



ARAŞTIRMA / RESEARCH

Evaluation of the delivery time and adverse neonatal outcomes in urinary culture-positive preterm delivery and preterm premature rupture of membranes

İdrar kültürü pozitif erken doğum ve erken membran rüptüründe doğum süresi ve olumsuz neonatal sonuçların değerlendirilmesi

Sibel Özler¹; Efser Oztaş²; Derya Solmaz³; Basak G Güler⁴; Ali Özgür Ersoy⁵; Ali T. Çağlar⁵; Nuri Danişman⁶

¹Selcuk University Medical School, Department of Perinatology, Konya, Turkey

²Eskisehir State Hospital, Department of Perinatology, Eskisehir, Turkey

³Zekai Tahir Burak Women's Health Education and Research Hospital, Dept. of Gynecology and Obstetrics, Ankara, Turkey.

⁴Istinye University, Department of Gynecology and Obstetrics, Istanbul, Turkey

⁵Zekai Tahir Burak Women's Health Education and Research Hospital, Department of Perinatology, Ankara, Turkey.

⁶Acıbadem University, Department of Perinatology, Istanbul, Turkey

Cukurova Medical Journal 2020;45(1):39-47.

Abstract

Purpose: We aimed to investigate the relationship between adverse neonatal outcomes and the time period of labor in between urinary tract infection in preterm premature rupture of membranes (PPROM) to preterm labor (PL).

Materials and Methods: We evaluated a total number of 1033 pregnant patients who admitted to our center between 2008 and 2014, with retrospective analysis. Study groups consisted of 446 PPRM and 587 PL patients who had urine cultures.

Results: We determined cervical lengths which were measured by transvaginal ultrasonography, with OR = 0.806 and amniotic fluid index (AFI), OR = 0.961 in PPRM group, which had positive urine culture, and also cervical length OR = 0.862 in PL group which had positive urine culture and to be associated with shorter than seven days of delivery. Additionally, we determined that only the AFI, with OR= 0.982, to be associated with adverse neonatal outcomes in the PPRM group, having positive urine culture.

Conclusion: AFI and cervical length can also be used to predict adverse neonatal outcomes and time of delivery in urine culture positive PPRM and PL patients.

Keywords: Preterm premature rupture of membranes; preterm birth; urinary system infection.

Öz

Amaç: Preterm erken membran rüptüründe (PPROM) ve preterm doğumda (PD) idrar yolu enfeksiyonunun olumsuz neonatal sonuçları ve doğum süresine ile arasındaki ilişkinin araştırılmasını amaçladık.

Gereç ve Yöntem: 2008-2014 yılları arasında merkezimize başvuran 1033 gebe hastayı retrospektif olarak değerlendirdik. Çalışma grupları 446 PPRM ve 587 PD hastasından oluşuyordu.

Bulgular: İdrar kültürü pozitif PPRM hastalarında transvajinal ultrasonografi ile ölçülen servikal uzunluk (OR = 0.806,) ve amniyon sıvısı indeksi (AFI), (OR = 0.961) ve idrar kültürü pozitif PD hastalarında sadece servikal uzunluk OR = 0.862 doğum süresinin yedi günden daha kısa olacağı ile ilişkili idi. Ayrıca idrar kültürü pozitif olan PPRM grubunda AFI'nin (OR = 0.982) olumsuz neonatal sonuçlarla ilişkilendirileceğini belirledik.

Sonuç: İdrar kültürü pozitif PPRM ve PD hastalarında olumsuz neonatal sonuçları ve doğum zamanını öngörmeye AFI ve servikal uzunluk da kullanılabilir.

Anahtar kelimeler: Preterm membranların erken rüptürü; erken doğum; gebelikte üriner sistem enfeksiyonu.

Yazışma Adresi/Address for Correspondence: Dr. Sibel Özler, Selcuk University Medical School, Department of Perinatology, Konya, Turkey E-mail:sibel2ozler@gmail.com

Geliş tarihi/Received: 30.09.2019 Kabul tarihi/Accepted: 24.12.2019 Published online: 15.01.2020

INTRODUCTION

The urinary system is the most common system getting infected during pregnancy due to the hormonal changes resulting in dilation in it, and delay in the emptying of the system because of the increasing pressure on the ureters in advancing gestational weeks^{1,2}. Urinary system infections are observed in 20 % of all pregnancies^{3,4}. Asymptomatic bacteriuria (ASB), acute cystitis, and acute pyelonephritis are the types of urinary system infections, seen during pregnancy⁵. ASB has a 6 % recurrence rate, and 40% of the patients having a recurrence, develop acute pyelonephritis⁶. American College of Obstetricians and Gynecologists (ACOG), recommend taking spot urinary samples from all of the pregnant and advice taking a urinary culture from the ones having positivity for infection⁷.

