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Original Article

Relationship Between Clinical and Laboratory Parameters at Admission and Pregnancy Outcomes in Cases of Preterm Premature Rupture of Membranes

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Abstract

Background*:Preterm premature rupture of membranes (PPROM) is a significant complication in pregnancy, often associated with adverse maternal and fetal outcomes. Understanding the relationship between clinical and laboratory parameters at admission and pregnancy outcomes in PPROM cases is essential for effective management and intervention***.**
Methods: *The study was conducted retrospectively to examine the relationship between clinical and laboratory parameters at the time of admission and the latent period in pregnant women with PPROM. Records of pregnant women diagnosed with PPROM between 2015-2017 in the obstetrics department of a university hospital were reviewed. The patients were grouped according to gestational weeks, clinical parameters at admission were recorded, and their relationships with the latent period were analyzed.*
Results: *When the data obtained in the study were analyzed, it was shown that cervical length (p = 0.008) and the gestational week at the time of admission had an effect on the latent period (p <0.001). However, the other parameters examined, such as amniotic fluid index (AFI), C-reactive protein (CRP), white blood cells (WBC), and Hemoglobin (HGB), were not found to have a statistically significant relationship with the latent period.*
Conclusions: *In cases of PPROM that do not require urgent medical intervention, a multidisciplinary approach should be used. In this way, the latent period can be extended and fetal outcomes can be improved. In this direction, clinical and laboratory parameters at the time of presentation should be carefully considered, and detailed evaluations with ultrasonographic examination and vaginal examination should be continued.*

Keywords*: Early membrane rupture, Cervical length, Preterm premature membrane rupture, Prematurity*

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Introduction

Premature Rupture of Membranes (PROM) is the rupture of fetal membranes before the onset of labor contractions. Preterm Premature Rupture of Membranes (PPROM) is defined as the rupture of membranes before 37 weeks of gestation (1). PPROM holds a significant place among the causes of prematurity, and gestational age and birth weight are important determinants of mortality and morbidity in premature infants (2). PPROM occurs in approximately 0.3%-0.4% of all pregnancies (3). In these cases, the rates of preterm birth reach 20%-50% (4). Other significant issues that may be observed besides prematurity include maternal and fetal infections, hypoxia, asphyxia, lung hypoplasia, respiratory distress syndrome, or fetal deformity (5).

Management of PPROM cases, which pose a risk to maternal and fetal health, is highly important. In this context, the main goal in PPROM is to prolong the "latent period" — the time from the rupture of membranes to delivery — and to reduce the rates of preterm birth (6). The latent period is the duration that starts with the leakage of amniotic fluid and continues until the birth of the fetus (7). Prolonging the latent period positively contributes to improving fetal outcomes (8).

The latent period in PPROM is influenced by factors such as the gestational age at the time of presentation, cervical length, and the presence of pregnancy complications. One of these factors is the clinical laboratory parameters at the time of presentation (8).

In light of all this information, assessments such as "cervical length measurement" and "gestational age" in PPROM cases can be beneficial for determining the duration of labor and the treatment approach, as well as for reducing potential complications. In addition to these, this study aims to evaluate parameters such as "Amniotic Fluid Index" and laboratory analyses including "White Blood Cell (WBC), Hemoglobin (HGB), and C-reactive protein (CRP)" to see if there is any relationship with the latent period.

Material and Method

The study was conducted retrospectively to examine the relationship between clinical and laboratory parameters at the time of admission and the latent period in pregnant women with PPROM. Records of pregnant women diagnosed with PPROM between 2015-2017 in the obstetrics department of a university hospital were reviewed. Initially,

data from 205 pregnant women were accessed, but 61 women with an additional medical history (diabetes mellitus, gestational diabetes, hypertensive disorders, placental abruption, placenta previa, thyroid dysfunctions, maternal cardiovascular diseases, chronic infectious diseases, rheumatologic diseases, severe anemia, fetal growth restriction, fetal anomalies, intrauterine fetal demise) were excluded from the study. The study was completed with data from 144 pregnant women. The patients were divided into five groups according to their gestational weeks (<24, 24-28, 28-32, 32-34, >34 weeks).

The socio-demographic data (age, education level), obstetric data (gestational age, fetal biometric measurements, cervical length, amniotic fluid volume, mode of delivery, gestational week at delivery, birth weight, obstetric complications), medical treatment protocol, and laboratory findings of the pregnant women were obtained and evaluated from hospital records. A diagnostic and management protocol for PPROM cases is implemented at the specified hospital.

