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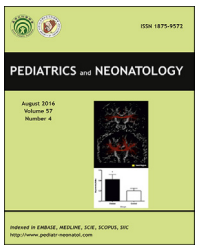

ORIGINAL ARTICLE

Neonatology Oxidative Status in Preterm Infants with Premature Preterm Rupture of Membranes and Fetal Inflammatuar Response Syndrome

Elif Özalkaya [a,*], Güner Karatekin [a], Sevilay Topçuoğlu [a], Hande Özgün Karatepe [a], Taner Hafızoğlu [b], Pervin Baran [c], Fahri Ovalı [d]

[a] *Neonatal Intensive Care Unit, Zeynep Kamil Maternity and Children Training and Research Hospital, İstanbul, Turkey*
[b] *Neonatal Intensıve Care Unit, Sakarya University, Sakarya, Turkey*
[c] *Departments of Biochemistry Laboratory, Ankara Ataturk Training and Research Hospital, Ankara, Turkey*
[d] *Neonatal Intensıve Care Unit, Istanbul Medeniyet University, Faculty of Medicine, Istanbul, Turkey*

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Background: The aim of this study, to determine an index of oxidative stress index in preterm infants less than 34 weeks gestational age with premature preterm rupture of membrane (PPROM) and fetal inflammatory response syndrome (FIRS).
Methods: This study was designed as a prospective study. Fifty-one premature infants less than 35 weeks of gestational age were included in the study. The umbilical cord blood concentrations of IL-6, TAC (total antioxidant capacity) and PON-1 (paraoxonase-1) levels and TOS (total oxidative stress) were studied. The oxidative stress index (OSI = TAC/TOS) was calculated in all of prematüre infants. PPROM was defined as rupture of membranes at least 24 hours before the onset of labor. FIRS was defined by an umbilical cord IL-6 level greater than 11 pg/mL. Premature infants included in the study were divided into 4 groups. Group 1 included preterm infants without FIRS and with PPROM ($n = 16$), while Group 2 included preterm infants without PPROM and with FIRS ($n = 9$), Group 3 consisted of premature infants with PPROM and FIRS ($n = 21$) and Group 4 included premature infants without PPROM or FIRS ($n = 5$).
Results: Umbilical cord TOS level was found to be higher in the preterm infants without FIRS and with PPROM (36.1 μmol H_2O_2 Equiv./L) compared to the preterm infants without PPROM or FIRS (11.9 μmol H_2O_2 Equiv./L) ($p = 0.03$). Umbilical cord PON-1 level was found to be lower

* Corresponding author. Zeynep Kamil Maternity and Children Training and Resarch Hospital, Zeynep Kamil Mahallesi, Burhanettin Ustünel Caddesi, Number 10, Istanbul 34668, Turkey.
E-mail address: elifozalkay@gmail.com (E. Özalkaya).

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in the preterms without FIRS and with PPROM (32 U/L), preterms without PPROM and with FIRS (30. 3 U/L) and the preterm infants with both PPROM and FIRS (48.6 U/L) compared to the preterm infants having no PPROM or FIRS (85.6 U/L) ($p = 0.001$).
Conclusion: High pro-oxidant capacity was found in PPROM and low antioxidant capacity in PPROM and FIRS.
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1. Introduction