Acute pyelonephritis may end in serious maternal complications like maternal septic shock, respiratory insufficiency due to pulmonary edema, disseminated intravascular coagulation, and acute renal failure⁸. From 20% to 50 % of it is also associated with preterm labor (PL), the incidence of which is 5-8% worldwide^{9,10}. Premature birth is the leading cause of perinatal morbidity and mortality¹¹. Four mechanisms are accused of playing a role in the development of PL, which are activation of the maternal-fetal hypothalamic-hypophysial tract; infection or inflammation of the genitourinary system; overdistension of the uterus; and ablation of placenta. In these four mechanisms, the one most frequently seen, and most suspected is the infection/inflammation of the genitourinary system. Wing et al. showed increased PL incidence in the patients having acute pyelonephritis⁹. Kasset al. reported 10- 20 % decrease in PL in the patients having ASB, after antibiotic treatment¹².

Preterm premature rupture of the membranes (PPROM) remains the leading cause of preterm deliveries and neonatal mortality and morbidity. <34 weeks in women with PPRM, clinical chorioamnionitis occurred in 17.8% of the pregnancies. Neonatal mortality was 7.4%, and the rate of NICU admission was 72.9%¹³. In addition, the risk of periventricular leukomalacia, early neonatal bacterial infection, bronchopulmonary dysplasia or cerebral palsy increases in PPRM cases compared to preterm delivery¹⁴.

In this study, we aimed to investigate the relationship between urinary system infection and the delivery

time and adverse pregnancy outcomes, in the patients who had PL and preterm premature rupture of membranes (PPROM).

MATERIALS AND METHODS

A total of 1033 inpatients, who admitted to our perinatology clinic between 2010 and 2014, having PL and PPRM were included in the research, and their urinary culture results were studied retrospectively.

Of the patients, 466 had PPRM, whereas 587 of them had PL. The patients of the PL group had 80 % cervical effacement and/ or 2 cm or more cervical dilation accompanied with four uterine contractions in 20 minutes or 8 in 60 minutes, having total amplitudes more than 120 Montevideo units¹⁵. The patients in the PPRM group were confirmed to have amniotic fluid leakage in the examination with the sterile speculum.

All patients in the study group were measured for fetal biometric parameters, with the help of Toshiba Aplio 500; amniotic fluid indexes (AFI) were calculated after measurement in every four chambers. Cervical length for each patient was measured via transvaginal sonography in the sections covering 75% of the screen and in which internal os, external os, cervical canal, and endocervical canal were seen all together.

The infection parameters for all of the patients were analyzed via white blood cell count (WBC), neutrophil count, neutrophil/ lymphocyte ratio (NLR), and C-reactive protein (CRP) in our laboratory, with Beckman Coulter (High Wycombe, UK) Gen-S. Urine culture was obtained from pregnant women with pyuria, bacteriuria, or nitrite in the spot urine analysis. Mid urine samples were used for urine cultures, and the results which had more than 10⁵ colonies/mL were accepted as positive.

Prophylactic antibiotic treatment was applied to all patients with diagnosis of PPRM, and PL, after samples for urine cultures were taken. The treatment strategy was changed due to the exact pathogen after a positive culture, and prophylactic regimen was stopped if the patient had a negative culture.

The study protocol was performed according to the principles of the Declaration of Helsinki and approved by the local ethical committee of Zekai Tahir Burak Women's Health Education and

Research Hospital. [approval date / number: 24.03.2014/39].

In our study, we used the clinic, ultrasonographic, and laboratory data, which were collected at the beginning of the hospitalization of the patients. Neither the cervical-vaginal or urinary cultures, nor the spot urine samples were taken during the hospitalization period were included in the study. Cervical-vaginal cultures were collected during their hospitalization period. The patients having urinary catheters, having respiratory system infections, abscess of Bartholin's gland or a dental abscess were also excluded.

Presence of one of the following criteria was accepted as an adverse neonatal outcome: 1) APGAR score < 7 in 5 minutes, 2) pH of blood sampled from umbilical artery < 7.0, 3) need for intubation in the first 24 hours after delivery, 4) meconium aspiration, 5) presence of hypoglycemia, hyperbilirubinemia, hypothermia, intraventricular hemorrhage, necrotizing enterocolitis, seizures, sepsis, respiratory distress syndrome, and neonatal death in the first 28 days postpartum¹⁶.

Vital parameters for all of the patients were recorded with simultaneous fetal monitorization results. Betamethasone treatment (2x 12mg, intramuscular injection, 24 hours apart) for fetal pulmonary maturation and tocolysis with nifedipine (3x 10mg, bolus, and per-oral, in every 20 minutes in the first hour, then 4x20 mg for the continuum per-oral) were applied to all patients.

Statistical analysis

Data analysis was done with SPSS 17 (SPSS Inc., Chicago, IL, United States). The mean of the variables, with 95% confidence interval (CI), count of the patients and the percentage of the data were used. The Kolmogorov-Smirnov test was used to determine whether the distributions of continuous variables were normal; the Levene's test evaluated the homogeneity of variances. Continuous variables were shown as mean \pm standard deviation (SD) or median (min-max), where applicable. While the Student's t-test compared the mean differences between case and control groups, otherwise, the Kruskal-Wallis test was applied for comparisons of the median values, and the Pearson's Chi-Square test analyzed nominal data. Multivariate logistic regression analysis was used to determine a relationship between adverse neonatal outcomes and laboratory, clinical and

ultrasonographic parameters.

