

Maternal Characteristics and Obstetric Outcomes of Pregnancies Complicated by Preterm Premature Rupture of the Membranes

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Introduction: Preterm premature rupture of the membranes (PPROM) is defined as spontaneous membrane rupture without the onset of labor before 37 weeks of gestation. The study compared pregnant women with PPRM and those with intact membranes among pregnant with preterm labor, and to evaluate adverse obstetric outcomes.

Materials and Methods: Our study was conducted by retrospectively examining the birth records of pregnant women who gave birth between 24.-37. gestational weeks in the Department of Gynecology of Okmeydanı Training and Research Hospital between February 1, 2018, and December 31, 2020. PPRM (+) (n:197) and (-) (n:161) groups were compared for obstetric and perinatal outcomes.

Results: A total of 358 patients were included in the study. Mean maternal age and abortion values of the PPRM (+) were significantly higher than the PPRM (-) ($p=0.031$, and $p=0.001$, respectively). The presence of GDM, neonatal intensive care unit admissions, 1- and 5- minute Apgar scores of ≤ 7 in the PPRM (+) group was found to be higher than the PPRM (-) group ($p=0.045$, $p=0.0001$, $p=0.0001$, and $p=0.0001$, respectively). When adjusted for maternal age abortus (OR, 1.01; 95% CI, 1-1.04 $p=0.042$) and NICU admission (OR, 0.96; 95% CI, 0.94-0.99, and $p=0.0001$), were found to be statistically significant in multivariate risk analysis.

Conclusion: PPRM is associated with significant maternal, fetal, and neonatal risks. The approach to these patients varies depending on gestational age and maternal and fetal infection.

Keywords: Adverse obstetric outcomes, gestational diabetes, neonatal intensive care, preterm premature rupture

Introduction

Preterm premature rupture of the membranes (PPROM) is defined as spontaneous membrane rupture without the onset of labor before 37. weeks of gestation. PPRM increases the risk of preterm labor, intrauterine infection, fetal hypoxia, and intrauterine death. Poor fetal and obstetric outcomes are closely related to

gestational age. PPRM can be seen in 3% of all pregnancies and one-third of preterm births and is one of the leading causes of neonatal mortality and morbidity (1, 2). Cervical ripening, uterine myometrial contractility, and cervical insufficiency play important roles in the development of PPRM (3). Low socioeconomic level, smoking, history of preterm birth, urinary

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and genital infections, polyhydramnios, low maternal body mass index, smoking, vaginal bleeding, amniocentesis, and cerclage are accepted as risk factors for PPRM (4).

The diagnosis of PPRM is made by clinical suspicion, patient history, and some tests and early diagnosis is important. Subclinical intra-uterine infection is known as the major etiological factor and has been associated with umbilical cord compression, placental abruption, and preterm birth (5).

Conservative approach, magnesium sulfate, antibiotic treatment, or active induction of labor after administration of steroids can be applied in PPRM (6). Treatments from emergency delivery to watchful waiting dependent on the gestational age, duration of latent period, presence of accompanying medical and obstetric complications, infection, meconium, positive vaginal culture, and non-reactive non-stress test (NST) results, and the type of presentation. Emergency delivery should be considered, especially if there are signs of fetal distress due to cord prolapse, compression, and chorioamnionitis. Delivery occurs approximately 48 h after PPRM. Since uterine contraction is generally correlated with infection, tocolytic therapy is not recommended strongly (7). Our study aims to compare pregnant women with PPRM with those with intact membranes among pregnant women with preterm labor, and to evaluate adverse obstetric outcomes.

Materials and Methods

Our study was conducted by retrospectively examining the birth records of pregnant who gave birth between 24-37. gestational weeks in the Gynecology of Okmeydani Training and Research Hospital between February 1, 2018, and December 31, 2020.

Ethical Statement

The Ethics Committee approval was obtained for the present study. Data were retrieved from a computerized database. Among these

patients, pregnant women diagnosed with preterm premature rupture of membranes (PPROM) were recorded. Gestational age was calculated according to the last menstrual period or findings of ultrasound performed before the 20th gestational week. Gravida, parity, abortion numbers, gestational week, Apgar, indications for cesarean section, laboratory values, type of delivery were recorded for all patients.

