Experimental
&
Clinical Article

Obstetrics; *Maternal Fetal Medicine and Perinatology*

Perinatal Outcome of Previable Premature Rupture of Membranes Before 24 Weeks of Gestation: A Single-Centered Retrospective Cohort Study

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ABSTRACT

OBJECTIVE: Preterm premature rupture of membranes (PPROM) has unfavorable consequences for the neonate and the mother if it occurs before 24 weeks of gestation. We aim to present our series to elucidate the course of previable PPROM and to detect maternal and neonatal outcomes.

STUDY DESIGN: A single-centered retrospective cohort study that involves singleton patients diagnosed with spontaneous PPROM before 24 weeks. Data were retrieved from medical records, and maternal and neonatal outcomes were noted.

RESULTS: Seventy-eight women were diagnosed with PPROM before 24 weeks, 42 patients (54%) opted for termination of pregnancy, and seven patients (9%) had spontaneous abortion. Twentynine patients (37%) gave live birth after a median latency of 47 days. Neonatal complications were respiratory distress syndrome (n=19; 65%), early sepsis (n=10; 34%), late sepsis (n=5; 17%), bronchopulmonary dysplasia (n=5;17%), retinopathy of prematurity (n=3; 10%), pneumothorax (n=5; 17%), intracranial hemorrhage (n=2; 6%), necrotizing enterocolitis (n=1; 3%) and meningitis (n=1; 3%). In the liveborn group, the neonatal survival rate was 62%. Of the survivors, twelve babies (66%) were discharged without composite neonatal morbidity. Maternal complications in the expectant management group included clinical chorioamnionitis (n=12, 33%) and placental abruption (n=2, 5%).

CONCLUSION: In previable PPROM, overall half of the babies survive after expectant management. While a prolonged latency period and subsequent delivery at advanced gestational ages improve neonatal outcomes, such a conservative approach poses a substantial risk for chorioamnionitis.

Keywords: Chorioamnionitis, Neonatal sepsis, Pregnancy outcome, Preterm premature rupture of membranes

Gynecol Obstet Reprod Med 2024;30(1):1-9

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Submitted for Publication: 06.10.2023 Revised for Publication: 17.02.2024
Accepted for Publication: 02.04.2024 Online Published: 04.04.2024

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QR Code	Access this article online
	Website: www.gorm.com.tr e- mail: info@gorm.com.tr
	DOI:10.21613/GORM.2023.1445

How to cite this article: Dogan Y. Kockaya E. Eser DM. Gunlemez A. Perinatal Outcome of Previable Premature Rupture of Membranes Before 24 Weeks of Gestation: A Single-Centered Retrospective Cohort Ctudy. Gynecol Obstet Reprod Med. 2024;30(1):1-9

Introduction

Before viability, preterm premature rupture of membranes (PPROM) affects 0.1-0.4 % of gravidas (1,2). Deciding the limit of viability is challenging, it has been considered as 24 weeks of gestation, however, with the advances in neonatal intensive care over the last decades, neonates born after 22 weeks of gestation may have a chance of extrauterine survival depending on institutional factors.

Alternative management strategies in PPROM are immediate delivery versus expectant management. The goal of delaying delivery is to provide time for the fetus to mature and thereby reduce neonatal morbidity and mortality from preterm birth without ensuing serious maternal or fetal complications.

In previable PPROM, the most common maternal morbidities are chorioamnionitis, placental abruption, retained placenta, endometritis, and sepsis (2). Neonatal complications are mainly consequences of prematurity and infection, including respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), pulmonary hypoplasia, sepsis, necrotizing

enterocolitis (NEC), and intraventricular hemorrhage (IVH) (3). The estimated rate of composite neonatal morbidity ranges between 12.5% and 85.7% (4). In this context, counseling parents about management options is essential, considering the risks and prognosis of previable PPROM. Another compelling issue is that the exact timing of delivery cannot be anticipated for patients managed conservatively.

Although it is well known that PPROM carries risks for the fetus, neonate, and mother, few researchers have addressed the issue of PPROM before viability since its incidence is low. We aim to present our series to elucidate the course of previable PPROM and to detect maternal and neonatal outcomes.