Also, Logistic regression analyses were used to evaluate the labor period lasting less than 7 days in each PL and PPRM groups. Pearson's correlation and Spearman's rho tests were used to examining the correlations of variables. The data were reviewed at the 95% confidence level, and a p-value of <0.05 was considered significant.

RESULTS

A total of 1033 patients, having the diagnosis of PL or PPRM were included in the study. Of those, 446 were in the PPRM group, and 587 of them were in the PL group. Each group was sub-grouped into two, as having a positive urine culture and not. One hundred and sixteen (26%) patients of the PPRM group and 128 (21.8%) patients of the PL group had positivity in their cultures; whereas 330 (74%) patients of the PPRM group and 459 (78.2%) of the PL group did not. The subgroups did not differ in terms of age, gravity, body mass index (BMI), smoking, weight gained during pregnancy, the week in which labor started, birth week and birth weight. Besides, there was not a significant difference in the AFI and cervical lengths of the PPRM and PL patients, who have positivity in their urine cultures and who did not (Table 1).

The PL and PPRM patients who had positive urine cultures and who did not were divided into six subgroups according to the time period passed from the beginning of the labor process to the delivery time as first 24 hours, 1-3 days, 4-7 days, 8- 15 days, 16-21 days and more than 21 days. There was not a significant difference between these groups in the time period lasting till the delivery (Table 1).

In the PPRM group, the subgroup having positive urine culture was examined for the spot urine analyses. Twenty-three patients (19.82%) had normal results, whereas 29 of them (25%) had bacteria and 39 of them (33.64%) had leucocyte. The urine culture negative subgroup of the PPRM group included 153 patients (46.36%) having normal results; 42 patients (12.72%) having bacteria and 67 patients (20.32%) having leucocyte. The urine culture positive and negative subgroups were significantly different for these urine parameters ($p < 0.001$); whereas they did not differ for nitrite and protein levels (Table 2). In the PL group, the spot urine analyses for culture-positive and negative subgroups were as follows: nitrite positivity in 11 (8.7%)/ 15 (3.27%) patients;

bacteria in 40 (31.24%)/ 78 (16.97%) patients, and leucocyte in 41(32%)/ 90 (19.6%) patients respectively. There was statistically significant difference between the groups (p<0.001). In the PL group, 22 patients (17.18%) of the culture-positive

group and 208 patients (45.32%) of the culture-negative group had normal spot urine analyses; which was significantly lower in the culture-positive group (p< 0.001) (Table 2).

Table1. Comparison of demographic and ultrasonographic parameters of PPRM and PL groups

	PPROM n= 446			PL n= 587		
	Positive Urine Culture n=116 (26 %)	Negative Urine Culture n=330 (74 %)	p value	Positive Urine Culture n=128 (21.8%)	Negative Urine Culture n=459 (78.2%)	p value
Age (year)*	27.00 ± 5.76	28.53 ± 6.27	NS	26.15 ± 5.98	26.54 ± 5.95	NS
Gravidy(n)**	1.92 [1-4]	2.25 [1-7]	NS	1.96 [1-8]	2 [1-8]	NS
Body Mass Index (BMI)*	28.34 ± 5.39	29.36 ± 5.41	NS	28.86 ± 4.75	29.49 ± 7.93	NS
Weight Gained During Pregnancy (kg) *	10.47 ± 4.29	11.38 ± 4.78	NS	11.51 ± 3.62	12.57 ± 4.81	NS
Smoking (n)***	19 (48.73 %)	76 (19.7 %)	NS	37(82.2%)	177 (85.9%)	NS
Start of Labor (Week)**	30.15 (24.86-36.81)	30.62 (24.00-37.00)	NS	30.73(26.71-36.14)	31.26 (24.28-36.57)	NS
Cervical Length (mm)*	28.48 ± 10.90	27.54 ± 10.45	NS	29.83 ± 11.05	29.27 ± 11.13	NS
Amniotic Fluid Index (AFI)*	60.81 ± 38.03	61.76 ± 33.46	NS	110.34 ± 24.38	110.82 ± 9.85	NS
Week of Delivery**	32.95 [24.28-40.23]	33.20 [33.86-41.57]	NS	35.20[22.43-41.28]	35.64 [22.28-41.28]	NS
Time Period Up To Delivery ***	first day	29 (18.12%)	NS	21(16.5%)	77 (18.27%)	NS
	2-3 days	18 (15.51 %)		19(14.8%)	42 (10.6%)	
	4-7 days	22 (18.96 %)		19 (14.8 %)	72 (18.59%)	
	8-15 days	9 (7.75 %)		15 (11.7%)	56(13.7%)	
	15-21 days	12 (10.34 %)		16 (12.5%)	47 (10.23%)	
	>21 days	26 (22.41 %)		75 (22.72 %)	38 (29.7%)	
Birth Weight (g)*	1972.46 ± 770.39	2107.94 ± 849.97	NS	2461.17 ± 856.11	2639.69 ± 852.768	NS

Results were analyzed by independent sample t-test, Kruskal Wallis Test, Nonparametric Post-hoc Test. * Mean ± SD, **; Median [min-max] ***; Pearson's chi-square test analyzed nominal data. A p value< 0.05 is considered as statistically significant. NS: nonsignificant. BMI; Body Mass Index.

