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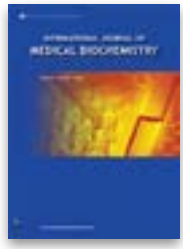

Research Article

Assessment of the circulating soluble endothelial cell adhesion molecules and pentraxin 3 levels in predicting preterm delivery within 72 h

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Abstract

Objectives: The study aimed to evaluate maternal serum soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble E-selectin (sE-selectin), and PTX-3 concentrations in patients with threatened preterm labor (TPL) and to predict preterm delivery within 72 h after hospitalization. Premature birth is defined as the risk of the newborn being in labor before the 37th week of pregnancy is completed. Preterm birth affects 9–13% of whole pregnancies. The major causes of neonatal morbidity and mortality.

Methods: This study consisted of 54 women with TPL and 31 healthy pregnant women. The TPL group was further divided into two subgroups; patients who gave birth within 72 h after the hospitalization was applied to as a preterm delivery group and who gave birth at ≥37 weeks were referred to as the term delivery group. Maternal serum levels of sICAM-1, sVCAM-1, sE-selectin, and PTX-3 were measured with the use of ELISA kits.

Results: Maternal serum sICAM-1 and PTX-3 levels were significantly higher in a preterm delivery group compared with the other two groups (preterm vs. control and preterm vs. term $p < 0.001$). Serum sVCAM-1 and s E-selectin levels were significantly lower in the preterm group compared with the other two groups (preterm vs. control and preterm vs. term $p<0.001$). Gestational age at birth and sVCAM-1, sE-selectin levels are positive correlated ($r=0.679$, $p<0.001$; $r=0.624$, $p<0.001$) and sICAM-1, PTX-3 levels were negatively correlated ($r=-0.630$, $p<0.001$; $r=-0.732$, $p<0.01$). Cervical length measurement showed a negative correlation with PTX-3 and sICAM-1 ($r=-0.420$, $p<0.001$; $r=-0.376$, $p<0.001$) showed a positive correlation with and sVCAM-1 and sE-selectin levels ($r=0.811$, $p<0.001$; $r=0.651$, $p<0.001$).

Conclusion: This study shows a clear relationship between the gestational week at birth and maternal serum levels of sICAM-1, sVCAM-1, sE-selectin, and PTX-3. These biomarkers with TPL predict preterm labor within 72 h in patients with a complicated and short cervix.

Keywords: Pentraxin-3, preterm labour, sE-Selectin, sICAM-1, sVCAM-1

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Preterm birth (PTB), which is remarked as the delivery of an infant before completion of 37 weeks gestation, affects 9–13% of pregnancies and is responsible for a remarkable, proportion of neonatal morbidity and mortality [1]. Most of the women who suffer signs of preterm labor will not deliver within 1 week after the onset of symptoms and 50% will continue the pregnancy to term [2, 3]. An accuratedescription of women who are truly in preterm labor allows the appropriate application of interventions such as prophylaxis for Group B streptococcal infection, antenatal corticosteroid therapy, magnesium sulfate for neuroprotection, and transfer of the patient to a facility with an appropriate nursery grade, if nec-

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essary, which can all enhance neonatal outcome [4]. Despite the clinical relevance of preterm labor, the diagnosis of true preterm labor is subjective, unreliable, and varies substantially among published studies [5]. Different biomarkers have been tested for their capability to predict which women with symptomatic preterm labor are really at high risk for PTB. Fetal fibronectin and cervical length evaluation have been shown to have a good negative predictive value regarding imminent PTB [6–8]. Although the etiology of PTB is unclear and believed to be multifactorial; infection, inflammation, vascular endothelial dysfunction, and uteroplacental ischemia are all considered to be concerns to preterm delivery syndrome [9]. Current evidence suggests that the events leading to PTB are linked to the premature initiation of inflammatory trials and alterations in angiogenic processes [10–12]. In normal pregnancy, labor is initiated by a switch from aninert to a contractile condition. This shift may be partly dueto, a switch of signals from anti-inflammatory to pro-inflammatory pathways [13]. While the induction of inflammatory pathways plays a role in the induction of labor at term;biomarkers to identify these varieties have been sought in the hope of identifying molecules that may sign the cause of preterm labor [10, 14]. The discontinuance of normal angiogenic processes early in pregnancy may also contribute to PTB by altering the balance between pro- and anti-angiogenic factors required for normal placental vascular remodeling and fetal growth [15]. Histopathological-proof of abnormal placentation has been reported in cases of spontaneous preterm delivery [16, 17]. Changed placentation, insufficient vascular development, and disruptions to the normal transformation of spinal arteries can lead to increased placental vascular resistance coupled with deductible blood flow in the intervillous space [17, 18].