Material and Method

This study is designed as a retrospective cohort study from September 2016 to February 2022 involving patients diagnosed with PPROM at Kocaeli University Hospital before 24 weeks of gestation. The search was performed using inpatient medical records. Patients' demographic information, medical history, clinical follow-up, laboratory, and pathology results were retrieved from the hospital's electronic medical records. The Ethics Committee of Kocaeli University approved the study on 10 August 2023 (KU GOKAEK-2023/13.21). The present study was carried out in adherence to the ethical tenets delineated in the 1964 Declaration of Helsinki, and all patients provided informed consent.

Rupture of membranes was identified either by direct visualization of fluid discharge from the cervical os, either spontaneously or with the Valsalva maneuver. In clinically equivocal cases, placental alpha 2 microglobulin-1 (PAMG-1, Amnisure®, QIAGEN Sciences Inc., Germantown, MD) or insulin-like growth factor-binding protein-1 (IGFBP-1, ActimPROM®, Medix Biochemica, Espoo, Finland) rapid immunoassay tests were used. Ultrasonography was used for amniotic fluid volume evaluation; amniotic fluid index (AFI) <2 cm was accepted as anhydramnios, AFI <5 cm, or deepest vertical pocket <2 cm was oligohydramnios, and AFI > 5 cm was normal.

The management of previable PPROM in our institution included hospitalization, daily monitoring of vital signs, including body temperature, and evaluation for uterine tenderness and vaginal discharge. A complete blood count, biochemistry, including C-reactive protein (CRP), and urine culture were sent. All parents were counseled extensively by a team including a maternal-fetal medicine expert and a neonatologist about the jeopardy and prognosis of the alternative approach: termination of pregnancy versus expectant management. As a result, termination of pregnancy was deemed a viable alternative in all cases of previable PPROM, based on the family's decision. Patients opting for expectant management remained inpatient for a week initially for clinical follow-up and broad-spectrum antibiotics; 1 gr ampicillin iv every 6 hours for 48 hours, followed by 500 mg amoxicillin po every 8 hours for 5 days, were prescribed for the maternal interest. Termination of the pregnancy was performed via labor induction. In the expectant management group, after hospital discharge, close outpatient surveillance was conducted for fetal viability and signs of infection. In all cases, first-trimester crown-rump length was used for gestational age confirmation.

After the limit of viability, women were rehospitalized until delivery. Daily nonstress tests and biophysical profiles were used for antepartum fetal assessment. Fetal growth was evaluated every other week. On readmission at 24 weeks of gestation, 12 mg betamethasone was administered in 2 doses 24 hours apart (5). In the event that the patient experienced preterm labor or had a reason for delivery within 2 weeks after the initial steroid dose and before reaching 34 weeks of pregnancy, a rescue dose of 12 mg of betamethasone in two doses, 24 hours apart, was administered. Before 32 weeks of gestation, in patients with anticipated delivery in 24 hours, a 4.5 gr magnesium sulfate loading dose was initiated, followed by a 1 gr/hour maintenance dose iv infusion for neuroprotection (6). Spontaneous onset of labor, clinical chorioamnionitis, and placental abruption were the indications for early preterm delivery. Tocolytics were not administered. Delivery was planned after 34 weeks of gestation till 37 weeks unless otherwise indicated (7).

Age, body mass index, maternal medical history, obstetric history, history of previable PPROM, complete blood count, CRP, and urine results of the patients were noted. Collected clinical data included gestational age at rupture, duration of latency till delivery, route of delivery, placental pathology for chorioamnionitis, birth weight, duration of neonatal intensive care unit stays, and neonatal blood cultures.

The reviewed maternal outcomes were as follows: retained placenta, postpartum bleeding, chorioamnionitis, placental abruption, and sepsis. Clinical chorioamnionitis was diagnosed if there was maternal fever (>37.8°C) plus two or more of the following criteria: uterine tenderness, maternal tachycardia, fetal tachycardia, foul-smelling discharge, and maternal leukocytosis (8). Histological examination of placentas was searched to find out pathological chorioamnionitis. Placental abruption was diagnosed if vaginal hemorrhage accompanied abdominal pain and a hematoma attached to the placenta was visualized after birth.