Table 2.Comparison of laboratory data of the PPRM and PL groups

	PPROM n= 446			PL n= 587			
	Urine culture positive n=116 (26 %)	Urine culture negative n=330 (74 %)	p value	Urine culture positive n=128 (21.8%)	Urine culture negative n=459 (78.2%)	p value	
Microscopy of spot urine sample***	Normal	23 (19.82%)	<0.001	22 (17.18%)	208(45.32%)	<0.001	
	Nitrite	8 (6.89%)		11 (8.7%)	15 (3.27%)		
	Bacteria	29 (25%)		42 (12.72%)	40 (31.24%)		78 (16.97%)
	Leukocyte	39 (33.64 %)		67 (20.32 %)	41 (32%)		90(19.6%)
	Protein	17 (14.65 %)		48 (14.54 %)	14(10.9%)		68(14.81%)
White Blood Cell Count (WBC) (10 ³ /mm ³)*	13.09 ± 3.88	11.73 ± 3.55	0.024	12.86 ± 4.22	12.00 ± 3.85	NS	
Neutrophil (10 ³ /mm ³) *	10.37 ± 3.82	9.05 ± 3.40	0.024	10.06 ± 4.12	9.24 ± 3.68	NS	
Lymphocyte(10 ³ /mm ³)*	1.83 ± 0.61	1.83 ± 0.63	NS	1.80 ± 0.75	1.84 ± 0.67	NS	
MPV (fl)*	9.82 ± 0.93	10.07 ± 0.90	NS	10.16 ± 1.12	10.05 ± 0.95	NS	
PDW (%)*	11.84 ± 2.04	12.45 ± 2.25	NS	12.12 ± 2.56	12.18 ± 2.34	NS	
PLCR (pg/mL)*	24.65 ± 6.68	25.94 ± 6.41	NS	25.98 ± 7.64	26.67 ± 17.87	NS	
m-CRP (mg/mL)**	96.77[0.29-225.27]	97.09 [0.20-87.71]	NS	35.54[0.28-208.25]	27.82 [0.26-256.27]	NS	
Sedimentation (mm/hr)**	18.23 [6-48]	12.0 [10-28]	NS	49.16 ± 18.08	43.28 ± 19.15	NS	
Neutrophil/ lymphocyte ratio*	6.85 ± 4.65	5.59 ± 3.23	0.038	7.41[1.57-24.95]	4.32[1.40-30.28]	NS	

Results were analyzed by independent sample t-test, Kruskal Wallis Test, Nonparametric Post-hoc Test. * Mean ± SD, **; Median [min-max] ***; nominal data were analyzed by Pearson's chi-square test. A p value< 0.05 is considered as statistically significant. Statistically significant p values are marked as bold in table. NS: nonsignificant. WBC; white blood cell,MPV; mean platelet volume, PDW; platelet distribution width, Plcr; platelet large cell ratio, m-CRP; C-reactive protein.

The hematologic inflammation parameters were compared in the PPRM and PL groups. The results of PPRM patients having positive and negative urine culture results were as follows: WBC $13.09 \pm 3.88/ 11.73 \pm 3.55 \text{ mm}^3$, neutrophil count $10.37 \pm 3.82/9.05 \pm 3.40$, and NLR $6.85 \pm 4.65/ 5.59 \pm 3.23$ respectively. The inflammatory parameters were significantly higher in the culture-positive PPRM patients than the culture-negative group ($p=0.024$,

$p=0.024$, and $p=0.038$, respectively) (Table 2). In the PPRM group, 75% of the culture-positive patients had infection with *Escherichia coli*, 16.7% with *Klebsiella pneumoniae*, 8.3% with *Klebsiella oxytoca*; whereas 75% of the culture-positive patients of the PL group had infection with *Escherichia coli*, 16.7% with *Klebsiella pneumoniae*, 4.2% with *Proteus mirabilis*, and 4.2% with *Staphylococcus aureus* (Table 3).

