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ORIGINAL ARTICLE

# The relationship between the latency period, infection markers, and oxidant and antioxidant states in women with preterm premature rupture of membranes

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**Abstract**
*Background* A major cause of perinatal morbidity and mortality has been reported to be preterm premature rupture of membranes (PPROM). Our objective was to evaluate oxidant–antioxidant balance, infection parameters, time interval between rupture of membranes and delivery (latency period), and the relationship among all these parameters.
*Methods* Seventy-five cases with PPROM between 24 and 34 gestational weeks were included in the study. A control group of 41 women who gave birth at term were considered as the control group. The relationship among maternal plasma total oxidative stress (TOS), malondialdehyde (MDA), total antioxidant status (TAS), leukocyte counts, CRP, vitamin C and E levels, gestational week, neonatal birthweight, and latency period was evaluated.
*Results* In cases with PPROM, rupture occurred at an average of 29.4 gestational weeks and premature babies were born at an average of 31.6 gestational weeks. The mortality rate of babies born to PPROM women was 18.7% (14/75) died at or following birth. In the PPROM group, TOS, MDA, and leukocyte counts were found to be significantly higher compared to the control group ($p < 0.001$). Besides, a significant negative correlation was detected among the latency period, TOS, CRP, and leukocyte counts ($p < 0.05$).
*Conclusions* Appropriate treatment protocols that strengthen antioxidant defense systems and taking into consideration the signs of infection can decrease the incidence of PPROM and/or mortality rates of babies born to PPROM women.

**Keywords** PPROM · Latency period · Inflammatory marker · Oxidant and antioxidant states

## Introduction

Preterm premature rupture of membranes (PPROM) is defined as dehiscence and tearing of membranes prior to 37 weeks of gestation. Management of cases is one of the challenging and controversial issues of perinatal medicine. PPROM occurs in nearly 3–4% of all pregnant women and is responsible for 35% of all premature births. Although the mechanisms leading to the weakening and rupture of fetal membranes in term and preterm pregnancies have not been expounded definitively yet, weakening of membranes near term due to physiological changes together with strain forces created by uterine contractions and recurrence risk of PPROM in future pregnancies of women with a history of PPROM provide strong evidence for the disruption of mechanical integrity of the membranes [1, 2].

In the pathogenesis of PPROM, subclinical intrauterine infection has been held responsible as the most important etiological factor for neonatal and indirectly maternal morbidities [2, 3]. Infection, inflammations [4], multiple pregnancies, deficiency of some nutrients during pregnancy as vitamins and minerals [5, 6], smoking [7], coitus, blunt abdominal or uterine trauma, low socioeconomic status, and many others were risk factors for the occurrence of PPROM. Also, reactive oxygen species (ROS)-induced

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damage to amnion epithelium or collagen synthesis in the chorioamniotic membrane can lead to PPROM development [8, 9]. In 2014, Rankumar Menon proposed that oxidative stress (OS) is an inevitable component of pregnancy, and it is tightly regulated until labor and delivery. He also reported that both at term and preterm labor, pathways are mediated not only by OS but also by OS-induced damage to intrauterine tissues, especially causing premature aging of fetal tissues and/or rupture of membranes [10]. Antioxidant vitamin C is essential for the formation of collagen tissue and acts synergistically to scavenge several ROS by reducing oxidative stress. According to the available data, ROS can cause fetal membrane damage and lower vitamin C concentrations in the second trimester might be related to the risk of infection, premature birth, preeclampsia, congenital anomalies, an increased incidence of PPROM, and a shorter latency period before delivery [8, 11–13].

In the present study, it was aimed to evaluate the known risk factors, including inflammatory markers (leukocyte count and CRP), oxidative stress markers (MDA, TOS), and antioxidants (vitamins C and E, and TAS), to estimate the duration of latency period (the time interval between rupture of membranes and delivery) following PPROM, and to investigate the effects on the latency period of gestational week and all these factors.

## Methods

### Study design

Among referrals to the Department of Obstetrics and Gynecology in our University Hospital within 18 months, 75 women with singleton pregnancies who were diagnosed with PPROM between 24 and 34 gestational weeks were included in the study as the study group. PPROM was diagnosed with the observation of overt vaginal fluid leakage, or when leakage was suspected, turnusol test was performed to confirm the membrane rupture. From an unselected population of pregnant women undergoing their routine pregnancy follow-up, 41 gestational age-matched pregnant women who delivered at term were selected as the control group. The inclusion criteria for women in both groups were singleton pregnancy, no clinical sign of infection, and the absence of clinical evidence of any major systemic disorder or no fetal abnormalities. Patients with multiple pregnancies, macrovascular and/or microvascular complications, delivery within 24 h of admission, major congenital anomalies, fetal growth restriction, and chronic medical diseases or other known major diseases were excluded from the study. All the patients with PPROM received antibiotherapy (ampicillin) and steroid, and were hospitalized for monitorization with strict bed rest, fetal heart monitoring, and uterine activity assessment being performed daily. The delivery ensued when chorioamnionitis signs developed or fetal distress occurred. We have identified chorioamnionitis clinically in 7 cases in the PPROM group. This research was based on the principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Ethics Committee for Research on Human Subjects of our University (number 07/07, 22.04.2011), and all participants signed an informed written consent form prior to the study. All the information was kept confidential.