Premature preterm rupture of membranes (PPROM) is defined as the rupture of the amniotic sac at least 24 hours before the onset of labor in preterm infants with a gestational age of < 37 weeks.[1] In 60–70% of cases, PPROM is associated with maternal inflammatory response syndrome (chorioamnionitis, microbial invasion of the amniotic cavity) and/or fetal inflammatory response syndrome (FIRS) (funisitis).[2,3] FIRS occurs due to activation of the innate immune system of the fetus with or without PPROM.[4] FIRS is defined either clinically by an umbilical cord blood concentration of IL-6 greater than 11 pg/mL or histologically by findings of funisitis.[5,6] PPROM is responsible for almost one-third of preterm births,[7] whereas FIRS is responsible for high morbidity and mortality among preterm infants.[8–10] Oxidative stress is defined as an increased pro-oxidant status due to an imbalance between pro-oxidant and antioxidant agents.[11,12] Premature aging of the fetal membranes due to increased oxidative stress may play a role in the pathophysiology of PPROM.[13,14] The involvement of oxidative stress in the pathogenesis of FIRS is unknown. Increased oxidative stress and lower antioxidant capacity have been reported in maternal blood and vaginal washing fluids in PPROM.[15,16] There are a limited number of studies on preterm infants which demonstrate the relationships between oxidative stress and either PPROM or FIRS. In this study, umbilical cord blood oxidative stress markers [total antioxidant status (TAS), total oxidative stress (TOS), paraoxonase-1 (PON-1)] were evaluated in preterm infants with PPROM and/or FIRS.

2. Methods

2.1. Patients and study design

In total, 5254 babies were born in Zeynep Kamil Maternity and Children Training and Research Hospital between August 2009 and January 2010, with 550 hospitalized in the neonatal intensive care unit and 154 born at less than 37 weeks' gestation. Of these, 63 preterm infants aged under 34 weeks' gestation were eligible for the study. IL-6 and/or oxidative stress markers were not studied in the umbilical cord blood samples collected from 12 preterm infants. Thus, 51 preterm infants aged under 34 weeks' gestation were included.

2.2. Definition

PPROM was defined by the occurrence of amniotic fluid leak more than 24 hours before the onset of labor. ROM was diagnosed by sterile speculum examination with a combination of vaginal pooling and nitrazine and ferning tests. FIRS was diagnosed by the finding of umbilical cord blood levels of IL-6 > 11 pg/mL.[6] Oligohydramnios was defined as an amniotic fluid index < 5 cm. Respiratory distress syndrome was diagnosed with the association of clinical presentation and characteristic radiological findings described by Giedion et al.[17] Bronchopulmonary dysplasia was diagnosed by an oxygen need at 36 weeks of postmenstrual age.[18] Retinopathy of prematurity was defined according to The International Classification of Retinopathy of Prematurity.[19] Early onset neonatal sepsis was defined as any systemic bacterial infection documented by a positive blood culture and the presence of symptoms or clinically highly suspected sepsis (presence of symptoms and elevated C-reactive protein and/or affected white blood cell count) during the first 72 hours of life. Intraventricular hemorrhage was diagnosed by ultrasonography and classified as described by Volpe.[20] In our clinic, transcranial ultasound of premature patients with the birth weight < 1500 g is routinely obtained in the 1st, 3rd, and 7th days of life.

2.3. Blood sampling and biochemical studies

2.3.1. Cord blood concentrations of total antioxidant capacity (TAC, mmol trolox equiv/L), TOS (μmol H_2O_2 equiv/L), PON-1 (U/L), IL-6 (pg/mL)

Samples (2 mL) of umbilical cord blood were drawn into the tubes with EDTA following birth. Blood samples were centrifuged for 3 minutes at 5000 rpm, and plasma samples were stored at −80°C. Serum TAC and TOS levels were measured, as described by Erel.[21] Erel's method for serum TAC level measurement is based on the bleaching of the characteristic color of a more stable 2,2,2-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid) radical cation by antioxidants. The results were expressed in mmol trolox equivalents/L. Erel's TOS measurement is based on the oxidation of ferrous ion to ferric ion in the presence of various oxidative species and the measurement of the ferric ion by xylenol orange. The results were expressed in mmol H_2O_2 equivalents/L. Oxidative stress index [arbitrary unit = TOS (μmol H_2O_2 equiv/L) / TAC (mmol trolox equiv/L)] was calculated as the percent ratio of TOS to TAC.[22] PON-1 (U/L) activity was measured spectrophotometrically

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by a modified Eckerson method.[23] The quantitative cytokine (IL-6) studies were performed using the commercial ELISA kits (RayBio® Human IL-6) and Immunite 100 analyzer (Siemens, The IMMULITE® 1000 system) in Istanbul University, Cardiology Institute, Department of Immunology Statistics.