Ultrasonography was performed in all patients to evaluate fetal dimensions, placenta and to calculate the amniotic fluid index. Patients with maternal pregestational diabetes, polyhydramnios, 24-37 weeks of gestation, multiple pregnancies, smokers, alcohol users, pregnant women under 18 years, those with diagnoses of fetal chromosomal anomalies, maternal heart disease, autoimmune disorders, overt thyroid disorder, intrauterine fetal death, PPRM Latency period longer than 48h and chronic drug users were excluded from the study. The patients were followed up with daily vital signs, uterine tenderness, and a daily non-stress test (NST) in the delivery service after admission.

To confirm the PPRM, sterile speculum examinations were performed to visualize amniotic fluid leaking from the cervical canal (if any). Nitrazine test was also used as an aid in diagnosis. Suspected patients underwent a more sensitive diagnostic AmniSure ROM test, which works with the principle of using monoclonal antibody pairs to detect placental alpha microglobulin (PAMG-1). Pregnant women with intact membranes without PPRM were determined as the control group. The control group was formed by matching patients with the same gestational age at delivery to every woman from the study group. These two groups were compared for obstetric and perinatal outcomes.

Antibiotic prophylaxis was administered to each patient with PPRM. To ensure maturation of the fetal lung, all pregnant women below 34

weeks of gestation at delivery were given a total intramuscular dose of 12 mg betamethasone at 12 hour-intervals. However, tocolysis was not applied to pregnant women with PPROM under 34 gestational weeks. In pregnant women with PPROM at more than 34 gestational weeks without any relevant contraindications labor was induced with oxytocin.

Small for gestational age (SGA) was defined as birth weight below the 10th percentile for that gestational age. The diagnosis of gestational diabetes mellitus (GDM) was made in 2 steps as recommended by the American College of Obstetricians and Gynecologists (ACOG) (8). The diagnosis of preeclampsia was made according to the criteria determined by the International Society for the Hypertension in Pregnancy (9).

Statistical Evaluation

Statistical analyzes were performed with NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. In addition to descriptive statistical methods (mean, standard deviation, median, interquartile range) in the evaluation of the data, the distribution of the variables was examined with the Shapiro-Wilk normality test. The independent t-test was used for the comparison of the paired groups of the variables with normal distribution, and Mann - Whitney U for the pairwise comparison of the groups with non-normally distributed variables. Chi-square and Fisher reality tests were used in the comparison of qualitative data. Logistic regression was used to determine the factors affecting the presence of PPROM. The results were accepted at the significance of $p < 0.05$.

Ethics Approval

The present study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the University of Health Sciences, Okmeydanı Training and Research Hospital (Date: 14/10/2021/ No: 48670771-514.01.02/366).

Results

A total of 358 patients included in our study were divided into 2 groups as follows: Group 1, PPROM (-) control group (n:161), and Group 2 PPROM (+) (n:197). Demographic characteristics and obstetric outcomes of the patients are shown in Table 1. When Groups 1 and 2 were compared, no statistically significant difference was observed between the 2 groups as for delivery type, gravida, parity gestational age at delivery, fetal weight, presentation, nulliparity, ≥ 35 maternal age, hemoglobin, hematocrit, WBC values, and gender distributions.

Mean maternal age and abortion values of the PPROM (+) group were found to be statistically significantly higher than the PPROM (-) group ($p=0.031$, and $p=0.001$, respectively). One- and 5- minute Apgar score averages of the PPROM (+) were lower relative to the PPROM (-) group ($p=0.004$, and $p=0.027$, respectively).

Indications for Cesarean sections are shown in Table 2. No statistically significant difference was observed between PPROM (-) and (+) as for the distributions of previous cesarean sections, fetal distress, progress failure, cephalopelvic disproportion, malpresentation, cord prolapse, and placenta previae. Adverse maternal and fetal obstetric outcomes are shown in Table 3. No significant difference was observed between PPROM (-) and PPROM (+) groups as for the distribution of SGA, abruptio placentae, and preeclampsia ($p=0.949$, $p=0.115$, $p=0.384$ respectively). The presence of GDM, neonatal intensive care unit admissions, 1-, and 5- minute Apgar scores of ≤ 7 in the PPROM (+) was higher than PPROM (-) ($p=0.045$, $p=0.0001$, $p=0.0001$, and $p=0.0001$, respectively).