### Biochemical analysis

Venous blood samples were obtained from each woman in the study group during the diagnosis of PPROM and routine examinations of the healthy pregnant controls matched according to the gestational age. Blood samples were collected into two tubes containing potassium EDTA and then centrifuged at 4000 rpm for 10 min at 4 °C after the evaluation of leucocyte count in one of these tubes; their plasma layers were portioned and stored at −80 °C for all measurements.

CRP levels were analyzed with an ADVIA 2400 brand autoanalyzer (ADVIA 2400 Chemistry system, Siemens, Japan) using commercial kits. The analysis of malondialdehyde (MDA) which is the end product of lipid peroxidation was realized by the spectrophotometric method [14]. For the determination of total oxidative status (TOS) and for the quantitative evaluation of total antioxidant capacity (TAS), a colorimetric PerOx (TOS/TOC) ELISA test kit (Immundiagnostik AG, Stubenwald-Allee 8a, D 64625 Bensheim, Germany) and an ImAnOx (TAS/TAC) ELISA kit (Immundiagnostik AG, Stubenwald-Allee 8a, D 64625 Bensheim, Germany), respectively, were used.

Plasma vitamins C and E levels were evaluated using an HPLC (Shimadzu 10A VP HPLC model device and ClinRep kits) system.

### Statistical analysis

The groups were compared for demographic characteristics, gestational weeks at both rupture of membranes and delivery, latency period, mode of delivery, and fetal birthweight. All statistical analyses were performed using SPSS 21.0 package (SPSS Inc, Chicago, IL, USA). Data were expressed as mean ± standard deviation unless otherwise indicated. Characteristics and outcome variables in both groups were analyzed using the Student's *t* test and categorical variables were compared by Chi-square test and Fisher's exact test. Multivariate regression analysis was used to evaluate the association between latency period and

the various factors. The factors that produced a point estimate at a $p$ value of <0.05 with univariate analysis were subjected to multivariate regression analysis. Adjusted odds ratio (OR) with 95% confidence interval (CI) was calculated. A $p$ value <0.05 was considered statistically significant.

## Results

In the current study, 75 women diagnosed with PPROM and 41 gestational age-matched controls were included and analyzed. No differences were noted between the groups regarding maternal age and parity. Smoking habits and the rate of previous vitamin supplementation were also similar between the groups. Mean latency period and mean gestational age at delivery for PPROM cases were 16.03 days (16.03 ± 16.87; median 7, min 1.0, max 55.0) and 31.6 weeks (31.63 ± 4.01; median 32.2, min 24, max 40), respectively. Chorioamnionitis was detected in 7 cases in the PPROM group. Because of the scarce number of cases, relevant parameters were not compared.

Fetal birthweight (1755 vs. 3054 g; $p < 0.001$) was significantly lower in the PPROM group compared to the control group, as expected. The mortality rate of babies who were born to PPROM women was 18.7% (14/75) and it was only 2.44% in the control group. In the PPROM group, 14 babies died were between 24 and 31 weeks of gestation (28.96 ± 3.2 weeks). Demographic characteristics and the concentrations of maternal blood biochemical markers in both groups are demonstrated in Table 1. The mean maternal leukocyte count was 12,541.95 ± 2991.27/mm$^3$ in the PPROM group which was significantly higher than that of the control group ($p < 0.001$). Mean levels of maternal plasma TOS and MDA in the PPROM group were significantly higher compared with the control group ($p < 0.001$). Mean plasma TOS levels in 7 cases identified clinically with chorioamnionitis in the PPROM group were markedly higher (745.21 ± 226.22). No statistically significant difference was noted between the groups regarding CRP and TAS ($p = 0.082$ and $p = 0.232$, respectively).

Vitamin E levels were not significantly different between the groups (20.55 ± 7.08 μg/ml in the PPROM vs. 18.13 ± 6.27 μg/ml in the control group; $p = 0.74$), whereas vitamin C level was observed to be significantly lower in the PPROM group compared to the control group (7.39 ± 2.37 vs. 13.83 ± 3.16; $p < 0.001$).