2.4. Data analysis

During the assessment of the data obtained in the study, SPSS version 15 (SPSS Inc., Chicago, IL, USA) program was used for statistical analysis. Median values of nonparametric tests were reported with minimum and maximum values. Non-normally distributed numerical and ordinal variables were compared using the Mann–Whitney U test. Student *t* test was used for the comparison of parametric variables. Chi-square test was used to compare the categorical variables. Analysis of variance test was used to compare mean values among more than two groups.

3. Results

In total, 51 preterm infants included in the study were divided into four groups according to the presence of PPROM and/or FIRS. Preterm infants with PPROM but without FIRS constituted Group 1 ($n = 16$), preterm infants with FIRS but without PPRROM constituted Group 2 ($n = 9$), preterm infants with both FIRS and PPROM constituted Group 3 ($n = 21$), and preterm infants without FIRS and PPROM constituted Group 4 ($n = 5$). When demographics of the groups were compared, birth weight was found to be lower in preterms with FIRS and PPROM (Group 3) than in those with PPROM (Group 1) and those without FIRS and PPROM (Group 4) ($p = 0.04$ and 0.03; respectively); gestational week was lower in the preterms with FIRS and PPROM (Group 3) than in preterms without FIRS and PPROM (Group 4) ($p = 0.03$). No statistically significant difference was found among the groups in terms of sex, Cesarean delivery and antenatal steroids and oligohydroaminos or anhydramnios incidence (Table1). When preterm morbidity was evaluated, the incidence of respiratory distress syndrome was found to be higher in preterms with FIRS and PPROM (Group 3) than in preterms with PPROM (Group 1) ($p = 0.001$); the incidence of mortality was higher in preterms with FIRS (Group 2) than in preterms with PPROM (Group 1) ($p = 0.04$). There were no statistically significant differences among the groups in terms of the incidence of intrventricular hemorrhage, bronchopulmonary dysplasia, and retinopathy of prematurity (Table 2). Umblical cord TOS level was found to be higher in preterms with PPROM (Group 1) than in preterms without PPROM and FIRS (Group 4) ($p = 0.05$). Umbilical cord PON-1 level was found to be lower in preterms with PPROM (Group 1), preterms with FIRS (Group 2), and preterms with both PPROM and FIRS (Group 3) than in preterms without PPROM and FIRS (Group 4) ($p = 0.001$). No statistically significant difference was found among the groups in terms of umbilical cord levels of TAC and oxidative stress index (Table 3).

4. Discussion

In our study, we demonstrated that umbilical cord prooxidant (TOS) level was high and antioxidant capacity (PON-1) was low in preterm infants with PPROM, whereas antioxidant capacity (PON-1) was low in preterm infants with FIRS and those with both FIRS and PPROM. Our study is the second to evaluate the relationship between FIRS and cord oxidative stress. The small number of patients and lack of histologic definition of FIRS limit the study.

In a study by Musilova et al,[24] oxidative stress markers were found in the cord blood of the preterm infants with PPROM, whereas in a study by Kaceverosky et al,[25] oxidative stress markers were not found in the amniotic fluid. In the present study, we found high cord levels of TOS in preterms with PPROM and low cord levels of PON-1 in preterm infants with PPROM and FIRS. Our result supports the thesis that oxidative stress is responsible for the premature aging of the fetal membranes, especially in PPROM occuring before 34 weeks of gestation.[13,14,26,27] The number of studies investigating whether FIRS is accompanied by oxidative stress is insufficient. A majority of the previous studies evaluated the relationship of histologic chorioamnionitis and microbial invasion of amniotic cavitiy (MIAC) with oxidative stress. Soydinç et al[16] found high

Table 1 Demographic data of the preterms of Groups 1, 2, 3, and 4.