Vascular endothelial cells are activated under inflammation and oxidative stress, in these conditions expression of adhesion molecules include the soluble intercellular adhesion molecule-1(sICAM-1), the soluble vascular cell adhesion molecule-1 (sVCAM-1), and soluble E-selectin (sE-selectin) increase [19, 20]. Pentraxin-3 (PTX-3) is an inflammatory molecule that belongs to the same family of C-reactive protein (CRP)and is produced by innate immune cells in response to inflammatory mediators, such as IL-1, tumor necrosis factor, and bacterial products [21–23].

In this study, we investigated the serum sICAM-1, sVCAM-1, sE-selectin, and PTX-3 levels and aimed to predict which women are likely to have PTB in 72 h and benefit from specific interventions.

Materials and Methods

This case–control study was conducted at Istanbul University, Cerrahpasa Faculty of Medicine, Department of Obstetrics and Gynecology between Jan 2018 and Dec 2019. The University's Local Ethics Committee (Number: 279870) approved the study and informed consent was acquired from all participants. The study population consisted of consecutive singleton pregnant women between 27and 33weeks of gestationwith cervical length measurements between 20 and 25 mm who were admitted to our Obstetrics and Gynecology Department diagnosed with threatened preterm labour (TPL). TPL was determined as the presence of at least four regular and painful uterine contractions in 20 min or six contractions in 60 min, which continued for at least 30 s, as measured by an electronic cardiotocography tool. On initial evaluation, a detailed history and a sterile speculum examfollowed by a digital exam, cervical length measurement with transvaginal ultrasound, obstetrical ultrasound, external cardiotocography, daily body temperature, basal hematological and biochemical blood sample pro, file, and routine urine culture were performed in all subjects. Gestational age was determined using the last menstrual period and crown-rump length measurement in the first trimester. Transvaginal ultrasonographic assessment of cervical length was carried out on admission using the Toshiba Xario ultrasound machine (Toshiba Medical Systems Corporation, Tokyo, Japan) with a 6.0MHz transducer transvaginalginal probe was placed in the anterior vaginal fornix and the cervical length was determined as the distance between the internal and external cervical os. The shortest distance of three measurements was used. The patientswith any existing inflammatory disease (urinary infectionand chorioamnionitis) or fever of unknown origin, any pregnancy complication, severe anemia, who, smoke and also with a history of having preterm labor or delivery, second-trimester abortion, repeated pregnancy loss, cervical incompetence, fetal congenital anomalies, uterine anomalies, any maternal systemic disease, hypertensive disorders, gestational diabetes mellitus, and premature rupture of membranes were not included the study. The patients with placenta previa or those who had previously undergone cervical surgery were also excluded from the study. 86 consecutive singleton pregnant women were enrolled in this study. Patients diagnosed with TPL (54 patients) were divided into two groups according to pregnancy outcome: 27 women who delivered in 72 h after hospitalization were referred to themas the "preterm delivery group" and 27 women who gave birthat ≥37 weeks were referred to as "term delivery group." The control group consisted of 31 healthy women without signs of preterm labor who eventually delivered term newborns. All the pregnant women were followed until delivery and obstetric data wererecorded for each participant.

Follow-up procedure: Decisions concerning admission, antenatal corticosteroid therapy, prophylaxis for Group B streptococcal infection, and magnesium sulfate for neuroprotection were carried out according to the Committee on Practice Bulletins-Obstetrics no. 159 of the American College of Obstetricians and Gynecologists. After the beginning investigation of the clinical course of each patient in the study, patients' data and follow-up outcomes were recorded prospectively until the birth. Route and timing of delivery were decided on a case-by-case basis, and cesarean sections were performed only for obstetric indications. The primary outcome was spontaneous delivery within 72 h after admission.