Due to the association between TOS, CRP, leukocyte count, and latency period, these parameters were subjected to multivariate logistic regression analysis. A significant relationship between the latency period and especially TOS levels and leukocyte counts was detected (Table 2). The latency period is inversely correlated with the TOS level and leukocyte count.

## Discussion

Although PPROM is frequently encountered as an important problem leading to maternal, fetal, and/or neonatal morbidity, debates about its diagnosis and treatment are still on the agenda. Cross-sectional studies have shown a correlation between increased cytokine and ROS levels or decreased antioxidant protection associated with amniotic

**Table 1** Demographic characteristics and biochemical markers in PPROM and control groups

| | PPROM ($n = 75$) | Control ($n = 41$) | $p$ value |
|---|---|---|---|
| Age (years) | 28.33 ± 5.64 | 26.90 ± 4.10 | 0.155 |
| Parity, median (IQR)* | 1 (0–2) | 1 (0–2) | 0.09 |
| Previous vitamin supplementation, $n$ (%) | 41 (54.7%) | 22 (50.0%) | 0.86 |
| Smoker, $n$ (%) | 10 (13.3%) | 4 (9.1%) | 0.44 |
| Latency periods (days), median (IQR)* | 7 (1–55) | – | – |
| Gestational age at delivery (weeks) | 31.63 ± 4.00 | 38.53 ± 1.28 | <0.001 |
| Birth weight (g) | 1755.33 ± 853.13 | 3054.50 ± 458.40 | <0.001 |
| Leukocyte ($10^3$/mm$^3$) | 12.57 ± 3.01 | 9.91 ± 2.01 | <0.001 |
| CRP (μg/ml) | 10.16 ± 12.94 | 6.44 ± 4.69 | 0.082 |
| TAS (μmol/l) | 343.91 ± 25.19 | 350.72 ± 31.58 | 0.232 |
| TOS (μmol/l) | 549.69 ± 213.76 | 384.29 ± 142.49 | <0.001 |
| MDA (nmol/ml) | 4.36 ± 1.41 | 2.33 ± 1.62 | <0.001 |
| Vit E (μg/ml) | 20.55 ± 7.08 | 18.13 ± 6.27 | 0.74 |
| Vit C (μg/ml) | 7.39 ± 2.37 | 13.83 ± 3.16 | <0.001 |

Data presented as $n$ (%) or mean (standard deviation) unless otherwise noted

* Presented as median (interquartile range). Statistical significance is given as $p < 0.05$

**Table 2** Pearson's correlation test and multiple logistic regression analysis between the latency period and the affected variables

| | Latency period | Leukocyte | CRP | Vit C | TAS | TOS | MDA |
|---|---|---|---|---|---|---|---|
| Latency period | 1 | **−0.423*** | **−0.263**** | 0.211 | −0.135 | **−0.377*** | 0.201 |
| *p* value | | **0.0001** | **0.022** | 0.069 | 0.262 | **0.001** | 0.084 |

| Model | *B* | Std. error | Beta | *t* | *p* value | 95% Confidence interval for *B* | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower bound | Upper bound |
| (Constant) | 51.893 | 7.92 | | 6.552 | 0.000 | 36.085 | 67.701 |
| Leukocyte | −0.002 | 0.001 | −0.325 | −3.081 | **0.003** | −0.003 | 0.001 |
| CRP | −0.185 | 0.142 | −0.137 | −1.300 | 0.198 | −0.472 | 0.099 |
| TOS | −0.024 | 0.008 | −0.321 | −3.067 | **0.003** | −0.042 | −0.008 |

Statistically significant variables are in bold. *$p < 0.001$; **$p < 0.05$

infection and the pathogenesis of PPROM [8, 15]. In PPROM, when components of the membrane are exposed to ROS, ensuing histological alterations have been demonstrated in in vitro studies, and excessive collagen degradation in specimens of chorioamnion and amniotic fluid samples has been displayed in clinical studies. In the present study, oxidative stress markers (maternal plasma MDA and TOS levels), infection markers (whole blood leukocyte counts and plasma CRP levels), and plasma vitamin C levels (having an important role in the collagen metabolism) were analyzed both in PPROM and healthy pregnant women. We evaluated the importance of these parameters in PPROM and specifically their significance on the latency period between membrane rupture and the delivery. The present study indicated that pregnant women with PPROM had higher MDA, TOS, and leukocyte counts. On the other hand, no significant differences were found in maternal plasma TAS levels compared to pregnant women who delivered at term. The oxidative stress in pregnancy may increase the risk of PPROM that is mediated by extreme or sustained peroxidation of amniotic epithelium and chorioamniotic collagen. These data were in concordance with previous reports which suggested the association between oxidative stress and PPROM [16–19].