Neonatal complications noted were respiratory distress syndrome (RDS), sepsis, bronchopulmonary dysplasia (BPD), intracranial hemorrhage, necrotizing enterocolitis (NEC), meningitis, and pneumothorax. Sepsis was classified as early neonatal sepsis in the first 7 days of life or late neonatal sepsis if it occurred later. Neonates that were delivered before the 32nd week of gestation were evaluated with a cranial ultrasound for hemorrhage. The requirement of oxygen for at least 28 days besides 30% oxygen and/or mechanical ventilator sup-

port or continuous positive airway pressure at 36 weeks of gestation was defined as BPD (9). If one of the complications, including BPD, IVH, NEC, or retinopathy of prematurity (ROP) was present, it was termed as composite neonatal morbidity.

The proportion of neonates that survived until discharge out of the total number of live births was termed as neonatal survival rate. Further comparison was conducted on the clinical data of survivors and nonsurvivors. The correlation between latency till delivery and gestational age at membrane rupture was analyzed. Latency till delivery was compared in different amniotic fluid volume groups and cases with and without clinical chorioamnionitis. In cases of neonatal sepsis, the presence of clinical chorioamnionitis was searched for.

Data analysis

Data were analyzed using the IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA) program. Normality was assessed using the Shapiro-Wilk test. Continuous variables with a normal distribution were presented as mean ± standard deviation; for non-normally distributed data, the median (Interquartile range-IQR) was presented. Categorical variables were represented as frequency and percentage. Differences between groups with a normal distribution were calculated by independent t-test; for non-normally distributed groups, Mann-Whitney U and Kruskal-Wallis tests were used. The Dunn test was used for multiple comparisons. For categorical variable group comparison, the Chi-square test or Fisher exact test was used. Spearman correlation analysis was utilized for numerical variables. Statistical significance was set at $p<0.05$.

Results

We detected that 78 women were diagnosed with PPROM before 24 weeks of gestation during the study period (Figure 1). The average maternal age was 29±6 (18-45) years, and the body mass index was 28±4 (17-39) kg/m². The chronic diseases of the patients were maternal hypothyroidism in four patients, type 2 diabetes mellitus in three, asthma in four, cardiac disease in two, and hepatitis B in two patients. Four cases were IVF pregnancies. Four patients had a history of previable PPROM. Thirty-eight patients were nulliparous. The median gestational age at membrane rupture was $18^{5/7}$ weeks (IQR $16^{5/7}$ - $21^{4/7}$ weeks). (IQR $16^{5/7}$ - $21^{4/7}$ weeks). All cases received antibiotic treatment, and all of the patients that reached 24 weeks received steroid, 17 cases received magnesium sulfate for neuroprotection. Three patients were given rescue steroids. Bacteriuria was detected in nine patients.

Forty-two patients (54%) opted for the termination of pregnancy. Among the 36 patients that were expectantly managed, seven patients (19.4%) had spontaneous abortions in 10 days, and twenty-nine patients (80.5%) reached the limit of viability. Table I displays the demographic data and history of the patients. Maternal demographics were not different statistically between termination and expectant management groups.

Gestational age at membrane rupture was earlier in the termination group (median 17 vs. 20 weeks, $p<0.001$). The majority of women who electively terminated their pregnancies had amniotic fluid abnormalities; 35 had anhydramnios, six had oligohydramnios, and only one was normal. In the patients who opted for termination of pregnancy, anhydramnios was more common when compared with the expectant management group ($p<0.001$). Retained products of conception were identified in three patients, while clinical chorioamnionitis was observed in three patients within the termination group. Table II shows the overall patients' clinical data.

Among the 29 patients that reached viability, seven delivered vaginally, and 22 had cesarean section. The indications for cesarean section were prior cesarean section (n=8), breech presentation (n=5), failed induction of labor (n=3), placental abruption (n=2), placenta previa (n=2), history of myomectomy (n=1), and acute fetal distress (n=1). Nine cases had anhydramnios, nine had oligohydramnios, and 11 had a normal amniotic fluid index. The median gestational age at birth was $28^{4/7}$ weeks (IQR $24^{3/7}$-$35^{5/7}$ weeks), and the median latency till delivery was 47 days (IQR 8-124 days). The mean birth weight was 1250±1191 gr.

