

# The use of maternal delta neutrophil index for the prediction of chorioamnionitis in very early preterm premature rupture of membranes

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## Abstract

**Objective:** In this study, we aimed to assess the use of maternal delta neutrophil index for the prediction of chorioamnionitis in pregnancies complicated with very early preterm premature rupture of membranes, and to compare this index with other routine infection markers.

**Methods:** The files of all patients who admitted to the Obstetrics and Gynecology Clinic of Faculty of Medicine, İnönü University, due to preterm premature rupture of membranes between 16 and 24 weeks of gestation between April 1, 2014 and January 1, 2017 and applied expectant management were reviewed retrospectively, and the patients who were eligible for the inclusion criteria were included in the study. Receiver operating characteristic (ROC) curve analysis was used to determine cut-off values of serum leukocyte with chorioamnionitis, C-reactive protein (CRP), procalcitonin and delta neutrophil index (DNI) levels, and sensitivity and specificity values were calculated. In all analyses, 0.05 was considered as the significance level.

**Results:** A total of 73 patients matching with inclusion criteria were identified. While 43 (58.9%) of these patients were diagnosed with chorioamnionitis, no chorioamnionitis was found in 30 (41.1%) patients. While the cut-off value for DNI was 1.0 [area under receiver operating characteristic (AUROC) 0.943, 95% confidence interval (CI) 0.863–0.984,  $p < 0.0001$ ] with 93.02% sensitivity and 93.33% specificity, it was 13.9 (AUROC 0.650 95% CI 0.529–0.758,  $p = 0.0239$ ) for leukocyte with 51.16% sensitivity and 90% specificity, and 1.34 (AUROC 0.708, 95% CI 0.590–0.808,  $p = 0.0006$ ) for CRP with 67.44% sensitivity and 76.67% specificity.

**Conclusion:** Delta neutrophil index is an infection marker which may be useful for the prediction of chorioamnionitis during follow-up in patients who develop very early preterm premature rupture of membranes, can be checked by complete blood count, of which results can be obtained quickly and does not requires additional costs, and the diagnostic performance of the test seems higher than CRP, procalcitonin and leukocyte.

**Keywords:** Preterm premature rupture of fetal membranes, chorioamnionitis, serum markers.

## Özet: Çok erken preterm prematür membran rüptüründe koryoamniyoniği öngörmede maternal delta nötrofil indeksinin yeri

**Amaç:** Bu çalışmada çok erken preterm prematür membran rüptürü ile komplike olan gebeliklerde koryoamniyoniği predikte etmede maternal delta nötrofil indeksinin kullanımını değerlendirmeyi ve bu indeksi diğer rutin enfeksiyon belirteçleriyle karşılaştırmayı amaçladık.

**Yöntem:** İnönü Üniversitesi Tıp Fakültesi Hastanesi Kadın Hastalıkları ve Doğum Kliniği'ne 01.04.2014 – 01.01.2017 tarihleri arasında, gebeliğin 16–24. haftasında preterm prematür membran rüptürü nedeni ile başvuran ve bekleme yönetimi uygulanmış tüm hastaların dosyaları retrospektif olarak taranarak, çalışma kriterlerine uygun hastalar çalışmaya dahil edildi. Koryoamniyonitin olduğu serum lökosit, C reaktif protein (CRP), prokalsitonin ve delta nötrofil indeksi (DNI) seviyelerinin *cut-off* değerlerini saptamak için *receiver operating characteristic* (ROC) eğrisi analizi kullanıldı ve sensitivite ve spesifite değerleri hesaplandı. Tüm analizlerde anlamlılık düzeyi 0.05 olarak kabul edildi.

**Bulgular:** Çalışma kriterlerine uygun toplam 73 hasta saptandı. Bu hastalardan 43'ü (%58.9) izlem sırasında koryoamniyoniği tanısı alırken, 30'unda (%41.1) koryoamniyoniği saptanmadı. DNI için *cut-off* değeri %93.02 sensitivite, %93.33 spesifite ile 1.0 [area under receiver operating characteristic (AUROC) 0.943, %95 güven aralığı (CI) 0.863–0.984,  $p < 0.0001$ ], lökosit için *cut-off* değeri %51.16 sensitivite, %90 spesifite ile 13.9 (AUROC 0.650 %95 CI 0.529–0.758,  $p = 0.0239$ ), CRP için *cut-off* değeri %67.44 sensitivite, %76.67 spesifite ile 1.34 (AUROC 0.708, %95 CI 0.590–0.808,  $p = 0.0006$ ) saptandı.