Table 1. The clinical characteristics, laboratory parameters, and perinatal outcomes of the control and study groups

		Threatened preterm labor (n=54)		
	Control group (n=31)	Term delivery group (n=27)	Preterm delivery group (n=27)	p
Maternal age (years)	27.1±3.6	28.1±4.0	27.6±4.4	NS
BMI (kg/m^2)	23.4±3.1	24.1±2.9	23.2±3.4	NS
Gravidity	1.5±0.3	1.2±0.8	1.3 ±1.1	NS
Gestational age at sampling (weeks)	32.5±1.4	33.1±1.6	32.4±1.5	NS
Gestational age at delivery (weeks)	38.2±0.8	38.1±0.9	33.1±1.5	<0.001*,$^+$
Birth weight (g)	3365±153	3242±188	2567±314	<0.001*,$^+$
Cervical length (mm)	37.6±5.2	24.6±1.8$^\#$	22.6±1.6	<0.001*
Hb (mg/dL)	12.6±4.8	11.8±1.4	11.4±1.3	NS
CRP (mg/L)	1.7 (0.4–2.2)	1.8 (0.8–2.4)	2.2 (1.5–2.9)	NS

Data are expressed as means±SD, or median (interquartile range) for non-normally distributed variables. *: Represents comparison between control and preterm, p<0.001; $^+$: Represents comparison between term and preterm, p<0.001; $^\#$: Represents comparison between control and term, p<0.001. BMI: Body mass index; Hb: Hemoglobin; CRP: C-reactive protein; NS: Not significant.

Blood samples were collected at first admission by venbefore delivery or administration of betamethasone or any other drugs (e.g., magnesium sulfate and tocolytic drugs). Blood samples were centrifuged at 2000rpm for 20min. Serum samples were isolated and stored at–80C until analysis. All the assays were carried out with the investigators blinded to the group. The samples were thawed immediatelybefore the assay. Quantitative immunologic determinations of sICAM-1, sVCAM-1, sE-selectin, and PTX-3were performed in serum samples by enzyme-linked immunosorbent assay techniques with ELISA Parameter (R&D Systems, Minneapolis, MN, USA) kits. The procedural details suggested by the manufacturer were strictlyfollowed. All determinations were done in duplicate. The readings of blank samples were subtracted from the mean of the duplicate readings. Sensitivity, intra- and interassay coefficients of variation (%CV) were 5.113 ng/L, 5–8; 4.002 ng/mL, 10–12; 0.528 ng/mL, 9–11;0.051 ng/mL, 4–6, for sICAM-1, sVCAM-1, sE-selectin, and PTX-3, respectively.

Statistical analysis

All analyses were performed using the Statistical Package for the Social Sciencessoftware version 21 (Chicago, IL). The Kolmogorov–Smirnov test was used to estimate, the normality of the distribution of the variables. Descriptive statistics for patients' characteristics were computed for constant and categorical variables. The data were presented as mean±standard deviation. The significance of differences between variables of the patient subgroups was defined, by the ANOVA/Bonferroni test. All analyses were two-tap-values p<0.05 were respectedas statistically significant. sICAM-1, sVCAM-1, PTX-3, and, sE-selectin levels were transformed logarithmically to achieve normal distributions. The data were presented as median (interquartile range) for theseparameters. Comparison between subgroups (control, termdelivery, and preterm delivery) was using formed used the ANOVA test. When an entire significance was observed between subgroupsposthoc tests were using formed used the Bonferroni test; corrected p<0.017 was considered to show a statistically significant result. Boxplot diagrams for were used the graphical visualization of biomarker results. Boxes show the median line, the 25th, and the 75th centiles (top and bottom lines of the box). Receiver-operating characteristic (ROC) analysis was used to determine the predictive threshold of maternal serum s ICAM-1, sVCAM-1, PTX-3, and sE-selectin levels for predicting delivery within 72 h after hospitalization. The Pearson correlation analysis was used to describe the relationship between the variables.

Results

The clinical characteristics, laboratory parameters, and perinatal results of the control and study groups are shown in Table 1. Maternal characteristics including age, BMI, gravidity, gestational age at blood sampling, CRP, and Hb levels were not significantly different between groups (p>0.05). As expected, cases of the preterm delivery group had significantly shorter gestations (p<0.001), infants with the lower birth weights (p<0.001) compared to control and term delivery groups. The mean cervical length measurement was significantly higher in the control group (p<0.001); there was no significant difference in cervical length between the term and preterm delivery groups.