PPROM is characterized by altered collagen cross-link profiles, reduced collagen concentrations, and increased ROS formation and/or antioxidant depletion. It is associated with extensive changes in collagen metabolism, collagenolytic activity, and collagen solubility, suggesting that weakening of the amnion in the preparation for rupture may be determined partly by factors controlling the synthesis and degradation of collagen. Association of PPROM has been demonstrated with increased concentrations of biomarkers of oxidative damage in pregnant women [19–21].

Vitamin C is important in protecting and maintaining the strength of the chorioamniotic membranes. In the present study, no significant differences were found in maternal plasma vitamin E levels between the PPROM and control groups, which, is however, in agreement with previous reports; we found low plasma vitamin C levels in combination with high plasma MDA and TOS levels in women with PPROM. Although the protective role of antioxidant vitamins against preterm labor and preterm membrane rupture has been indicated in many studies in the literature [11, 12], contradictory opinions have also been reported [22, 23]. Menon et al. [10] suggested the hypothesis that an alternate non-infectious pathway mediated by oxidative stress and apoptosis in PPROM may promote proteolysis resulting in membrane weakening and rupture. Clinically, low plasma vitamin C concentrations contribute to poor collagen production in fetal membranes and may be associated with an increased risk of PPROM [24]. Another study demonstrated that increased levels of unconjugated maternal estriol, which are listed among the risk factors for early membrane rupture (PROM) and PPROM, could be reduced with vitamin C supplementation which is a safe and effective way of decreasing the risk of PPROM [25]. Recent studies found that the supplementation of vitamins C and E in women with PPROM was associated with a longer latency period before delivery [14, 26, 27]. In the present study, the rate of previous vitamin supplementation was similar between the groups, and no additional vitamins were supplemented in the PPROM group.

A latent period exists between membrane rupture and the onset of labor. One half of the childbirths between 28th and 34th gestational weeks occur within 24 h and 80–90% of them within the first week after membrane rupture [28]. Since one of the main problems of the pregnancies between 26th and 36th gestational weeks is prematurity, prolongation of pregnancy to term should be targeted. In the present study, the mortality rate of babies born to PPROM women was 18.7%. As expected, gestational age at birth of those babies who died was found to be significantly lower ($28.96 \pm 3.2$ weeks) than that of babies who were born to

women with PPROM and survived (32.24 ± 3.94 weeks; $p < 0.001$). The perinatal mortality rate was reported to range from 25 to 86% in previous studies [29, 30], and the mortality rate of babies in the present study is 18.7%. The aim of conservative treatment is to extend the latency period; however, prolongation of pregnancy carries several risks such as intra-amniotic infection, altered neonatal hemodynamic transition, and adverse neurodevelopmental results. In the present study, neonatal mortality rate is acceptable, only 7 cases had chorioamnionitis, and no maternal death from infection was observed.

The mean latency period was 16.03 days (median 7, min 1.0, max 55.0) in the PPROM group; 11 of these women (14.7%) gave birth immediately at the end of the first 24 h and 39 of them (52%) gave birth within the first week. A significant correlation was detected between the latency period, TOS (r: −0.377; $p = 0.001$), CRP (r: −0.263; $p = 0.022$), and white blood cell count (r: −0.423, $p = 0.0001$). In other words, infection and/or increases in oxidative stress lead to premature birth by reducing latency period. Since prematurity and the presence of infection are important factors increasing perinatal complications in PPROM, these factors should be controlled when developing therapeutic approach.

The limitation of the present study is the small sample size. In addition, the inadequate number of chorioamnionitis cases (only 7 women) was also a disadvantage for the study results. Moreover, the cross-sectional design limited our ability to deduce the association between PPROM and latency period, oxidative–antioxidative status, and inflammation markers.

## Conclusion

PPROM is an obstetric pathology which might have adverse perinatal outcomes. Women with PPROM should be evaluated carefully and the treatment should be tailored individually taking into consideration all the factors such as gestational week and infection signs of the patient. In women with PPROM, oxidative stress and infectious markers were found to be significantly higher. Latency period between membrane rupture and delivery is critical in those women and it was found to be inversely correlated with oxidative stress and infectious markers. In addition to standard treatment protocol, antioxidant vitamin C supplements administered in the last trimester might prevent the occurrence of oxidative stress in the mother and probably in the baby, and it can be an efficacious strategy in decreasing the incidence of PPROM or prolongation of latency period. However, the establishment of the effectiveness of this treatment strategy requires conducting larger scale, dose-dependent molecular studies.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflicts of interest.

**Ethical standard** The Institutional Ethics Committee for Research on Human Subjects of Firat University reviewed and approved this study, which has been conducted following Helsinki recommendations and European Union and Turkish regulations.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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