	Group 1: With PPROM $N = 16$	Group 2: With FIRS $N = 9$	Group 3: With PPROM and FIRS $N = 21$	Group 4: Without PPROM and FIRS $N = 5$	*p*
Birth weight	1555.94 (750–2210)	1230.33 (580–2940)	1076 (640–2310)	1809 (1500–2340)	0.008 (a = 0.04, b = 0.03)
Birth week	30.4 (26–34)	27.9 (23–34)	27.8 (23–34)	32 (31–33)	0.007 (b = 0.03)
Male	6 (37.5)	1 (11.1)	12 (57.1)	4 (80)	0.04
C/S	3 (18.7)	2 (22.2)	3 (14.2)	0	0.71
Antenatal steroid	10 (62.5)	6 (66.6)	10 (47.6)	3 (60)	0.92
Oligohydroamnios	2 (12.5)	1 (11.1)	4 (19)	0	0.71
Anhydroamnios	0	0	5 (23.8)	0	0.04

FIRS = fetal inflammatory response syndrome; PPROM = premature preterm rupture of membranes.
a: Group 1 vs. Group 3; b: Group 3 vs. Group 4; c: Group 1 vs. Group 2; d: Group 1 vs. Group 4; e: Group 2 vs. Group 4.
Data are presented as *n* (%) or median (range).

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Table 2 Preterm morbidites of the preterms in Groups 1, 2, 3, and 4.

	Group 1:With PPROM $N = 16$	Group 2:With FIRS $N = 9$	Group 3:With PPROM and FIRS $N = 21$	Group 4:Without PPROM and FIRS N = 5	p
RDS	3 (18.7)	5 (55.5)	18 (85.7)	2 (40)	0.001 (a = 0.001)
BPD	0	0	3 (14.2)	0	0.20
ROP	1 (6)	1 (11.1)	6 (28.5)	0	0.53
EONS	13 (81.2)	5 (55.5)	10 (47.6)	1 (20)	0.06
IVH	0	3 (33.3)	2 (9.5)	0	0.2
Mortality	0	4 (44.4)	7 (33.3)	0	0.01 (c = 0.04)

BPD = bronchopulmonary dysplasia; EONS = early onset neonatal sepsis; FIRS = fetal inflammatory response syndrome; IVH = intraventricular hemorrhage; PPROM = premature preterm rupture of membranes; RDS = respiratory distress syndrome; ROP = retinopathy of prematurity.
a: Group 1 vs. Group 3; b: Group 3 vs. Group 4; c: Group 1 vs. Group 2; d: Group 1 vs. Group 4; e: Group 2 vs. Group 4.
Data are presented as *n* (%).

Table 3 Umblical cord blood TAC, TOS, PON-1 concentrations in Groups 1, 2, 3, and 4.

	Group 1: With PPROM $N = 16$	Group 2: With FIRS $N = 9$	Group 3: With PPROM and FIRS $N = 21$	Group 4: Without PPROM and FIRS $N = 5$	p
TAC (mmol trolox equiv/L)	2.9 (2–5)	3.2 (2–5)	3.2 (2–6)	3.2 (1–4)	0.84
TOS (μmol H_2O_2 equiv/L)	36.1 (6–94)	25.6 (5–75)	24.9 (8–50)	11.9 (4–15)	0.03 d = 0.05
PON-1 (U/L)	32 (7–87)	30.3 (5–52)	48.6 (23–90)	85.6 (35–112)	0.001 b = 0.007 d = 0.001 e = 0.001
OSI	1.2 (0.3–3.1)	0.79 (0.25–1.87)	0.82 (0.02–2.5)	0.41 (0.35–0.60)	0.07

FIRS = fetal inflammatory response syndrome; OSI = oxidative stres index; PON-1 = paraoxonase-1; PPROM = premature preterm rupture of membranes; TAC = total antioxidant capacity; TOS = total oxidative stress.
a: Group 1 vs. Group 3; b: Group 3 vs. Group 4; c: Group 1 vs. Group 2; d: Group 1 vs. Group 4; e: Group 2 vs. Group 4.
Data are presented as median (range).