**Sonuç:** Delta nötrofil indeksi çok erken preterm prematüre membran rüptürü gelişen hastalarda izlem sırasında koryoamniyoniği prediksiyonunda kullanışlı olabilecek, tam kan sayımı ile birlikte bakılabilen, hızlı sonuç alınabilen, ek maliyet gerektirmeyen bir enfeksiyon belirteci olup testin diagnostik performansı CRP, prokalsitonin ve lökosit göre daha yüksek görünmektedir.

**Anahtar sözcükler:** Fetal membranların preterm erken rüptürü, koryoamniyoniği, serum belirteçleri.

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## Introduction

Premature rupture of membranes (PRM), being in the etiology of 30% of the preterm labors, is considered as one of the most significant reasons of perinatal mortality and morbidity. Expectancy of fetal life is quite low if the rupture of membranes occurs especially during the early second trimester.<sup>[1]</sup> Although termination is recommended to these patients traditionally by considering maternal sepsis and poor fetal prognosis risks, it has been shown recently that expectant management is relatively safe for pregnant women and that it results in neonatal life even in small rates.<sup>[2]</sup> Moreover, there are studies suggesting that serial transabdominal amnioinfusion management in such patients can also improve perinatal outcomes significantly by restoring amniotic fluid volume.<sup>[3]</sup> The most important complication increasing the risks of perinatal mortality and morbidity for these patients in both expectant management serial transabdominal amnioinfusion management is the chorioamnionitis as a result of ascending movement of bacteria through subgenital tractus in the presence of the rupture of membranes.<sup>[4]</sup> Although many studies showed that chorioamnionitis increased cytokines in the amniotic fluid, fetal cord blood and maternal serum, there is no effective diagnostic marker for the early detection of chorioamnionitis. Recent studies have defined delta neutrophil index (DNI) showing immature granulocytes (IG) in the peripheral blood.<sup>[5]</sup> While the diagnostic and prognostic values of delta neutrophil index for sepsis, pneumonia and acute appendicitis is investigated, there is no sufficient number of studies in the literature for its use for the prediction of chorioamnionitis.<sup>[6]</sup>

In this study, we aimed to assess the use of delta neutrophil index for the prediction of chorioamnionitis in pregnancies complicated with very early preterm premature rupture of membranes, and to compare this index with other routine infection markers.

## Methods

The approval of the Committee of Scientific Investigation and Publication Ethics (Health Sciences, İnönü University) was obtained for the study, and the investigators complied with the Declaration of Helsinki by World Medical Association (including the amendments made in 2008) and the Good Clinical Practices (GCP) guidelines put into effect on December 29, 1995 as the annex to the Circular Note No. 51748 by the

Turkish Ministry of Health (Ethics Committee's Approval No. 2016/10-5). The files of all patients who admitted to the Obstetrics and Gynecology Clinic of Faculty of Medicine, İnönü University, due to preterm premature rupture of membranes between 16 and 24 weeks of gestation between April 4, 2014 and January 1, 2017 and applied expectant management were reviewed retrospectively, and the patients who were eligible for the inclusion criteria were included in the study.

The inclusion criteria of the study are as follows: 18–39 years old, 16+0–24+0 weeks of gestation (confirmed by ultrasonography during first trimester or early second trimester), singleton pregnancy, live pregnancy, not being on labor (lack of uterine contractions during hospitalization), detection of the rupture of membranes during speculum examination by the presence of amniotic fluid in posterior fornix and/or the detection of oligohydramnios during obstetric ultrasonographic examination (the deepest vertical pocket being <2 cm containing amniotic fluid during amniotic fluid evaluation in the obstetric ultrasonography) and/or the detection of vaginal pH being >5 and/or confirmation by the positive result of AmniSure<sup>(R)</sup> test which enables the presence of placental alpha microglobulin 1 protein in the vaginal fluid immunochromatographically. Multiple pregnancy, major fetal anomalies (fatal anomalies or anomalies that require prenatal and postnatal surgery), fetal death, chromosomal anomalies and genetic syndromes, placental abnormalities, presence of severe maternal infection, presence of maternal systemic disease and smoking/alcohol/drug use were determined as the exclusion criteria of the study.