Comparisons of sICAM-1, sVCAM-1, and, sE-selectin, PTX-3 in con, control, term delivery, and preterm delivery groups are shown in Table 2. After the Bonferroni correction for all molecules, serum ICAM-1 and PTX-3 levels were significantly higherin the preterm delivery group compared with the other two groups (preterm vs. control and preterm vs. term p<0.001); however, there was no statistically significant difference between control versus term delivery group (p=0.681 for s ICAM-1 and p=0.510 for PTX-3). Serum sVCAM-1 and sE-selectin levels were significantly lowerin the preterm group compared with the other two groups (preterm vs. control and preterm

Table 2. Comparision of the serum levels of sICAM-1, sVCAM-1, sE-selectin, PTX3 in control, term delivery, and preterm delivery groups

	Control group (n=31)	Term delivery group (n=27)	Preterm delivery group (n=27)	p
sICAM-1 (ng/mL)	285.13 (180.87–372.71)	285.21 (231.22–345.21)	692.29 (495.01–1283.85)	<0.001*,+
Pentraxin 3 (ng/mL)	2.44 (1.91–2.65)	2.02 (1.47–2.64)	8.36 (5.56–12.4)	<0.001*,+
E-selectin (ng/mL)	78.36 (70.74–85.81)	45.25 (41.43–55.21)#	24.35 (15.75–32.02)	<0.001#,*,+
sVCAM-1 (ng/mL)	490.85 (452.72–623.87)	174.76 (167.52–217.38)#	104.73 (95.35–135.49)	<0.001#,*,+

Data are expressed as median (interquartile range) for non-normally distributed variables. Values for all biomarkers were logarithmically transformed before interference analyses. Non transformed values are shown. Group means were compared by ANOVA, followed by post hoc analyses for two group pair wise comparisons with the Bonferroni's correction for multiple testing. *: Represents comparison between control and preterm, p<0.001; +: Represents comparison between term and preterm, p<0.001; #: Represents comparison between control and term, p<0.001. sICAM-1: soluble intercellular adhesion molecule-1; sVCAM-1: soluble vascular cell adhesion molecule-1; PTX3: Pentraxin 3.

vs. term p<0.001); andalso term delivery group had lower sVCAM-1 and sE-selectin levels compared with the control group (p<0.001 for both). ROC analysis was performed and the area and was er the curve (AUC) determined to evaluate the efficiency of these markers for predicting preterm delivery within 72h after admission (Fig. 1). The best cutoff values (sensitivity and specificity) were 421,8 ng/L for s ICAM-1 (92% sensitivity, 89% specificity); 2.92 ng/mL for PTX-3 (91.2% sensitivity, 95.3% specificity); 36.7ng/mL for sE selectin (92.2% sensitivity, 94.7% specificity);and 151.3 ng/mL for sVCAM-1 (92.8% sensitivity, 96.1% specificity). The AUC wassignificant for all molecules (p<0.001).

We next checked the associations between sICAM-1, PTX-3, sVCAM-1, sE-select, and other parameters in whole groups (Table 3). sVCAM-1, sE-selectin levels positively (r=0.679 p<0.001; r=0.624 p<0.001, respectively), and sICAM-1, PTX-3 levels negatively correlated (r=–0,630 p<0.01; r=–0.732 p<0.01) with gestational age at birth. Cervical length measurement negatively correlated with sICAM-1, PTX-3 (r=–0,420 p<0.001; r=–0.376 p<0.001, respectively) and positively correlated with sVCAM-1, sE-selectin levels (r=0.811 p<0.001; r=0,651 p<0.001, respectively). Maternal mean CRP levels were not statistically different between groups however CRP levels positively correlated with s ICAM-1, PTX-3 (r=0.245 p<0.01; r=0.243 p<0.01, respectively) and negatively correlated with sVCAM-1, sE-selectin levels (r=–0,308 p<0.001; r=–0.302 p<0.001, respectively) (Table 4).

Discussion

In the present study, we showed clear correlationbetween the gestational week at birthandserum sICAM-1, sVCAM-1, sE-selectin, and, PTX-3 levels suggesting that these biomarkers may predict preterm delivery within 72 h in patients with TPL and short cervix. It has been shown that patients with the rue the inthe preterm delivery group had the highest sICAM-1 and Pentraxin3 and the lowest sVCAM-1 and sE-selectin levels. To the best of our knowledge, this is the first study investigating the utility of maternal serum sICAM-1, sVCAM-1, sE-selectin, and PTX-3, levels to predict preterm delivery in women complicated with TPL and short cervix.