Table 3. The distribution of bacteria types produced in the urine cultures of PPRM and PL patients

Pathogen	PPROM	PL
<i>Escherichia coli</i>	75.0 %	75.0%
<i>Klebsiella pneumoniae</i>	16.7 %	16.7 %
<i>Proteus mirabilis</i>	0 %	4.2 %
<i>Klebsiella oxytoca</i>	8.3 %	0 %
<i>Staphylococcus aureus</i>	0 %	4.2 %

We evaluated the PPRM and PL patients who had positive urine cultures with logistic regression analyses to detect the factors predicting delivery to happen within seven days. We calculated the OR= 0.806 (95% CI= 0.705- 0.922, $p=0.002$) for cervical length, measured with transvaginal ultrasonography; and OR= 0.961 (95% CI= 0.932- 0.990, $p= 0.01$) for decrease in AFI; and demonstrated these two as the risk factors affecting delivery to happen within 7 days, after the labor process had started, in the culture-positive- PPRM group (Table 4). On the other hand, only the shortening in the cervical length was found to be a risk factor affecting delivery to happen

within seven days after the start of the labor, in the culture-positive group; with OR= 0.862 (95%CI= 0.795-0.934, $p<0.001$) (Table 5).

With the logistic regression analyses done to detect factors predicting adverse neonatal outcome in the culture-positive- PPRM and PL groups, we observed that a decrease in AFI was the only risk factor for the adverse neonatal outcome in the PPRM group [OR = 0.982 (95% CI=0.962-1.003, $p =0.028$)] (Table 6); whereas none of the clinical, ultrasonographic, and laboratory data was a risk factor for the PL group (Table 6).

Table 4. Logistic regression analyses of the variables in predicting delivery time to happen in 7 days in urine culture positive PPRM

	PPROM			
	Univariate		Multivariate	
	OR (95%CI)	P value	OR (95%CI)	P value
Age (year)	1.050 (0.954-1.156)	NS		
Body mass index before pregnancy	0.965 (0.930- 1.003)	NS		
Weight gained during pregnancy(kg)	0.919 (0.813- 1.038)	NS		
Smoking	1.021 (0.815-1.278)	NS		
Gravity	0.736 (0.417-1.299)	NS		
The week labor started	1.120 (0.990-1.266)	NS		
Cervical length measured by transvaginal ultrasonography (mm)	0.825(0.740-0.919)	<0.001	0.806 (0.705-0.922)	0.002
Amniotic fluid index (AFI)	0.968 (0.948-0.989)	0.003	0.961 (0.932- 0.990)	0.010
WBC ($10^3/\text{mm}^3$)	1.077 (0.928-1.250)	NS		

WBC; white blood cell, kg; a kilogram

Table 5. Logistic regression analyses of the variables in predicting delivery time to happen in 7 days in urine culture positive PL patients

	PL			
	Univariate		Multivariate	
	OR (95%CI)	P	OR (95%CI)	P
Age	1.062(0.974-1.158)	NS		
Body mass index before pregnancy	1.126(0.997-1.272)	NS		
Weight gained during pregnancy(kg)	0.899(0.775-1.044)	NS		
Smoking	0.957(0.617-1.484)	NS		
Gravidy	1.703(1.136-2.554)	0.010	1.504 (0.839-2.697)	NS
The week labor started	1.023(0.896-1.169)	NS		
Cervical length measured by transvaginal ultrasonography (mm)	0.855(0.790-0.925)	<0.001	0.862 (0.795-0.934)	<0.001
Amniotic fluid index (AFI)	0.993(0.972-1.014)	NS		
WBC (10 ³ /mm ³)	0.967(0.845-1107)	NS		

WBC; white blood cell, kg; a kilogram

Table 6. Logistic regression analyses of the factors in predicting adverse neonatal outcomes in culture-positive PPROM

	PPROM			
	Univariate		Multivariate	
	OR (95%CI)	P	OR (95%CI)	P
Age	1.045 (0.941-1.160)	NS		
Body mass index before pregnancy	0.983(0.887-1.088)	NS		
Weight gained during pregnancy(kg)	0.861 (0.750-0.988)	0.033	0.892 (0.764-1.042)	NS
Gravidy	1.200(0.639-2.253)	NS		
The week labor started	0.968 (0.851-1.102)	NS		
Cervical length measured by transvaginal ultrasonography (mm)	0.924 (0.863-0.988)	0.021	0.932(0.962-1.003)	0.053
Amniotic fluid index (AFI)	0.975 (0.956-0.994)	0.010	0.982(0.962-1.003)	0.028

Cervical length, measured by transvaginal ultrasonography, and AFI were found to be negatively related to delivery time sooner than 7 days and adverse neonatal outcomes, in the culture-positive PPROM group ($r = -0.581, p < 0.001$, and $r = -0.412, p = 0.001$, for cervical length, respectively) ($r =$

$0.317, p = 0.014$, and $r = -0.379, p = 0.003$, for AFI, respectively). Cervical length was also observed to be negatively related to the delivery time, sooner than seven days, ($r = -0.598, p < 0.001$) in the culture-positive PL group. No correlation was observed with adverse neonatal outcome in this group (Table 7).