In the clinic where the research was conducted, the diagnostic and management protocol for preterm premature rupture of membranes (PPROM) includes physical examination, ultrasound (USG), laboratory tests, detection of placental alpha microglobulin-1 (PAMG-1) (AmniSure® test), and Non-Stress Test (NST). The diagnosis of membrane rupture is confirmed by detecting PAMG-1 in vaginal fluid. To monitor for the development of chorioamnionitis in patients, daily tracking of fever, abdominal pain, abdominal tenderness, and fetal tachycardia is initiated, along with Hemogram and CRP monitoring. To ensure fetal lung maturation, patients for whom labor is planned receive intramuscular injections of betamethasone ampoules at a dose of 2x2 every 24 hours (9). All patients are started on intravenous Ampicillin-Sulbactam 1 g, 4x1 dose for 10 days (9). For pregnant women over 32 weeks, daily NST evaluation is performed, and all patients undergo daily ultrasound assessments of the placenta, amniotic fluid evaluation, and fetal movement examination.

According to the protocol, pregnant women diagnosed with PPROM who are less than 23 weeks pregnant are offered the option of termination. Women who wish to continue the pregnancy are admitted to the hospital for monitoring and treatment.

Statistical Analysis

The data were analyzed using IBM SPSS 22 software. Descriptive statistics, including mean, standard deviation, frequency, percentage, and arithmetic mean, were used

for evaluation. The Shapiro-Wilk test was employed to determine the normal distribution of the data. One-way analysis of variance (ANOVA) was chosen for data with a normal distribution, while the Kruskal-Wallis H test and Mann-Whitney U test were selected for data that did not show normal distribution. Tukey and Tamhane T2 tests were chosen as post-hoc tests. Categorical variables were analyzed using the Chi-square test and Exact test. Pearson correlation and Spearman correlation tests were utilized to determine the relationship between the data. In test results, $p<0.05$ was considered statistically significant.

Results

It was determined that the mean age of the pregnant women was 29.04±6.1, with 46.3% being primigravida, 51.9% being nulliparous, and 69.8% having never had a miscarriage. The mean gestational age at the initial presentation of patients was determined to be 29.8±7 weeks (Table 1).

Table 1. Distribution of pregnant women according to age and obstetric history.

Gravida	**n**	**(%)**
1	25	46,3
2	7	13,0
3	7	13,0
4	8	14,8
5	3	5,6
6	3	5,6
12	1	1,9
Para	**n**	**(%)**
0	28	51,9
1	8	14,8
2	12	22,2
3	4	7,4
4	2	3,7
Abortus	**n**	**(%)**
0	37	69,8
1	10	18,9
2	4	7,5
3	1	1,9
10	1	1,9

In the grouping based on gestational weeks at the time of presentation, it was found that 36 patients (25.4%) were less than 24 weeks, 16 patients (11.3%) were between 24-28 weeks, 20 patients (14.1%) were between 28-32 weeks, 16 patients (11.3%) were between 32-34 weeks, and 54 patients (38%) were over 34 weeks. The average gestational age at birth was determined to be 30.8±6.7 weeks, and the average birth weight was 2049±973.7 grams in the study. It was observed that 93.7% of patients received antibiotic therapy, 55.3% had cesarean delivery, 57.5% developed chorioamnionitis, and 21.9% had placental abruption (Table 2).

Table 2. Distribution of Pregnant Women According to Clinical and Obstetric Characteristics.

Pregnancy groups	**n(%)**
< 24 weeks	36 (% 25,4)
24- 28 weeks	16 (% 11,3)
28- 32 weeks	20 (% 14,1)
32- 34 weeks	16 (% 11,3)
> 34 weeks	54 (% 38)
Antibiotherapy status	134 (% 93,7)
Caesarean section	68 (% 55,3)
Chorioamnionitis	42 (% 57,5)
Abruptio plasenta	16 (% 21,9)
Birth week (Mean± SD)	30,8±6,7
Birth Weight (Mean (±SD)	2049±973,7 gram

When examining the relationship between parity and the latent period, although the latent period was shorter in multiparous women compared to nulliparous women, it was not statistically significant (0.07 vs. 0.28 days) (p = 0.153) (Table 3).