Table I: *Demographic and obstetric data of the overall patients*

	Termination of pregnancy (n=42)	Expectant management		p*
		Spontaneous abortion (n=7)	Live birth (n=29)	
Maternal age, years	29.1±6.7	34.4±4.7	29.5±5.5	0.172
Maternal BMI, kg/m²	27.6±3.8	26.2±3.9	28.1±5.2	0.433
Chronic disease	9 (21.4%)	1 (14.2%)	6 (20.6%)	0.932
Nulliparous	21 (50%)	5 (71.4%)	12 (41.3%)	0.787
Multiparous	21 (50%)	2 (28.5%)	17 (58.6%)	0.703
Prior miscarriage history	13 (30.9%)	1 (14.2%)	9 (31%)	0.771
Prior live birth history	21 (50%)	2 (28.5%)	16 (55.1%)	0.818
Prior previable PPROM history	1 (2.3%)	1 (14.2%)	2 (6.8%)	0.330
ART pregnancy	1 (2.3%)	2 (28.5%)	1 (3.4%)	0.330
Smoker	4 (9.5%)	2 (28.5%)	2 (6.8%)	1.000

BMI: Body mass index; PPROM: Premature rupture of membranes; ART: Assisted reproductive technology
**p value comparison between termination and expectant groups, statistical significance was set at p <0.05*

Table II: *Clinical data of the overall patients*

	Termination of pregnancy (n=42)	Expectant management		p*
		Spontaneous miscarriage (n=7)	Live birth (n=29)	
GA at membrane rupture, weeks	$17^{3/7}$ ($16^{3/7}$- $19^{2/7}$)	$18^{0/7}$ ($17^{2/7}$ - $20^{2/7}$)	$22^{1/7}$ ($18^{1/7}$ - $23^{1/7}$)	<0.001
GA at delivery/abortion, weeks	$17^{4/7}$ ($16^{6/7}$- $19^{3/7}$)	$18^{2/7}$ ($17^{3/7}$ -$20^{3/7}$)	$28^{4/7}$ ($24^{3/7}$- $35^{5/7}$)	<0.001
Latent period, days	1 (1-2)	2 (1-3)	47 (8-124)	<0.001
Amniotic fluid volume				
Anhydramnios	35 (83.3%)	4 (57.1%)	8 (27.5%)	<0.001
Oligohydramnios	6 (14.2%)	0 (0%)	10 (34.4%)	0.141
Normal AFI	1 (2.3%)	3 (42.9%)	11 (37.9%)	<0.001
Blood parameters				
WBC at admission, (/mm^3)	11.450 (9.600-13.900)	15.100 (9.800-17100)	11.700 (10.000-15.250)	0.222
CRP at admission, (mg/L)	10,3 (17-21)	36 (6-40)	13 (6-24)	0.502
Chorioamnionitis				
Histological chorioamnionitis	N/A	2 (28.5%)	11 (37.9%)	N/A
Clinical chorioamnionitis	3 (7.1%)	2 (28.5%)	10 (34.4%)	0.004
Placental abruption	0 (0%)	0 (0%)	2 (6.8%)	0.209
Retained products of conception	3 (7.1%)	0 (0%)	0 (0%)	0.244

GA: Gestational age; WBC: White blood cells; CRP: C reactive protein; N/A: Not available because all placentas in the termination group were not examined histologically. Data presented as percentage (%), mean ± standard deviation, or median (interquartile range).
**p value comparison between termination and expectant groups, statistical significance was set at p<0.05*

Clinical chorioamnionitis was suspected in twelve patients among the 36 cases in the expectantly managed group (33%). Histopathological examination confirmed infection in all suspected placentas, with an extra case in the expectant group. Two patients experienced placental abruption (5%).

In the group that pregnancy proceeded to viability, cases with chorioamnionitis had a significantly shorter latency till delivery than cases without infection (median 35 vs. 112 days, p=0.027). Latency till delivery was found to be shorter in oligohydramnios cases (median 45 vs. 128 days, p=0.029). Also, latency till delivery had a strong inverse relationship with gestational age at membrane rupture (rs=-0.86, p<0.001).