Table 7. Correlation analyses of culture-positive PPROM and PL patients

	PPROM		PL	
	Delivery time < 7 days	Adverse neonatal outcome	Delivery time < 7 days	Adverse neonatal outcome
Cervical length (mm)	$r = -0.581$ $p < 0.001$	$r = -0.317$ $p = 0.014$	$r = -0.598$ $p < 0.001$	$r = -0.350$ $p = 0.265$
Amniotic fluid index (AFI)	$r = -0.412$ $p = 0.001$	$r = -0.379$ $p = 0.003$	$r = -0.078$ $p = 0.546$	$r = 0.145$ $p = 0.636$

r; correlation coefficient, p-value; statistical significance, <0.05 statistically significant

When the cervicovaginal cultures of PPRM and PL patients sampled during their hospitalization process were analyzed, 66 of 446 cultures (14.7%) belonging to PPRM patients were found contaminated. The remaining 166 patients (37.2%) had positivity in their urine cultures, whereas 214 (47.9%) of the patients had negative urine cultures. Seventy-seven of 478 PL patients (16.04%) had positivity in their urine cultures, whereas 401 of them (83.95%) did not. There was no significant difference in the laboratory analyses of determinants for infection, between the culture positive and negative subgroups of PPRM and PL groups. Multivariate regression analyses were applied to each culture-positive subgroups, and no significant effect on adverse neonatal outcome was found for the following parameters: age, BMI, weight gained during pregnancy, smoking, amount of amniotic fluid, cervical length measured transvaginally.

Among 116 PPRM patients having positive urine cultures, 31 newborns were followed up in the neonatal intensive care unit for infection. Thirteen of them were born in the first 24 hours; 4 of them in 2-3 days; 4 of them in 4-7 days; 2 of them in 8-15 days; 2 of them on 15-21; and 6 of them after 21 days. Among the 128 PL patients having positive urine cultures, 17 of the newborns were followed up for neonatal infection. Eight of them were born in the first 24 hours, whereas 2 of them were born on 2-3 days; 1 of them was born on the 5th day; 2 of them in 8-15 days; and 4 of them after 21 days.

DISCUSSION

All the deliveries between 20 - 37^{0/7} gestational weeks are defined as PL^{10,17}. PPRM is the rupture of membranes before the 37th gestational week without the uterine contractions¹⁸. Genitourinary infections have been densely observed for their roles in the etiopathogenesis of PL, which has not been clearly understood yet. ASB is observed in 2-10 % of all pregnancies, and if it is not treated, acute pyelonephritis develops in 30 % of the cases which may end in PL and low birth weight¹⁹. William et al. demonstrated the significant relationship between the urogenital infections and the history of previous PL in their study, examining 676 women for the correlation of PL and epidemiologic factors and genitourinary infections²⁰.

Urine culture is the gold standard method in the diagnosis of urinary system infection⁵. Because of the

lengthy culture time and the possibility for contamination in cases where culturing methods are not obeyed, clinical evaluation of the patients may be used. Symptoms of the patients (dysuria, suprapubic sensitivity, flank pain, fever, etc.), spot urine analyses, and infection parameters (WBC, neutrophil count, N/L ratio, CRP) may be evaluated together for earlier diagnosis in PL patients. We observed an increase in the infection parameters and spot urine analyses in the culture-positive PL group but also could not find any negative relationship between these parameters and labor duration and adverse neonatal outcomes.

Guerra et al. reported that there was no correlation between the results of spot urine analyses and urine cultures²¹. Feitosa et al. recommended confirmation of spot urine results with urine culture²².

E. coli is the most common pathogen for urinary infections and responsible for 80-90% of cases^{23,24}. The other pathogens are *Proteus mirabilis*, *Klebsiella*, *Pseudomonas*, and *Streptococcus* species⁵. We also detected *E. coli* as the most common pathogen (75%) in PL patients, and the others were *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Staphylococcus aureus*.

The most serious problem in the PL is prematurity-related complications like respiratory distress syndrome, infections, and even sepsis developing in the neonatal period. Preventing or minimizing these complications is very important. Sampling for cervical culture in PL patients to define the correct factor in the etiopathogenesis and decrease the potential neonatal complications is used. Betamethasone treatment to improve fetal lung maturation and tocolytic treatment for slowing down PL are also preferred. It is important to decrease PL rates to reduce prematurity. The researches show that cervical length measurement with transvaginal ultrasound is important in predicting the time period between the start of labor and delivery. Iamset et al. reported that 18% of patients having a cervical length less than 25mm at the 24th gestational week had delivery before a 35th gestational week. It is also known that PL beginning before the 24th gestational week has a shorter period of time up to delivery when compared to PL starting towards the end of the second trimester²⁵. Mehra et al. examined that short cervix in transvaginal sonography and AFI ≤ 5 cm were independent variables in PPRM patients for the existence of labor in 7 days²⁶. AFI more than 5 cm and a cervical length longer than 2 cm presents a low possibility for the occurrence of labor in 7 days.

Lorthe et al. observed that gestational age was effective in the prolongation of the latent period up to delivery, whereas it was not useful in neonatal prognosis in PPRM patients²⁷. In our PPRM group, we observed that the decrease in the AFI was a factor effective in predicting labor to happen in a time period shorter than seven days. Cervical length measurement via transvaginal ultrasound was also observed to predict preterm delivery shorter than seven days, in both PL and PPRM groups.