Table 3. Parity - Latent Period Relationship.

	Nullipar	**Multipar**	**p**
Latent Period, med (min- max)*	0,28 (0,14- 8,8)	0,07 (0- 0,3)	0,153

Mann-Whitney U test Med: Medyan, min: Minumum, max: Maksimum *day

The analysis results of the gestational weeks and the latent period in patients were found to be as follows: for those <24 weeks, it was 0.28 (0.00-9.28), for 24-28 weeks it was

0.85 (0.00-2.71), for 28-32 weeks it was 0.71 (0.00-3.72), for 32-34 weeks it was 0.29 (0.00-2.44), and for >34 weeks it was 0.14 (0.00-1.30). It was observed that as gestational weeks decreased, the latent period increased, and there was a significant relationship (p<0.001) (Table 4).

Table 4. Distribution According to Weeks of Gestation and Latent Period.

Gestation Week	Latent Period, med (min- max)	p
<24	0,28 (0,00- 9,28)	
24- 28	0,85 (0,00- 2,71)	
28-32	0,71 (0,00-3,72)	p<0,001
32-34	0,29 (0,00-2,44)	
>34	0,14 (0,00-1,30)	

Kruskal Wallis H test; a;0,05; Med: Medyan, min: Minimum, max: Maksimum

Correlation analysis was performed between the latent period and variables such as cervical length, amniotic fluid index, HGB, WBC, and CRP. Only cervical length showed a significant difference (p=0.008) (Table 5).

Table 5. Latent Period - Cervical Length, HGB, WBC, CRP, AFI Relationship.

	Latent period	
	r	p
Cervical Length[a]	0,420	0,008
Hemoglobin[a]	-0,061	0,483
White Blood Cell[a]	0,101	0,282
C-Reaktiv Protein[a]	-0,058	0,570
Amniotic Fluid Index[b]	0,142	0,098

a:Pearson Correlation test; b:Spearmann Correlation test

Table 6 presents the relationship between gestational weeks and complications such as mode of delivery, chorioamnionitis, and placental abruption. It was found that as gestational weeks decreased, the rate of cesarean section increased, but in the group with gestational age less than 24 weeks, the rate of vaginal delivery was higher. The rates of chorioamnionitis increased as gestational weeks decreased, and

significantly decreased after 34 weeks. However, there was no significant difference observed among the groups regarding placental abruption (p=0.647) (Table 6).

Table 6. Distribution of Pregnant Women According to Mode of Delivery and Complications.

	<24 weeks	**24-28 weeks**	**28-32 weeks**	**32-34 weeks**	**>34 weeks**	**X^2**	**p**
Caesarean section, n (%)	6 (% 19,4)	11 (% 84,6)	15 (% 93,8)	12 (% 80)	23(% 48,9)	34,7	0,001
Chorioamnionitis, n (%)	14 (% 87,5)	7 (% 77,8)	9 (% 75)	8 (% 88,9)	4 (% 14,8)	32,6	0,001
Abruptio Plasenta, n (%)	5 (% 31,3)	3 (% 33,3)	2 (% 16,7)	2 (% 22,2)	4 (% 14,8)	2,4	**0,**647

X^2: Chi-Square test. Exact test.

Discussion

Although our medical knowledge and experiences are growing day by day, uncertainties persist in the field of preterm premature rupture of membranes (PPROM), and visible success has not been achieved. Mortality and morbidity rates associated with PPROM remain high, and PPROM continues to be a significant clinical problem. Therefore, a critical aspect in deciding whether to pursue a monitoring approach or make a delivery decision in patients diagnosed with PPROM is to make a reasonable decision by considering the advantages and disadvantages between the risk of developing intrauterine infection and the risk of developing complications. While the gestational weeks of 32-34 are suggested by many as appropriate for delivery, there is no consensus on issues such as reducing complications, improving prognosis, or determining the duration of antibiotic therapy, so much more work needs to be done in this regard (10). Therefore, patients diagnosed with PPROM should be monitored for vital signs in a fully equipped center, carefully monitored for symptoms such as fever, abdominal pain, and abdominal tenderness, monitored for laboratory parameters, and should be monitored by a ready team for urgent intervention when necessary. In patients under observation, steroid administration should be considered with regard to fetal lung maturation, and prophylactic antibiotic therapy should be initiated to prevent the development of intrauterine infections, particularly chorioamnionitis.