If pregnancies ended in spontaneous miscarriage were added, the overall neonatal survival rate in the expectant group was 50%. Eighteen babies (62%) survived among 29 live births. Twenty-one neonates stayed in the NICU (72%), and the median length of stay was 8 days (IQR 1,5-31), ten babies were discharged, and 11 were deceased (Figure 1). The majority of newborns (nine babies) did not exceed one week in the nonsurvivor group.

In the live birth group, nineteen neonates had RDS (65%), 10 neonates had early sepsis (34%), five had late sepsis (17%), five neonates had bronchopulmonary dysplasia (17%), three neonates had retinopathy of prematurity (10%), five neonates had pneumothorax (17%), two had intracranial hemorrhage (6%), one had necrotizing enterocolitis (3%), and one had

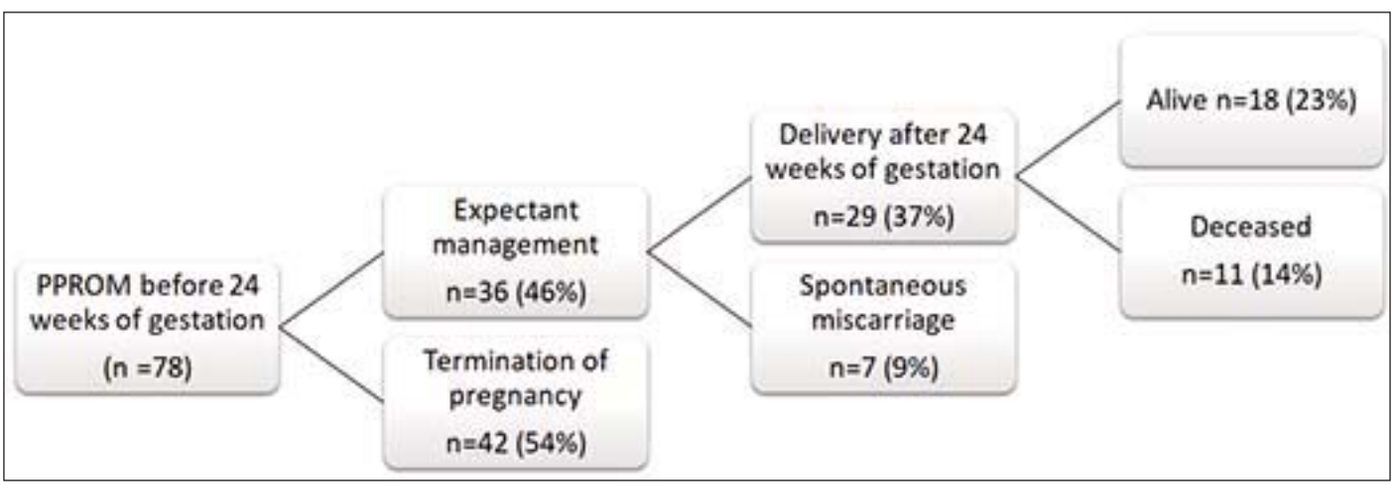

Figure 1: *Summary of the outcome of patients diagnosed with preterm premature rupture of membranes (PPROM) before 24 weeks of gestation.*

meningitis (3%). The microorganisms identified in blood cultures were Staphylococcus haemolyticus in two neonates, Enterococcus faecalis in one, and Klebsiella pneumoniae in one neonate. Overall short-term morbidity was seen in 19 liveborn neonates (65%). The rate of composite neonatal morbidity was 27.7% in survivors (n=5). Neonatal outcomes are shown in Figure 2.

Clinical data of surviving and non-surviving neonates is displayed in Table III. The median gestational age at membrane rupture was not different statistically in both groups. Latency period was longer (median 116 vs. 12 days, p<0.001), gestational week at delivery was later (median 35 vs. 24 weeks, p<0.001), and birth weight (median 2283 vs. 729 g, p<0.001) was significantly higher in the survivor group. Among the survivors, three neonates were born extremely preterm (<28 weeks of gestation), four were early preterm (between 28 and 34 weeks of gestation), five were late preterm (between 34 and 37 weeks of gestation), and six were term. Conversely, in the nonsurvivors, nine were extremely preterm, and two were early preterm. Sepsis was much more common in nonsurvivors (p<0.001). In early neonatal sepsis cases, mothers suffered from clinical chorioamnionitis more (p<0.001), but it was not different in cases with late sepsis (p=0.775).