levels of oxidative stress markers in the maternal plasma and vaginal fluid in chorioamnionitis.[16,17] Kacerovsky et al[25] found no relationship between MIAC and histologic chorioamnionitis and oxidative stress markers, and Musilova et al[24] found no relationship among MIAC, histologic chorioamnionitis and funisitis, and oxidative stress markers. In our study, cord levels of PON-1 were demonstrated to be lower in preterms with FIRS and in those with both FIRS and PPROM. The only study to evaluate cord oxidative stress in FIRS is the study conducted by Musilova et al.[24] Musilova et al[24] concluded that oxidative stress, which was not increased in funisitis, did not play a primary role in FIRS. According to Musilova et al,[24] FIRS is secondary to microbial invasion and infection that develop after PPROM, which results in initially increased oxidative stres. Preterm infants without PPROM may be born with FIRS, as shown in our study and the previous studies.[28,29] FIRS develops with the activation of the natural immune system of the fetus. The natural immune system of the fetus can be activated through numerous mechanisms other than infections. In our study, lower cord PON-1 levels found in the preterm infants with FIRS but without PPROM suggested that increased oxidative stress may have a role in the activation of the natural immune system of the fetus.

5. Conclusion

In this study, oxidative stress was found to be associated with PPROM and FIRS.

Conflicts of interest

The authors declare no conflict of interest.

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References

1. Caughey AB, Robinson JN, Norwitz ER. Contemporary Diagnosis and management of preterm premature rupture of membranes. *Rev Obstet Gynecol* 2008;**1**:11–22.
2. Cobo T, Kacerovsky M, Palacio M, Hornychova H, Hougaard DM, Skogstrand K, et al. A prediction model of histological chorioamnionitis and funisitis in preterm prelabor rupture