All patients who were complicated with very early preterm premature rupture of membranes and applied expectant management were hospitalized and administered antibiotherapy (4×2 g ampicillin intravenously for the first 48 hours, and then 2×1 g ampicillin per oral + 1×500 mg azithromycin for 3 days per oral); they were monitored for maternal clinical findings (fever, pulse, blood pressure, respiratory rate, malodorous discharge, and uterine sensitivity) and fetal heart beats, and infection markers [complete blood count, C-reactive protein, CRP, procalcitonin] in the maternal blood were evaluated weekly until the end of pregnancy. Antenatal corticosteroids were administered at 24 weeks of gestation (two doses of 12 mg betamethasone with 24-h interval), and in cases where delivery was inevitable, the rescue dose (one course of intramuscular betamethasone) was applied if the last dose of corticosteroid administration was 2 weeks

ago. In pregnancies between 24 and 32 weeks of gestation where delivery was predicted to be inevitable, magnesium sulfate was administered according to the standard protocols due to its protection effects on fetal brain. As long as there is no gestational complication requiring delivery, the deliveries of the patients were planned at 34 weeks of gestation and their delivery management was carried out in our clinic by research assistants working at the Department of Obstetrics and Gynecology in accordance with follow-up and delivery protocols prepared according to the Management Guidelines for Delivery and Cesarean Section by Turkish Ministry of Health. The diagnosis of chorioamnionitis was established according to the presence of at least one of the findings for maternal tachycardia concomitant with maternal fever ( $\geq 38^{\circ}\text{C}$ ), uterine sensitivity, maternal leucocytosis [white blood cell (WBC)  $\geq 15,000/\text{mL}$ ] and malodorous amniotic fluid, which cannot be attributed to other reasons, as well as leukocyte infiltration or aggregation with diffuse polymorphic nuclei and the presence of inflammation in decidua (deciduitis), umbilical cord (funisitis) and/or blood vessels (vasculitis) in at least one major magnification on chorioamniotic layer histologically.

Maternal serum was obtained from 10 ml blood collected venously to EDTA blood collection tube according to standard protocols; the serum samples were analyzed after venous blood samples were centrifuged at 3000 g for 10 minutes at  $+4^{\circ}\text{C}$ . Procalcitonin was measured by ultrasensitive immunoassay method using TRACE (time-resolved amplified cryptate emission) technology. While this method directly measures concentrations between 0.02 and 50 ng/mL, it can measure concentrations up to 5000 ng/mL after simple dilution. Leukocyte (WBC) count was done with Beckman Coulter GLH750 (Beckman Coulter, Inc., Brea, CA, USA), CRP levels were measured with Abbott Diagnostics Architect c16000 System (Abbott Diagnostics, Lake Forest, IL, USA) using immunoturbidimetry. All analyses were carried out by complying with manufacturer protocols, and critical analyses thresholds were determined as  $15.0/\text{mm}^3$  for leukocyte, 0.5 ng/ml for procalcitonin, and 1 mg/dL for CRP. Specific automated cell analysis device (ADVIA 120/2120; Siemens, Tarrytown, NY, USA) was used to determine delta neutrophil index. This device uses two independent leukocyte count methods which are myeloperoxidase (MPO) and lobularity / nuclear density channel. DNI values were calculated by following formula:  $\text{DNI} = (\text{leukocyte subfraction measured by using}$

cytochemical reaction in MPO channel) – (leukocyte subfraction measured by using weak beam reflection in nuclear lobularity channel).

The placentae of patients who gave birth were sent for histopathological evaluation in terms of chorioamnionitis. The placentae were fixed with formalin, and the macroscopic and microscopic evaluations were carried out according to the placenta evaluation guidelines developed by the College of American Pathologists.<sup>[7]</sup> Tissue samples taken from 5 different locations which were cord insertion location, placenta edge, middle area of placenta, cord and extraplacental membranes were fixed on paraffin blocks. All tissue samples were taken as 1.5  $\mu\text{m}$  stripes and stained with hematoxylin-eosin, and leukocyte infiltration or aggregation with diffuse polymorphic nuclei in at least one major magnification on chorioamniotic layer was defined as chorioamnionitis.