The results of multivariate logistic regression risk analysis performed for the PPROM group are shown in Table 4. Abortus (OR, 1.35; 95% CI, 1.02-1.78 $p=0.037$) and NICU admission (OR, 0.27; 95% CI, 0.15-0.49 $p=0.0001$) were found to be statistically significant parameters. When adjusted for maternal age abortus (OR, 1.01;

Table 1. Demographic characteristics and obstetric outcomes

Variables		PPROM (-) <i>n</i> :161		PPROM (+) <i>n</i> :197		p
Age (years)		27,63±6,65		29,2±6,92		0,031*
Gravida	Mean (SD)	2,98±1,98		2,65±1,69		0,126‡
	Median (IQR)	3 (2-4)		2 (1-3,75)		
Parity	Mean (SD)	1,66±1,65		1,43±1,37		0,164‡
	Median (IQR)	1 (1-2)		1 (0-2)		
Abortus	Mean (SD)	0,32±0,81		0,59±1,07		0,001‡
	Median (IQR)	0 (0-0)		0 (0-1)		
Gestational age (weeks)		34,85±2,34		34,7±2,23		0,560*
Fetal Weight (gr)		2562,31±620,11		2485,72±603,29		0,239*
Apgar Score 1 min		7,36±1,28		6,98±1,19		0,004*
Apgar Score 5 min		8,68±1,09		8,45±0,92		0,027*
Hemoglobin (gr/dl)		11,32±1,53		11,04±1,64		0,100*
Hematocrit (%)		33,83±4,04		33,3±4,45		0,244*
Leucocytes (n/mm ³)		15139,31±4717,47		14560,73±4930,92		0,261*
Delivery	Vaginal	77	47,83%	84	42,64%	0,326+
	Cesarean	84	52,17%	113	57,36%	
Gender	Female	79	49,07%	86	43,65%	0,307+
	Male	82	50,93%	111	56,35%	
Nulliparity		37	22,98%	60	30,46%	0,113+
Maternal age ≥35		30	18,63%	44	22,34%	0,390+
Presentation	Cephalic	153	95,03%	187	94,92%	0,963+
	Breech	8	4,97%	10	5,08%	

* Independent t-test †Mann Whitney U test +Chi square test. PPRM: Preterm premature rupture of membrane

Table 2. Indications for Cesarean Sections

Variables		PPROM (-) n:161		PPROM (+) n:197		p
Previous Cesarean		45	53,57%	49	49%	0,638+
Fetal Distress		28	33,33%	38	38%	0,615+
Progress Failure		1	1,19%	4	4%	0,476+
Cephalopelvic Disproportion		0	0,00%	1	1%	0,999‡
Malpresentation		6	7,14%	7	7%	0,971+
Placenta Previa		4	4,76%	0	0%	0,052‡
Cord Prolapsus		0	0%	1	1%	0,999‡

+Chi-square test, ‡Fisher's Exact Test. PPRM: Preterm premature rupture of membrane

Table 3. Adverse maternal and fetal obstetric outcomes

Variables		PPROM (-) n:161		PPROM (+) n:197		p
SGA		29	18,01%	36	18,27%	0,949
GDM		9	5,59%	23	11,68%	0,045
Abruptio Placentae		5	3,11%	2	1,02%	0,115
Preeclampsia		22	13,66%	21	10,66%	0,384
NICU Admission		30	18,63%	90	45,69%	0,0001
Apgar Score ≤7 1 min		60	37,27%	128	64,97%	0,0001
Apgar Score ≤7 5 min		10	6,21%	24	12,18%	0,048

+Chi-square test. SGA: Small for gestational age, GDM: Gestational Diabetes Mellitus, PPRM: Preterm premature rupture of membrane, NICU: Neonatal intensive care unit

95% CI, 1-1.04 $p=0.042$) and NICU admission (OR, 0.96; 95% CI, 0.94-0.99, and $p=0.0001$), were significant in multivariate risk analysis.

