for predicting neonatal sepsis. Thus, we conclude that maternal presepsin level is not a prognostic inflammatory marker for PPROM patients.

In the literature, there were many reports that support the importance of CRP levels in chorioamnionitis patients (11,19,25,26). However, we did not find any difference in the CRP levels and WBC counts between chorioamnionitis (+) and (−) cases in PPROM patients.

This is the first study reporting presepsin levels in PPROM patients with chorioamnionitis. The main limitation of the study was its limited sample size, which precludes us from reaching a definitive conclusion about the value of presepsin in the diagnosis of chorioamnionitis in pregnancies with PPROM. We diagnosed chorioamnionitis only histologically. We think that addition of amniotic fluid culture to diagnose chorioamnionitis would have given better results about the value of presepsin in diagnosing chorioamnionitis because it is the microbial invasion that causes an increase in macrophage and neutrophil counts and probably triggers higher presepsin levels. Future studies can also be designed with the measurement of cord blood presepsin levels to predict neonatal sepsis.

In conclusion, the change in presepsin level over time after the diagnosis of PPROM can be used to predict chorioamnionitis and terminate the pregnancy before the clinical signs of chorioamnionitis are established. However, presepsin level itself was neither diagnostic nor prognostic for chorioamnionitis and neonatal sepsis. On the basis of the findings of this pilot study, further large-scale studies will be required to clearly define the diagnostic and prognostic value of presepsin for subclinical chorioamnionitis in PPROM.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Zeynep Kamil Gynecologic and Pediatric Training and Research Hospital (no. 37, date 02/21/2014).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - E.Ç., Ş.E.Ç.; Design - Ş.E.Ç., R.U.; Supervision - D.K.; Resource - E.Ç.; Materials - R.U.; Data Collection and/or Processing - E.Ç., H.A., N.K.; Analysis and/or Interpretation - M.B.Ş.; Literature Search - Ş.E.Ç.; Writing - E.Ç.; Critical Reviews - E.Ç.

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