Following data of the patients in study and control groups were recorded: age, gravida, parity, abortus, body mass index, leukocyte, CRP, procalcitonin and DNI values at complete blood count during first admission, gestational age (week) during PPRM, gestational age (week) during delivery, duration (day) between PPRM and delivery, delivery type, delivery indication (chorioamnionitis, ablatio placentae, preterm birth, fetal distress and labor induction at 34 weeks of gestation), birth weight, sex, hospitalization duration, and leukocyte, CRP, procalcitonin and DNI parameters at complete blood count during delivery.

Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Receiver operating characteristic (ROC) curve analysis was used to determine cut-off values of serum leukocyte with chorioamnionitis, CRP, procalcitonin and DNI levels, and sensitivity and specificity values under curve were calculated. In all analyses, 0.05 was considered as the significance level.

## Results

In this study period, a total of 73 patients who admitted due to preterm premature rupture of membranes between 16 and 24 weeks of gestation and applied expectant management were identified. While 43 (58.9%) of these patients were diagnosed with chorioamnionitis, no chorioamnionitis was found in 30 (41.1%) patients. While the patients developing chorioamnionitis during follow-up were included in the study group, the patients

**Table 1.** Clinical characteristics of chorioamnionitis and control groups.

	Chorioamnionitis (n=43)	Control (n=30)	p
Week for the rupture of membranes <sup>†</sup>	19.76±1.65	18.73±1.85	<b>0.018</b>
Body mass index (kg/m <sup>2</sup> )*	27 (22–39.8)	26 (18–34)	0.334
Leukocyte during admission (×10 <sup>9</sup> /L)*	12.8 (8.7–15.5)	11.0 (7.6–15.9)	0.257
CRP during admission (mg/L)*	1.0 (0.3–5.3)	1.0 (0.2–2.0)	0.658
Procalcitonin during admission (ng/mL)*	0.29 (0.02–0.40)	0.24 (0.16–0.44)	0.135
DNI during admission (%)*	1.3 (0.3–8.4)	0.7 (0.3–6.0)	<b>0.004</b>
Week for terminating pregnancy*	21 (17–26)	20 (16–24)	
Birth weight (g) <sup>†</sup>	357.558±114.623	326.233±104.910	0.231
Leukocyte during delivery (×10 <sup>9</sup> /L)*	14.0 (9.6–27.5)	11.7 (8.4–27.1)	<b>0.030</b>
CRP during delivery (mg/L)*	2.23 (0.04–18.00)	0.76 (0.02–4.87)	<b>0.003</b>
Procalcitonin during delivery (ng/mL)*	0.20 (0.02–40.00)	0.05 (0.02–0.42)	0.160
DNI during delivery (%)*	2.4 (0.5–27.7)	0.7 (0.1–3.0)	<b>&lt;0.001</b>

\*Median (min–max); <sup>†</sup>Mean ± standard deviation. CRP: C-reactive protein; DNI: Delta neutrophil index.

without chorioamnionitis were the control group. The clinical characteristics of study and control groups are shown in the **Table 1**. ROC analysis was performed to determine sensitivity, specificity and recommended cut-off values of delta neutrophil index, leukocyte, CRP and procalcitonin in terms of the prediction of chorioamnionitis. While the cut-off value for DNI was 1.0 (AUROC 0.943, 95% CI 0.863–0.984,  $p<0.0001$ ) with 93.02% sensitivity and 93.33% specificity, it was 13.9 (AUROC 0.650 95% CI 0.529–0.758,  $p=0.0239$ ) for leukocyte with 51.16% sensitivity and 90% specificity, and 1.34 (AUROC 0.708, 95% CI 0.590–0.808,  $p=0.0006$ ) for CRP with 67.44% sensitivity and 76.67% specificity. Sensitivity, specificity and recommended cut-off values of infection markers, which were found by ROC analysis for the prediction of chorioamnionitis, used during the follow-up of patients with very early PRM are shown in the **Table 2**. ROC curves are shown in **Fig. 1**.