Discussion

Preterm premature rupture of the membranes is associated with significant maternal, fetal, and neonatal risks. In addition, PPRM is accepted as one of the most important causes of preterm deliveries and neonatal mortality. In our study, when pregnant women with PPRM were compared with pregnant women with intact membranes, gestational diabetes mellitus, neonatal intensive care admission, 1- and 5-minute Apgar scores of ≤ 7 were found to be statistically significantly higher in patients with PPRM. Also, maternal age was older and the number of abortions was higher in PPRM.

The latency was defined as the time from rupture of membranes to delivery. Up to 50% of the patients with PPRM give birth within 1 week. In the remaining group, the time to birth varies according to the gestational week, presence of infection, and fetal condition (2). In one study, the latency period exceeded 48 h in 62.5% and 7 days in 24.3% of the pregnancies. Latency periods of twin pregnancies were relatively shorter. Gestational age at PPRM, twin pregnancy, and the latency period have been associated with neonatal mortality (10). In our study, patients whose latency periods did not exceed 48 hours were selected and only the singleton pregnancy group was investigated.

In one study, 100 patients with PPRM at 24 - 37 gestational weeks were examined and primigravida and multigravida were detected in 17% and 83% of the patients, respectively. However, no significant correlation was found between age groups and the presence of PPRM (11). Contrary to this study, in our study, the mean maternal age of the PPRM(+) group was found to be statistically significantly higher than that of the PPRM(-) group ($p=0.031$). However, any significant difference was not encountered between the two groups in terms

of the number of gravida and parity, while the number of abortions was statistically higher in patients with PPRM. Also, when nulliparity and advanced maternal age over 35 years were examined, no significant difference was found between the PPRM (+) and PPRM(-) groups.

Timely diagnosis of PPRM and early initiation of treatment can reduce neonatal morbidity. Expectant management involve hospitalization, administration of corticosteroid, broadspectrum antibiotics, and, if necessary, amniocentesis which is particularly considered before 34. gestational weeks (12). The approach to the patient with PPRM is summarized in the ACOG Practice Bulletin 2020 Guideline. In the late preterm (34 0/7–36 6/7 weeks of gestation) group, delivery with expectant management, induction of labor, or cesarean section should be considered, corticosteroids should be given for lung maturation, prophylactic antibiotics and appropriate treatment protocol should be applied in the presence of intraamniotic infection. In the preterm (24 0/7–33 6/7 weeks of gestation) group; expectant management, antibiotics, corticosteroids, treatment of intraamniotic infection, and magnesium sulfate administration are recommended for pregnant women below 32 weeks of gestation (6). The Infectious Diseases Committee of the Society of Obstetricians and Gynecologists of Canada (SOGC) Guideline also recommends the use of antibiotics in PPRM (13). Following these guidelines in our clinic, antibiotic prophylaxis was used for all PPRM patients between 24-37 weeks of gestation. Betamethasone at twice-daily intramuscular doses of 12 mg was used for patients at their 24-34 gestational weeks. Neuroprotective magnesium sulfate was given to all pregnant women before 32 gestational weeks.

PPROM may cause an increase in the risk of neonatal infection, but deciding on preterm birth also increases the risks that may occur in prematurity. Deciding the time of birth is

not always an easy issue. In a randomized controlled study conducted by Morris et al. in patients from 65 centers with ruptured membranes but without any signs of infection before the onset of labor between 34, and 36 gestational weeks and 6 days, respiratory distress, mechanical ventilation, and intensive care unit stay were found to be increased in the newborns in the immediate delivery group. Although antepartum or intrapartum hemorrhage, intrapartum fever, use of postpartum antibiotics, and longer hospital stay were more common in the expectant management group, lower cesarean section rates were observed. If there are no signs of infection near term, expectant management is thought to give better results regarding fetal and maternal prognosis when PPRM is closely monitored (14). In our clinic, labor induction was performed with oxytocin in pregnant women with PPRM who passed 34. gestational weeks before labor if any contraindication does not exist.