Discussion

In this study, we analyzed the maternal and neonatal outcomes in pregnancies complicated with PPROM in the previable period. We showed that the patients opting for termination of pregnancy had a higher frequency of anhydramnios and membrane rupture at earlier weeks. In expectantly managed patients, 80.5% of pregnancies continue beyond 24 weeks. In live births, the median latency to delivery is 47 days (range 1-182 days), and the neonatal survival rate to discharge is 62%. If a woman selects expectant management in a previable PPROM scenario, the chance of having a baby without composite morbidity is 33%.

The neonatal survival rate after previable PPROM ranges from 5% to 81% in the literature, however, studies show heterogeneity (1,10,11). Higher survival rates in some studies can be explained by the selection of patients at later gestational ages biases results toward those most likely to survive (11-13). Furthermore, recent studies indicate evolving clinical practice along with neonatal care leads to a decline in mortality rates. In EPIPAGE, a national population-based study, the neonatal survival rate was 68% (13). Whereas PROMEXIL, a recent prospective cohort study including 86 pregnancies, reported a survival rate of 26% (14). On the other hand, our study showed a 62% neonatal survival rate to discharge in live births, which is higher than several studies. The ratio of termination of pregnancy in our series is high (54%), pregnancies with an unfavorable prognosis tend to opt for interruption of pregnancy more, which may lead to higher rates of survival in the expectant group in our study. Also, in our calculation the denominator was liveborn infants, if miscarriages are added, the overall take-home baby rate after expectant management of previable PPROM would be 50%. This percentage is comparable to the 51.5% stated by Kiver et al (15). All of our patients received steroids and antibiotics, which can also have a positive impact on survival. Moreover, our patients had a longer period of latency, as a result, deliveries were at later gestational ages which increases the chance of survival.

One of the significant factors in the prognosis of PPROM

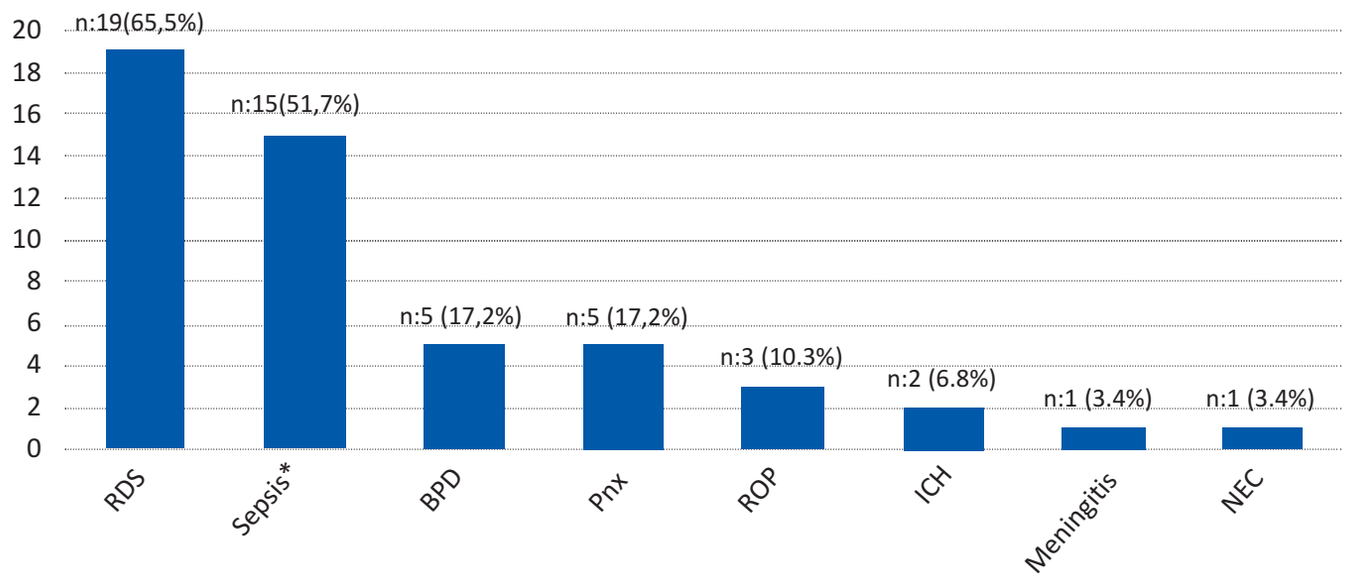

Figure 2: *Neonatal complications of the liveborn babies.*

*RDS: Respiratory distress syndrome; BPD: Bronchopulmonary dysplasia; Pnx: Pneumothorax; ROP: Retinopathy of prematurity; ICH: Intracranial hemorrhage; NEC: Necrotizing enterocolitis. *Sepsis includes both early sepsis and late sepsis*