Although the etiology of preterm labor is not fully understood, "chorioamnionitis" holds a significant place among risk factors. This risk is further increased in PPROM patients. Therefore, Group B Streptococcus positivity should be investigated in PPROM patients. Additionally, pathogens such as Neisseria Gonorrhoeae, Trichomonas vaginalis, species of Bacteroides, Chlamydia trachomatis, and Mycoplasmas can also be involved, albeit less frequently. These pathogens can cause defects in membrane integrity through certain enzymes they secrete. The presence of pathogens can be investigated through vaginal culture examination (11). When an infection develops with any of these pathogens, chorioamnionitis occurs. Since there is no definitive marker for chorioamnionitis, the diagnosis is confirmed based on clinical findings such as abdominal pain, fever, and abdominal tenderness following PPROM.

One of the acute phase reactants, CRP, increases in conditions such as infection, stress, and trauma. Hvilsom et al. suggested a relationship between elevated CRP levels in the later stages of pregnancy and preterm birth in their study (12). In another study, it was suggested that CRP could be considered a moderately significant marker for chorioamnionitis and related preterm delivery (13). However, contrary to these findings, our study did not observe a significant increase in CRP levels in cases of PPROM.

In daily practice, some inflammatory markers such as CRP, WBC, IL-6 are used for the follow-up and diagnosis of PPROM and chorioamnionitis; however, their clinical value is debatable due to the lack of specific markers and the physiological elevation of values such as WBC during pregnancy. Pandey et al. claimed that they could predict clinical outcomes with 85.7% sensitivity and 87.6% specificity by recording WBC values at admission in cases of PPROM, with a leukocyte count of 15,850 /mm3 (14). In contrast, Musilova et al. observed in their study that maternal WBC values at admission did not contribute to the prediction of PPROM and chorioamnionitis diagnosis (15). Turhan et al. stated that IL-6 had a more valuable predictive value than WBC and CRP in cases of PPROM (16). In our study, IL-6 value was not examined and the WBC value at admission was not found to be a significant finding in terms of influencing the latent period and predicting the development of chorioamnionitis.

It is believed that cervical length, which is measured by transvaginal ultrasound starting in the second trimester and is shorter than 25-26 mm, plays an important role in the etiology of preterm labor. Sweed

et al. observed in their study that the measured cervical length in PPROM patients had a significant relationship with the latent period, and as the cervical length increased, the latent period also increased (17). Hassan et al. suggested that a short cervix is a clinical reflection secondary to infections originating from fetal membranes (18). However, Carlan et al. compared women with a short cervix to those with normal cervical length and claimed that there was no significant difference between them in terms of the latent period (19). In our study, similarly to the general consensus, a linear relationship was found between cervical length and the latent period, and it was observed that the shorter the cervix, the shorter the latent period.

According to the information in the literature, the larger the gestational age, the shorter the latent period, and in term pregnancies, this period falls below twenty-four hours (20). Consistent with this information, in our study, it was observed that the latent period was longer in pregnancies with a smaller gestational age.

Amniotic fluid has the potential to protect the fetus against bacteria. Additionally, there are views suggesting that the amount of amniotic fluid also plays a protective role against potential infections (21, 22). In their study, Ekin et al. suggested that if oligohydramnios accompanies PPROM, there is a higher risk of both chorioamnionitis and preterm labor and other complications (21). Although Piazze et al. also suggested a linear relationship between the amount of amniotic fluid and the latent period to support this idea, our study did not find a relationship between the amount of amniotic fluid and the latent period (23).

As a result, in cases of PPROM where there is no indication for urgent medical intervention, the first choice should be a follow-up option with a multidisciplinary team. Because in this patient group, extending the latent period contributes to reducing fetal mortality and morbidity. While doing this, practices such as initiating antibiotic therapy and administering corticosteroids for fetal lung development should be considered. Vaginal culture examinations should be performed to investigate conditions predisposing to infection. Considering the data from our study, it should be kept in mind that a low gestational age at admission and cervical length measurement within normal limits according to gestational age may have a positive contribution to the latent period.

Although the contribution of other parameters examined in our study was not observed, cervical length measurement becomes important during the follow-up process in this patient group. Conducting

studies with larger patient groups is important for further development or confirmation of these ideas.

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