of membranes: analyses of multiple proteins in the amniotic fluid. *J Matern Fetal Neonatal Med* 2012;**25**: 1995–2001.
3. Tsiartas P, Kacerovsky M, Musilova I, Homychova H, Cobo T, Sävman K, et al. The association between histological chorioamnionitis, funisitis and neonatal outcome in women with preterm prelabor rupture of membranes. *J Matern Fetal Neonatal Med* 2013;**26**:1332–6.
4. Gotsch F, Romero R, Kusanovic JP, Mazaki-Tovi S, Pineles BL, Erez O, et al. The fetal inflammatory response syndrome. *Clin Obstet Gynecol* 2007;**50**:652–83.
5. Pacora P, Chaiworapongsa T, Maymon E, Kim YM, Gomez R, Yoon BH, et al. Funisitis and chorionic vasculitis: the histological counterpart of the fetal inflmmatory response syndrome. *J Matern Fetal Neonatal Med* 2002;**11**: 18–25.
6. Gomez R, Romero R, Ghezzi F, Yoon BH, Mazor M, Berry SM. The fetal inflammatory response syndrome. *Am J Obstet Gynecol* 1998;**179**:94–202.
7. Mercer B. Premature rupture of the membranes. *Clin Obstet Gynecol* 2011;**54**:305–6.
8. Yoon BH, Romero R, Kim KS, Park JS, Ki SH, Kim BI, et al. A systemic fetal inflammatory response and the development of bronchopulmonary dysplasia. *Am J Obstet Gynecol* 1999;**181**: 773–9.
9. Yoon BH, Romero R, Yang SH, Jun JK, Kim IO, Choi JH, et al. Interleukin-6 concentrations in umbilical cord plasma are elevated in neonates with white matter lesions associated with periventricular leukomalacia. *Am J Obstet Gynecol* 1996;**174**: 1433–40.
10. Ramaswamy V, Horton J, Vandermeer B, Buscemi N, Miller S, Yager J. Systematic review of biomarkers of brain injury in term neonatal encephalopathy. *Pediatr Neurol* 2006;**40**: 215–26.
11. Al-Gubory KH, Fowler PA, Garrel C. The roles of cellular reactive oxygen species, oxidative stress and antioxidants in pregnancy outcomes. *Int J Biochem Cell Biol* 2010;**42**: 1634–50.
12. Agarwal A, Gupta S, Sharma RK. Role of oxidative stress in female reproduction. *Reprod Biol Endocrinol* 2005;**3**:28.
13. Menon R, Yu J, Basanta-Henry P, Brou L, Berga SL, Fortunato SJ, et al. Short fetal leukocyte telomere length and preterm prelabor rupture of the membranes. *PLoS One* 2012;**7**: e31136.
14. Menon R. Oxidative stress damage as a detrimental factor in preterm birth pathology. *Front Immunol* 2014;**5**:567.
15. Soydinç HE, Sak ME, Evliyaoğlu O, Evsen MS, Turgut A, Özler A, et al. Prolidase, matrix metalloproteinases I and 13 activity, oxidative-antioxidative status as a marker of preterm premature rupture of membranes and chorioamnionitis in maternal vaginal washing fluids. *Int J Med Sci* 2013;**10**: 1334–51.
16. Soydinç HE, Sak ME, Evliyaoğlu O, Evsen MS, Turgut A, Ozler A, et al. Maternal plasma prolidase, matrix metalloproteinases 1 and 13, and oxidative stress levels in pregnancies complicated by preterm premature rupture of the membranes and chorioamnionitis. *J* Turk Ger *Gynecol Assoc* 2012;**13**:172–7.
17. Giedion A, Haefliger H, Dangel P. Acute pulmonary x-ray changes in hyaline membrane disease treated with artifical ventilation and positive end-expiratory pressure (PEP). *Pediatr Radiol* 1973;**1**:145–52.
18. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001;**163**:1723–9.
19. An international classification of retinopathy of prematurity. The Committee for the Classification of Retinopathy of Prematurity. *Arch Ophthalmol* 1984;**102**:1130–4.
20. Volpe JJ. Hypoxic-ischemic encephalopathy: clinical aspects. In: *Neurology of the Newborn*. Philadelphia: WB Saunders; 2001. p. 331–94.
21. Erel O. A new automated colorimetric method for measuring total oxidant status. *Clin Biochem* 2005;**38**:1103–11.
22. Erel O. A novel automated direct measurement method for total antioxidant capacity using a new generation, more stable ABTS radical cation. *Clin Biochem* 2004;**37**:277–85.
23. Eckerson HW, Wyte CM, La Du BN. The human serum paraoxonase/arylesterase polymorphism. *Am J Hum Genet* 1983; **35**:1126–38.
24. Musilova I, Tothova L, Menon R, Vlkova B, Celec P, Hornychova H, et al. Umbilical cord blood markers of oxidative stress in pregnancies complicated by preterm prelabor rupture of membranes. *J Matern Fetal Neonatal Med* 2016;**29**:1900–10.
25. Kacerovsky M, Tothova L, Menon R, Vlkova B, Musilova I, Hornychova H, et al. Amniotic fluid markers of oxidative stres in pregnancies complicated by preterm prelabor rupture of membranes. *J Matern Fetal Neonatal Med* 2014;**27**:1–10.
26. Ilhan N, Celik E, Kumbak B. Maternal plasma levels of interleukin-6, C-reactive protein, vitamins C, E and A, 8-isoprostane and oxidative status in women with preterm premature rupture of membranes. *J Matern Fetal Neonatal Med* 2015;**28**:316–9.
27. Lam-Rachlin J, Romero R, Korzeniewski SJ, Schwartz AG, Chaemsaithong P, Hernandez-Andrade E, et al. Infection and smoking are associated with decreased plasma concentration of the anti-aging protein, α-klotho. *J Perinat Med* 2013;**41**: 581–94.
28. Liu Z, Tang Z, Li J, Yang Y. Effects of placental inflammation on neonatal outcome in preterm infant. *Pediatr Neonatol* 2014; **55**:35–40.
29. Choi J, Park JW, Kim BJ, Choi YJ, Hwang JH, Lee SM. Funisitis is more common in cervical insufficiency than in preterm labor and preterm premature rupture of membranes. *J Perinat Med* 2016;**44**:523–9.

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