Table III: *Clinical data of the live births*

	Survivor (n=18)	Nonsurvivor (n=11)	p*
Maternal age, years	29.5±5.7	29.3±4.4	0.940
Maternal BMI, kg/m²	27.9±5.2	28.6±5.4	0.936
GA at membrane rupture, weeks	$20^{1/7}$ ($17^{2/7}$- $23^{0/7}$)	$22^{0/7}$ ($20^{4/7}$- $23^{2/7}$)	0.120
GA at delivery, weeks	$35^{0/7}$ ($29^{2/7}$- $36^{2/7}$)	$24^{5/7}$ ($24^{2/7}$- $27^{0/7}$)	<0.001
Latent period, days	116 (44-134)	12 (2-45)	<0.001
Birth weight	2283.6±1147.7	729.4±289.7	<0.001
Amniotic fluid			
Anhydramnios	2 (11.1%)	6 (54.5%)	0.028
Oligohydramnios	7 (38.8%)	3 (27.2%)	0.694
Normal amniotic fluid volume	9 (50%)	2 (18.1%)	0.125
Laboratory parameters			
WBC at admission, (/mm³)	11.400 (9.500-14.700)	13.500 (11.700-15.500)	0.384
CRP at admission (mg/L)	10.85 (5-20)	17 (6-38)	0.912
Chorioamnionitis			
Histological chorioamnionitis	3 (16.6%)	8 (72.7%)	0.005
Clinical chorioamnionitis	3 (16.6%)	7 (63.6%)	0.001
Placental abruption	1 (5.5%)	1 (9%)	1.000
Gender			
Male	10 (55.5%)	8 (72.7%)	0.355
Female	8 (44.4%)	3 (27.2%)	0.448
Admitted to NICU	10 (56%)	11 (100%)	0.009
NICU stay, days	31 (28-108)#	4 (1-7)	0.002
Neonatal complication			
RDS	8 (44.4%)	11 (100%)	0.002
BPD	5 (27.7%)	0 (%0)	0.126
NEC	0 (0%)	1 (9%)	0.379
Pneumothorax	1 (5.5%)	4 (36.3%)	0.053
ROP	3 (16.6%)	0 (0%)	0.268
Sepsis	4 (22.2%)	11 (100%)	<0.001
Early sepsis	1 (5.5%)	9 (81.8%)	<0.001
Late sepsis	3 (16.6%)	2 (18.1%)	1.000
Meningitis	1 (5.5%)	0 (0%)	1.000
Intracranial hemorrhage	2 (11.1%)	0 (0%)	0.512

BMI: Body mass index; GA: Gestational age; WBC: White blood cells; CRP: C reactive protein; RDS: Respiratory distress syndrome; BPD: Bronchopulmonary dysplasia; NEC: Necrotizing enterocolitis; ROP: Retinopathy of prematurity; NICU: Neonatal intensive care unit.
Data presented as number of patients and percentage (%), mean ± standard deviation, or median (interquartile range).
**p value comparison between survivor and nonsurvivor neonates in the liveborn group, statistical significance was set at p<0.05; # only includes ten neonates that were admitted to NICU*

in early gestational weeks is the period between delivery and rupture of membranes. In our series, the median latency to delivery was 47 days, in contrast to previous studies that showed 6 to 13 days of latency (2,16,17). A wide range of distribution with a small number of patients in our study might have caused this prolonged interval. However, in a very recent study, Paulsen et al. reported a latency period of 44.7±34.8 days, consistent with our results (18). Furthermore, evidence suggests that increased latency duration is correlated with the administration of antibiotics before delivery (19,20). In our study, there was a significant inverse correlation between latency till delivery and gestational age at membrane rupture. In other words, earlier the incident, later the delivery, supporting previous findings in the literature (19,21).