PL observed with urinary system infections may also correlate with serious complications like neonatal sepsis, morbidity, and mortality. Similarly, when we evaluated the neonates having 1st and 5th minute APGAR scores less than 7, we observed that only the decrease in AFI in the culture-positive PPRM group was related to adverse neonatal outcome. The patients of the PL group, having culture positivity did not have a significant clinical, ultrasonographic, or laboratory variable related to adverse neonatal outcome. Yu et al. examined retrospectively the factors effective in neonatal outcomes in 510 PPRM patients who were at most in their 34th gestational weeks¹³. They found that the time of the membrane rupture and the duration up to the delivery were effective in neonatal outcome. Besides, Cobo et al. evaluated the effects of single vertical pocket measurement, gestational age, maternal age, and previous invasive procedures on neonatal outcome in early PPRM patients. They observed that only the second week from membrane rupture was related to adverse neonatal outcome¹⁶.

As a result, urinary system infections play a major role in the development of PL and PPRM. We observed that amniotic fluid index and cervical length measured transvaginally were effective in detecting delivery time, in PPRM patients having positive urine cultures. Bad neonatal outcome was only related to the amniotic fluid index. In the PL patients having a urinary infection, only the cervical length was useful in determining the delivery time; and no significant determinant for the adverse neonatal outcome was observed in this group. The diagnosis and treatment of urinary system infections triggering PL and ending in many fetal problems, via clinical and laboratory methods are easy to handle. Urinary system infections must be investigated in all PL patients to prolong the labor duration and decrease fetal complications. The search for a urinary infection, measuring AFI and cervical length in PL

and PPRM patients may help improve neonatal results.

Yazar Katkıları: Çalışma konsepti/Tasarımı: SÖ,EÖ, DS, BGG, AÖE, ATÇ, ND; Veri toplama: SÖ,EÖ, DS, BGG, AÖE, ATÇ, ND; Veri analizi ve yorumlama: SÖ,EÖ, DS, BGG, AÖE, ATÇ, ND; Yazı taslağı: SÖ,EÖ, DS, BGG, AÖE, ATÇ, ND; İçeriğin eleştirel incelenmesi: SÖ,EÖ, DS, BGG, AÖE, ATÇ, ND; Son onay ve sorumluluk: SÖ,EÖ, DS, BGG, AÖE, ATÇ, ND; Teknik ve malzeme desteği: SÖ,EÖ, DS, BGG, AÖE, ATÇ, ND; Süpervizyon: SÖ,EÖ, DS, BGG, AÖE, ATÇ, ND; Fon sağlama (mevcut ise): yok.

Etik Onay: Çalışma protokolü, Zekai Tahir Burak Kadın Sağlık Eğitim ve Araştırma Hastanesi yerel etik kurulu tarafından onaylanmıştır [onay tarihi / numarası: 24.03.2014 / 39].

Hakem Değerlendirmesi: Dış bağımsız.

Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.

Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

Author Contributions: Concept/Design : SÖ,EÖ, DS, BGG, AÖE, ATÇ, ND; Data acquisition: SÖ,EÖ, DS, BGG, AÖE, ATÇ, ND; Data analysis and interpretation: SÖ,EÖ, DS, BGG, AÖE, ATÇ, ND; Drafting manuscript: SÖ,EÖ, DS, BGG, AÖE, ATÇ, ND; Critical revision of manuscript: SÖ,EÖ, DS, BGG, AÖE, ATÇ, ND; Final approval and accountability: SÖ,EÖ, DS, BGG, AÖE, ATÇ, ND; Technical or material support: SÖ,EÖ, DS, BGG, AÖE, ATÇ, ND; Supervision: SÖ,EÖ, DS, BGG, AÖE, ATÇ, ND; Securing funding (if available): n/a.

Ethical Approval: The study protocol was approved by the local ethical committee of Zekai Tahir Burak Women's Health Education and Research Hospital. [approval date / number: 24.03.2014/39].

Peer-review: Externally peer-reviewed.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support

REFERENCES

1. Pathak B. Urinary tract infections in pregnancy: from symptomatic bacteriuria to pyelonephritis. In Management of Common Problems in Obstetrics and Gynecology (Eds : TM Goodwin, MN Montoro, LI Muderspach, RJ Paulson, S Roy). New York, Wiley, 2010.
2. Sobel JD, Kaye D. Urinary tract infections. In: Mandell GL, Bennett JE, Dolin R, editor(s). Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases. New York: Churchill Livingstone, 1995.
3. Sweet RL, Gibbs RS. Infectious Diseases of the Female Genital Tract. Philadelphia, Lippincott Williams & Wilkins, 2002.
4. Bacak SJ, Callaghan WM, Dietz PM, Crouse C. Pregnancy-associated hospitalizations in the United States, 1999-2000. Am J Obstet Gynecol. 2005;192:592-7.
5. Farkash E, Weintraub AY, Sergienko R, Wiznitzer A, Zlotnik A, Sheiner E. Acute antepartum pyelonephritis in pregnancy: a critical analysis of risk factors and outcomes. Eur J Obstet Gynecol Reprod Biol. 2012;162:24-7.
6. Nicolle LE. Asymptomatic bacteriuria: when to screen and when to treat. Infect Dis Clin North Am. 2003;17:367-94.
7. American College of Obstetricians and Gynecologists. ACOG Educational Bulletin No. 245. Antimicrobial