The Guideline of the French College of Gynecologists and Obstetricians contains recommendations similar to those made by ACOG. Hospitalization and antibiotic prophylaxis are recommended in PPRM. If tocolysis will be used, it should not exceed 48 hours. As applied in our clinical protocol, antenatal treatment with corticosteroids is used for pregnant under the gestational age of 34 weeks and magnesium sulfate below 32 gestational weeks at delivery. Follow-up of the clinically stable patients at home after 48 hours has been recommended. It is important to follow the signs of infection and fetal well-being during monitorization. However, there is no consensus on the frequency of follow-up. Expectant management is recommended for patients with uncomplicated PPRM. Oxytocin and prostaglandins are used for the induction of labor (15). In clinical protocol, hospitalization is at the forefront and follow-up of the patients at home is not recommended.

In a study investigating five randomized trials performed in pregnant with PPRM between 28 and 34 gestational weeks, differences were observed in obstetric strategies. Intentional delivery and expectant management were examined. Incidence rates of cesarean section and neonatal deaths were significantly higher in the intentional delivery group (16).

In another review, pregnant with PPRM in whom labor was induced immediately or managed expectantly were compared and any significant difference between both groups as for the presence of neonatal sepsis could not be found. Early planned birth was found associated with increase in the rates of neonatal respiratory distress syndrome (RDS), need for ventilation, labor induction, lower gestational age, admission to neonatal intensive care units, neonatal mortality, endometritis, cesarean, but the decrease in the rates of chorioamnionitis and length of hospital stay (17).

Pasquier JC et al. used antibiotics and antenatal treatment with corticosteroids in a prospective cohort study of pregnant with PPRM at 24-34 gestational weeks, but still, the incidence of cesarean section has remained at a rate of 58.7% in PPRM (18). In another study, fetal distress was found to be 4% in PPRM (11). In our study, fetal distress was as high as 38.00%. Publications are showing an increase in the rates of abruptio placentae in PPRM (19). Abruptio placentae were observed at a rate of 1.02% in PPRM and 3.11% in pregnant women with intact membranes without any statistically significant difference between both groups.

In the study of Yu H, et al., cesarean section (CS) was performed in 37.1% of pregnant women with PPRM. The most common indications for CS were breech presentation, fetal distress, or failure of labor to progress (10). In our study group, the rate of cesarean section in PPRM was found to be 57.36%. The most common indication was the previous cesarean in pregnant women with PPRM and intact

membranes. Fetal distress was the most common primary indication for cesarean section, followed by malpresentation. However, any statistically significant difference was not encountered between PPROM (+) and PPROM (-) groups as for cesarean section indications. In the study of Swiatkowska-Freund et al. in which they compared pregnant women with and without PPROM between 22 and 37 weeks of gestation at delivery, cesarean delivery was more common in pregnant women with intact membranes. Fetal distress and intrauterine infection were the most common indications for cesarean section in patients with PPROM. The presence of PPROM did not affect neonatal mortality, but the congenital infection was more common in the PPROM group (20).

Postpartum hemorrhage, RDS, meconium aspiration syndrome, lower 1-minute Apgar (<7) scores were more commonly observed in term pregnant women with PROM (21). In the study of Chandra et al., patients with the third trimester PPROM or PROM were compared and rates of neonatal intensive care unit (NICU) admission, neonatal and maternal morbidity were found to be significantly higher in the PPROM group (22). In another study, the rate of NICU admission was 72.9%. (10) In our study, the NICU admission rate was 45.69% in PPROM (OR, 0.96; 95% CI, 0.94-0.99 $p=0.0001$) which was found to be statistically significant according to multivariate risk analysis. In the study of Yu H et al., gestational diabetes was observed at a rate of 21.4 % in patients with PPROM (10). In another study, GDM was observed at a rate of 19% in PPROM (22). In our study, when compared with literature findings, GDM was observed at a lower rate (11.68%) in our PPROM patients, while it was significantly higher relative to pregnant women with intact membranes. Findings such as maternal and fetal tachycardia, uterine tenderness, and foul-smelling discharge should raise suspicion for chorioamnionitis. It was observed that chorioamnionitis developed in 13% of pregnant