We know that the risk of spontaneous PTB increases if the cervical length is 15 mm or less and, on the other hand, it is unlikely if the cervical length is birth ≥30mm [5]. Women with a cervical length between 15 and 30 mm are at intermediate risk for preterm delivery and other effective methods are needed to distinguish incipient preterm labor from false preterm labor.

Accumulated research data indicate that inflammatory processes play a significant role in spontaneous preterm labor [24–26]. An improved understanding of the link between inflammation and spontaneous PTB leads to a search for new biochemical markers to identify women at high risk for preterm delivery. Current evidence suggests that the events leading to PTB are linked to the premature initiation of inflammatory pathways and alterations in what are normally tightly regulated angiogenic processes [10–12]. Disruptions to normal angiogenic processes may also contribute to PTB by altering the balance between pro- and anti-angiogenic factors required for normal placental vascular remodeling and fetal growth [15]. It is now clear that disorders of deep placentation are present not only in preeclampsia and intrauterine growth retardation (IUGR) but in other obstetrical syndromes such asspontaneous abortion, abruption placenta, and preterm labor [27].

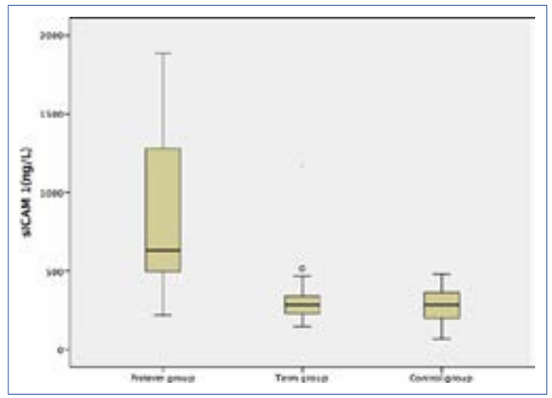

Figure 1. Mean maternal serum sICAM, concentrations of control, term and preterm delivery groups are illustrated.
sICAM-1: soluble intercellular adhesion molecule-1.

Table 3. Screening efficiency of the markers for predicting preterm delivery within 72 hafter admission in pregnancies with threatened preterm labor

Test	Area	95% CI	p	Sens	Spec
sICAM-1 (ng/L)	0.922	0.839–1.0	<0.001	92.3	89.0
PTX3 (ng/mL)	0.974	0.924–1.0	<0.001	91.2	95.3
E selectin (ng/mL)	0.994	0.979–1.0	<0.001	92.2	94.7
sVCAM-1(ng/mL)	0.994	0.982–1.0	<0.001	92.8	96.1

sICAM-1: soluble intercellular adhesion molecule-1; sVCAM-1: soluble vascular cell adhesion molecule-1; CI: Confidence interval; PTX3: Pentraxin 3; Sens: Sensitivity; Spec: Specificity.

In the literature, there are conflicting studies evaluating the value of inflammatory and angiogenic processes related to PTB and its prediction. Congo-Agudelo et al. [13] stated a systematic review and meta-analysis to predict spontaneous PTB in women with singleton pregnancies and no symptoms of preterm labor. They speculated that none of the evaluated biomarkers meet the criteria to be considered a useful test to predict spontaneous PTB in asymptomatic women. We expect that symptomatic patients with threatened preterm laborhave, unlike findings. Vascular endothelial cells are activated under inflammation and oxidative stress that occur during pregnancy and increase the expression of adhesion moleculesand selectins [19]. sVCAM-1 and also sICAM-1 are two different adhesion molecules involved in the process of trophoblast invasion of the spiral arteries. In normal placentation, the cytotrophoblasts increase the expression of sVCAM-1 as they invade the spiral arteries conversely sICAM-1 seems to be expressed in deficient endovascular cytotrophoblasts invasion, not in normal pregnancies [28, 29]. sICAM-1 has been observed in spiral arteries from pregnancies complicated by either preeclampsia or intrauterine growth restriction or both of these [28]. Chen et al. [30] showed that mean maternal levels of sICAM-1 and also sVCAM-1 were significantly higher, whereas sE-selectin levels were not significantly different in women who subsequently give birth prematurely. This was a large prospective, case–control study of young, generally healthy asymptomatic pregnant women not symptomatic patients. Conversely, Laudanski et al. [31] demonstrated that maternal sICAM-1, sVCAM-1, and sE-selectin levels were not effective in predicting PTB in women with TPL. They claim that preterm labor, at least in a part, is a result of genetic predisposition. Complex conditions, such as preterm labor, cannot be resolved using methods that analyze single factors. They suggest that using human genome expression may increase our knowledge of the causes of preterm labor, one of the major challenges of modern obstetrics. Only a few studies in the literature have investigated the role of PTX-3 in pregnancy. PTX-3 plays a role in the innate immune response in the maternal-fetal interface during gestational complications and is associated with inflammatory conditions [32, 33]. Cruciani and Martin et al. [33, 34] showed that the concentration of PTX-3 in the amniotic fluid was raised in spontaneous preterm labor. In another study, Cruciani et al. [33] reported that patients with an episode of TPLwhether these patients delivered preterm or at term had a higher median plasma PTX-3 concentration than normal pregnant women. Our results demonstrated that maternal PTX-3 levels were not significantly different between the control andterm delivery groups. However, the preterm delivery group had significantly higher levels of PTX-3.