- therapy for obstetric patients. *Int J Gynaecol Obstet.* 1998;61:299-308.
8. Gilstrap LC, Cunningham FG, Whalley PJ. Acute pyelonephritis in pregnancy: an anterospective study. *Obstet Gynecol.* 1981;57:409-13.
 9. Wing DA, Fassett MJ, Getahun D. Acute pyelonephritis in pregnancy: an 18 year retrospective analysis. *Am J Obstet Gynecol.* 2014;210:219.e1-6.
 10. Berghella V, Saccone G. Cervical assessment by ultrasound for preventing preterm delivery. *Cochrane Database Syst Rev.* 2019;(9):CD007235.
 11. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Mathews TJ, Osterman MJ. Births: final data for 2008. *Natl Vital Stat Rep.* 2010;59:1,3-71.
 12. Cai T, Mazzoli S, Mondaini N, Meacci F, Nesi G, D'Elia C et al. The role of asymptomatic bacteriuria in young women with recurrent urinary tract infections: to treat or not to treat?. *Clin Infect Dis.* 2012;55:771-7.
 13. Yu H, Wang X, Gao H, You Y, Xing A. Perinatal outcomes of pregnancies complicated by preterm premature rupture of the membranes before 34 weeks of gestation in a tertiary center in China: A retrospective review. *Biosci Trends.* 2015;9:35-41.
 14. Schmitz T, Sentilhes L, Lorthe E, Gallot D, Madar H, Doret-Dion M et al. Preterm premature rupture of the membranes: Guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF). *Eur J Obstet Gynecol Reprod Biol.* 2019;236:1-6.
 15. Chao TT, Bloom SL, Mitchell JS, McIntire DD, Leveno KJ. The diagnosis and natural history of false preterm labor. *Obstet Gynecol.* 2011;118:1301-8.
 16. Cobo T, Munrós J, Ríos J, Ferreri J, Migliorelli F, Baños N, et al. Contribution of amniotic fluid along gestation to the prediction of perinatal mortality in women with early preterm premature rupture of membranes. *Fetal Diagn Ther.* 2018;43:105-12.
 17. Romero R, Lockwood JC. Pathogenesis of spontaneous preterm labor. In Creasy and Resnik's *Maternal-Fetal Medicine: Principles and Practice*, Sixth edition (Eds RK Creasy, R Resnik), Philadelphia, Saunders Elsevier, 2004.
 18. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet.* 2008;371:75-84.
 19. Smaill FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev.* 2015;(8):CD000490.
 20. Agger WA, Siddiqui D, Lovrich SD, Callister SM, Borgert AJ, Merkitch KW et al. Epidemiologic factors and urogenital infections associated with preterm birth in a midwestern U.S. population. *Obstet Gynecol.* 2014;124:969-77.
 21. Guerra GV, de Souza AS, da Costa BF, do Nascimento FR, Amaral Mde A, Serafim AC. Urine test to diagnose urinary tract infection in high-risk pregnant women. *Rev Bras Ginecol Obstet.* 2012;34:488-93.
 22. Feitosa DC, da Silva MG, de Lima Parada CM. The accuracy of simple urine tests for diagnosis of urinary tract infections in low-risk pregnant women. *Rev Lat Am Enfermagem.* 2009;17:507-13.
 23. Jacociunas LV, Picoli SU. Avaliação de infecção urinária antes no Primeiro trimestre de gravidez. *Rev Bras Anal Clin.* 2007;39:55-7.
 24. Duarte G, Marcolin AC, Gonçalves CV. Infecções urinárias na gravidez: análise dos métodos diagnósticos e do tratamento. *Rev Bras Ginecol Obstet.* 2002;24:471-7.
 25. Iams JD, Goldenberg RL, Meis PJ, Mercer BM, Moawad A, Das A et al. The length of the cervix and the risk of spontaneous premature delivery. National Institute of Child Health and Human Development Maternal-Fetal Medicine Unit Network. *N Engl J Med.* 1996;334:567-72.
 26. Mehra S, Amon E, Hopkins S, Gavard JA, Shyken J. Transvaginal cervical length and amniotic fluid index: can it predict delivery latency following preterm premature rupture of membranes?. *Am J Obstet Gynecol.* 2015;212(3):401-9.
 27. Lorthe E, Ancel PY, Torchin H, Kaminski M, Langer B, Subtil D et al. Impact of latency duration on the prognosis of preterm infants after preterm premature rupture of membranes at 24 to 32 weeks' gestation: a national population-based cohort study. *J Pediatr.* 2017;182:47-52.