## Discussion

Chorioamnionitis is the infection of fetal membranes, amniotic fluid and placenta and/or deciduas, and it is also called as intraamniotic infection, amnionitis and amniotic fluid infection.<sup>[8]</sup> Chorioamnionitis, which can be defined clinically or histologically, may also develop hematogenously, transplacentally, or transuterinely as a result of invasive procedures such as amniocentesis and chorionic villus biopsy.<sup>[9]</sup> In this study, in which we investigated the use of DNI and other infection markers for the prediction of chorioamnionitis in patients who admitted to our clinic for very early PRM and were applied expectant management, we found that 58.9% of the patients developed chorioamnionitis. Margato et al. evaluated gestational and neonatal outcomes of the patients who developed the rupture of membranes before 24 weeks of gestation, and they reported chorioamnionitis rate as 71%. In their retrospective study, Kibel et al. reviewed the results of 104 pregnant women who were

**Table 2.** ROC analysis of biomarkers in the prediction of chorioamnionitis.

	AUC (95% CI)	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	p
DNI (%)	0.943 (0.863–0.984)	>1.0	93.02 (80.9–98.5)	93.33 (77.9–99.2)	<0.0001
Leukocyte (×10 <sup>9</sup> /L)	0.650 (0.529–0.758)	>13.9	51.16 (35.5–66.7)	90.00 (73.5–97.9)	0.0239
CRP (mg/L)	0.708 (0.590–0.808)	>1.34	67.44 (51.5–80.9)	76.67 (57.7–90.1)	0.0006
Procalcitonin (ng/mL)	0.597 (0.476–0.710)	>0.17	51.16 (35.5–66.7)	76.67 (57.7–90.1)	0.1471

AUC: Area under curve; CI: Confidence interval; CRP: C-reactive protein; DNI: Delta neutrophil index.