women with PPROM, and this rate increased as the gestational age decreased. Among pregnant women with PPROM, neonatal morbidities were found to be significantly higher in the group complicated with chorioamnionitis (23). In a study, septicemia was observed in 12% and chorioamnionitis

in 12% of the pregnant with PPROM (11). In another study, postpartum endometritis, chorioamnionitis, neonatal sepsis was less frequently detected in the antibiotherapy group compared with the antibiotic-negative group. However, rates of neonatal mortality did not differ between groups (24). There are studies showing that the rates of chorioamnionitis, neonatal infection, and the need for a surfactant decrease with the use of prophylactic antibiotics (25). In the study of Yu H et al., clinical chorioamnionitis occurred in 17.8% of the pregnancies. Neonatal mortality was found to be 7.4% (10). In our study, only one patient in the PPROM developed chorioamnionitis and the rate of chorioamnionitis was extremely low. (0.5%) in contrast to other studies. We think that prophylactic antibiotic administration to all PPROM patients in our clinic and the selection of patients with a latency period of fewer than 48 hours as the study group may explain this low rate of chorioamnionitis. When we compared pregnant women with and without PROM any significant difference was not detected in the number of white blood cells that we considered to be a marker of infection.

In the study of Gomez et al., intra-amniotic inflammation was investigated by performing amniocentesis between 18 and 32 gestational weeks in PPROM, and they concluded that antibiotic administration rarely eradicated intra-amniotic infection (26). Amniocentesis is not performed in our hospital to detect infection in PPROM. In a retrospective study by Newman DE et al. comparing extreme preterm deliveries with and without PPROM between 23-27 gestational weeks, 1- and 5. minute Apgar scores were found to be lower in the PPROM

group (27). In consistent with the literature, 1-, and 5- minute Apgar scores were observed to be extremely low in patients with PPROM.

Since the risk of perinatal complications increases with lower gestational age in PPROM and preterm birth, the most appropriate option in the follow-up of patients with PPROM is the approach based on gestational age. This approach involves emergency delivery or conservative treatment. The use of tocolysis in the treatment of PPROM has led to controversy and there is no definite consensus on this issue. Although tocolysis suppresses contractions, it can also mask the signs of an existing latent intrauterine infection. In one study it was found that aggressive tocolysis in PPROM did not increase latency and reduce neonatal morbidity compared with patients who did not undergo tocolysis or underwent limited tocolysis (28). In a study comparing pregnant women with PPROM who had or had not clinical chorioamnionitis or tocolysis, any difference was not found between the two groups in terms of birth weight, 1-, and 5- minute Apgar scores, rates of respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis (29). However, short-term tocolysis is recommended in patients who are started on antibiotics and corticosteroid therapy to achieve fetal lung maturation or to save time for maternal transport (30). Routine tocolysis is not applied to PPROM in our clinic. It is thought that tocolysis may hide the signs of infection.

We acknowledge that this study has limitations. Data related to socioeconomic status, maternal body mass index, nutritional status were not analyzed in this study. Amniocentesis was not applied to pregnant women with PPROM to determine intraamniotic infection and the diagnosis of chorioamnionitis was not made histopathologically.

In conclusion; preterm premature rupture of the membranes is an obstetric and still an up-to-date problem that causes maternal-fetal

morbidity and mortality. When the adverse obstetric outcomes were examined, the rates of GDM, neonatal intensive care admission, 1-, and 5-minute Apgar scores of ≤ 7 were found to be statistically significantly higher in patients with PPROM when compared with pregnant women with intact membranes.

The main aim of treatment should be to prevent premature birth, to prevent maternal and fetal infection, to reduce amniotic fluid loss and fetal distress. In cases where there are no contraindications, in pregnant women with PPROM, expectant management can be considered by performing careful monitoring. The approach to the patients varies depending on gestational age and maternal and fetal infection. Today, neonatal specialists and obstetricians need to determine the most appropriate treatment with a multidisciplinary approach. Patients should be followed up and treated in advanced centers where adult and neonatal intensive care services are provided. There is a need for multicentric and prospective clinical research studies examining long-term neurodevelopmental outcomes in infants.

Conflict of Interest

All authors declare no conflict of interest.

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