Serum ICAM-1 and PTX-3 levels were significantly higher in the preterm group compared to the term and control groups. It is thought that ICAM-1 and PTX-3 show lower serum levels in healthy and term pregnancies. Indicating a possible inflammatory process that indicates an increase in the acute phase of preterm labor [28, 34]. On the contrary, the lowest levels of sVCAM-1 and sE-selectin are likely to occur in patients in the PTB group indicating a persistent trophoblastic invasion defect and a failure in angiogenesis [35, 36]. Recent publications emphasize that PTB is a syndrome associated with ongoing placental insufficiencies, such as preeclampsia or IUGR [37]. We speculate that inflammation and placental bed disorders are the two main reasonsfor the variability in these selected biomarkers.

Table 4 .Correlation analyses between maternal serum sICAM1, PTX3, E-selectin, sVCAM1, and the other parameters in whole groups

	sICAM-1	PTX 3	E selectin	sVCAM-1
Maternal age	0.103	–0. 094	0.111	0.043
Gestational age sampling	–0.07	–0.141	0.034	–0.018
Gestational age at birth	–0.630**	–0.732**	0.679**	0.624**
BMI at blood sampling	–0.011	0.323	–0.053	0.141
Cervical length	–0.420**	–0.376**	0.651**	0.811**
CRP	0.245*	0.243*	–0.302**	–0.308**
sICAM-1	_	0.518**	–0.626**	–0.581**
PTX3	0.518**	_	–0.636**	–0.559**
sE selectin	–0.626**	–0.636**	_	0.832**
sVCAM-1	–0.581**	–0.559**	0.832**	_

*: p<0.05; **: p<0.01. sICAM-1: soluble intercellular adhesion molecule-1; sVCAM-1: soluble vascular cell adhesion molecule-1; PTX3: Pentraxin 3; BMI: Body maxx index; CRP: C-reactive protein.

The strengths of our study are its prospective design and strict criteria, which allow for much more accurate comparisons between biochemical markers. The subjects in the present study had no history of PTB and shorter cervical length measurements which can also strengthen the accuracy of the results. The main limitation of our study was the relatively small sample size of the study groups. Further studies with larger sample sizes and complicated pregnancies are required to validate these results.

Conclusion

Spontaneous PTB, defined as birth before 37 weeks of gestation, is a major contributor to perinatal morbidity and mortality. Inflammatory processes play a significant role in spontaneous preterm labor. An improved understanding of the link between inflammation and spontaneous PTB leads to a search for new biochemical markers to identify women at high risk for preterm delivery. The combination of these biomarkers may predict preterm delivery within 72 h in patients with threatened preterm labor and short cervix.

Conflict of Interest: The authors declare that there is no conflict of interest.

Ethics Committee Approval: The study was approved by The Istanbul University Cerrahpaşa Faculty of Medicine Ethics Committee (No: 279870, Date: 04/09/2015).

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Authorship Contributions: Concept – R.M., E.A.D., A.A.F.; Design – E.A.D., A.A.F., A.O., R.M.; Supervision – R.M., E.A.D., A.O.; Funding – E.A.D., A.A.F., A.O.; Materials – E.A.D., A.A.F., A.O.; Data collection &/or processing – E.A.D., A.A.F., A.O.; Analysis and/or interpretation – E.A.D., A.A.F., A.O.; Literature search – A.A.F., A.O., E.A.D.; Writing – E.A.D., A.A.F., A.O.; Critical review – R.M., E.A.D., A.O., A.A.F.

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