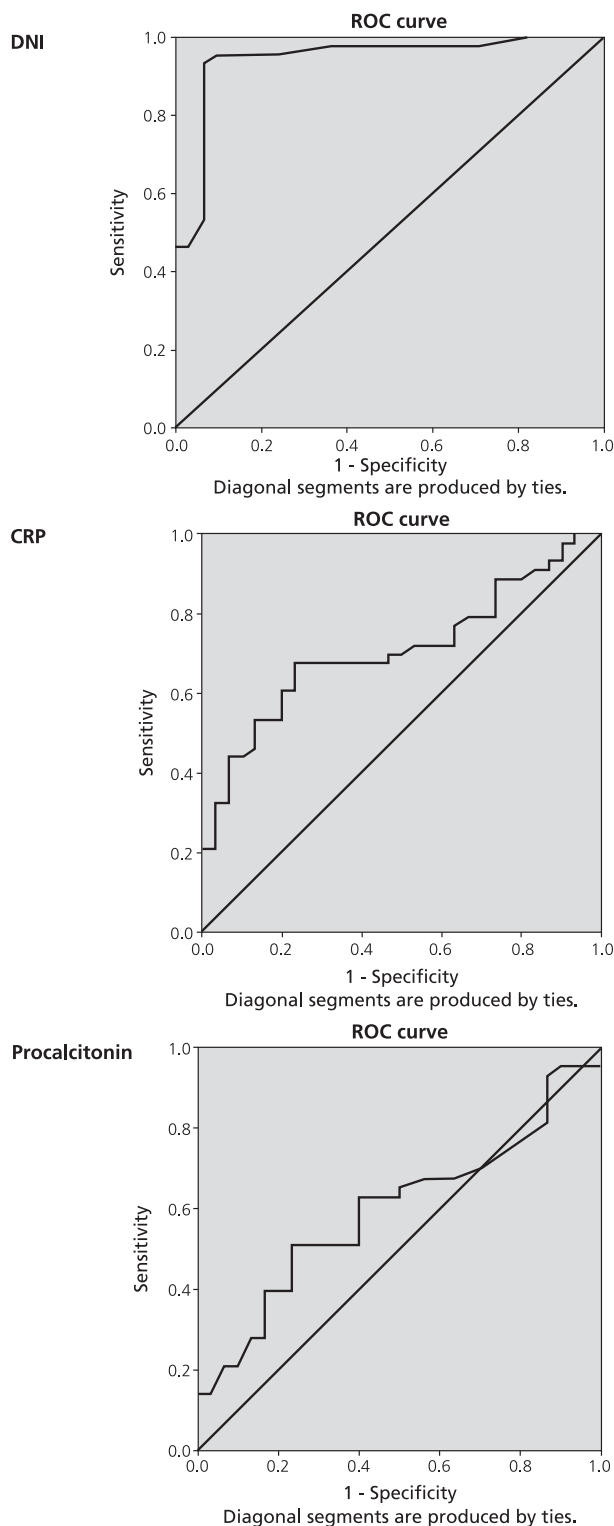


complicated with preterm premature rupture of membranes between 20 and 24 weeks of gestation, and found chorioamnionitis rate as 42.3%.<sup>[10]</sup> The presence of different chorioamnionitis rates reported in pregnancies complicated with preterm premature rupture of membranes between 20 and 26 weeks of gestation, which is called periviable period of pregnancy, is considered to be the result of different diagnosis criteria for chorioamnionitis used in the studies and reporting only clinical chorioamnionitis rates without assessing histological chorioamnionitis in most of the studies.

Prevention of chorioamnionitis in order to decrease maternal and perinatal mortality and morbidity is of more priority than the treatment of chorioamnionitis. Since there are less number of specific and sensitive diagnostic tests which are safe for mother and fetus, chorioamnionitis diagnosis is established first by clinical signs and symptoms.<sup>[11]</sup> The culture of amniotic fluid obtained by amniocentesis is a reference standard; however, it takes 48 hours to have test results and the effect of test on neonatal or maternal morbidity is unclear. Blood and vaginal swab cultures are other diagnostic tests used for chorioamnionitis, but the evidences supporting to use these tests for the diagnosis of chorioamnionitis are insufficient. Besides, some studies recommend not to use vaginal swab samples for preterm premature rupture of membranes.<sup>[12]</sup>

Although leukocyte count, CRP and procalcitonin, which are maternal serum markers frequently used in the diagnosis of chorioamnionitis, are shown to have different sensitivity and specificity values in different studies, it was shown that their capacity to predict chorioamnionitis is limited.<sup>[13]</sup> In this study, we evaluated the strength of counting maternal serum CRP, procalcitonin and leukocyte as well as DNI for the prediction of chorioamnionitis in pregnant women complicated with very early PRM, and we found that CRP and maternal leukocyte could predict chorioamnionitis with 67.4% and 51.1% sensitivity, respectively, but procalcitonin could not be used to predict chorioamnionitis.

Increased immature/total granulocyte rate and the increase in band neutrophils as a result of the entrance of less mature neutrophils into maternal circulation during stress or infection was defined as shift to the left, and it was used to identify systemic inflammatory response.<sup>[14]</sup> DNI, showing immature granulocyte rate in the blood circulation with a different method, has been reported as a new inflammatory marker. There are also studies reporting



**Fig. 1.** ROC curves showing the predictive values of DNI, CRP and procalcitonin.

that DNI, which was shown to be effective in the prediction of sepsis in adult and pediatric populations, can be useful to predict pneumonia development and acute complicated appendicitis.<sup>[5,15]</sup> In our study, we investigated the use of DNI for the prediction of chorioamnionitis, and found that DNI can predict chorioamnionitis with 93% sensitivity and specificity if threshold value is considered 1.0% and that it is more powerful marker for the prediction of chorioamnionitis compared to other maternal serum markers used widely. In parallel with our study, Cho et al. reported that DNI can be used as a serum marker to predict histological chorioamnionitis, and using lymphocyte count, CRP and DNI to predict placental inflammatory response can be useful.<sup>[16]</sup> In their meta-analysis, Park et al. evaluated the diagnostic accuracy of DNI as predictive and prognostic factor in the infected patients, and reported that DNI is a useful parameter in the diagnosis of infected patients and the prediction of mortality for the infected patients and that it should be used in the clinical practice more commonly.<sup>[17]</sup>

Considering the strength and limitations of this study, doing histopathological confirmation of all chorioamnionitis cases is the strength of our study unlike the studies where chorioamnionitis diagnosis is established only on the basis of clinical results. Having retrospective design and being unable to reveal the impact of DNI on perinatal outcomes or on the assessment of treatment response are the limitations of our study.

## Conclusion

Delta neutrophil index is an infection marker which may be useful for the prediction of chorioamnionitis during follow-up in patients who develop very early preterm premature rupture of membranes, can be checked by complete blood count, of which results can be obtained quickly and does not require additional costs, and the diagnostic success of the test seems higher than CRP, prolactin and leukocyte.

**Conflicts of Interest:** No conflicts declared.

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