Chorioamnionitis is the major infectious morbidity in PPROM patients. It can be either the cause or the result. Despite higher rates of chorioamnionitis estimated in some previous papers (11, 22), Sklar et al. reported a rate of 38% in a recent study including 108 expectantly managed patients (23). In a review, the rate of chorioamnionitis in previable PPROM was also reported as 37% (2). Our ratio was similar, chorioamnionitis was suspected clinically in 12 patients that were managed expectantly (33%). We found clinical chorioamnionitis cases had a significantly shorter median latency period than cases without infection, which correlates fairly well with Manuck et al.'s findings (10). This can be attributed to subclinical intraamniotic infection at the time of admission that might progress to clinically evident infection in a short while. Besides, this may reflect vigilance about the clinical findings indicating intrauterine infection entails prompt intervention. Maternal sepsis, endometritis, and postpartum hemorrhage are associated with previable PPROM, but none of our patients had these complications (2). A frequency of 21%-39% of retained products of conception has been reported in expectant management (1,17), but our three patients were in the termination group. This can be associated with a high cesarean section rate after viability in our cohort.

Amniotic fluid volume is significant in both the short-term and long-term prognosis of previable PPROM. Lack of amniotic fluid at early gestational ages may lead to fetal lung maldevelopment and limb deformities if it persists long enough (24,25). Fortunately, we did not detect skeletal deformities, a possible explanation is that patients with anhydramnios opted for termination of pregnancy more. Another finding in our series was, that delivery was sooner in patients with anhydramnios in the expectantly managed group. This points out that amniotic fluid abnormalities urge clinicians for immediate delivery in previable PPROM. The absence of oligohydramnios was found to be related to the prolongation of pregnancy beyond 24 weeks in a previous study (26). Lee et al. postulated that in cases with persistent oligohydramnios, a lower neonatal survival rate and more frequent developmental delay are expected (27). In the subgroup analysis in our series, nonsurvivors were more likely to have anhydramnios than survivors. It has been demonstrated that for each 5 mm of the deepest vertical pocket, the likelihood of neonatal survival rises by approximately 3 times during the follow-up (28). Weiner et al. emphasized that amniotic fluid volume at presentation is linked with severe neonatal respiratory morbidity in early PPROM (29).

As stated before, neonates delivered after previable PPROM confront complications such as RDS, BPD, and ROP as a consequence of prematurity. Respiratory morbidity was common in this study, the incidences of RDS, BPD, and pneumothorax were 65%, 17%, and 17%, respectively. This data compares favorably with other studies (2,18,30). Park et al. estimated that the incidence of pulmonary hypoplasia is 26.3% after prolonged PPROM before 25 gestational weeks, but our results do not appear to corroborate their observation (31). Pulmonary hypoplasia is a histopathological diagnosis, and stringent criteria for clinical diagnosis do not exist. Nevertheless, some of its features overlap with those of other neonatal causes of respiratory disorders. We believe that pulmonary hypoplasia might be underdiagnosed in our study because neonatal autopsy was not performed.

The rates of early sepsis and late sepsis were 34% and 17%, respectively, in this study. Growing evidence suggests that early and late-onset sepsis risk in neonates increases following exposure to chorioamnionitis (32). We found that clinical chorioamnionitis was more frequent in mothers of neonates with early sepsis ($p<0.001$), it was not statistically different in late neonatal sepsis ($p=0.775$), but a small number of cases may cause bias. Also, nonsurvivors in our study had a high sepsis incidence, either earlier birth or more exposure to chorioamnionitis caused them to be more vulnerable probably.

One of the strengths of our study is the inclusion of termination data that may provide a more comprehensive perspective within this scope. Also, we excluded iatrogenic membrane rupture after invasive procedures because membrane resealing is seen frequently. All patients were treated in a tertiary center using a standardized protocol that prevents heterogeneity of data.

Major limitations of our study are its retrospective design, lack of data on long-term neurological outcomes, and relatively small sample size that precludes risk stratification by gestational age. All cases received steroids, thus preventing us from conducting a comparative analysis of the effects experienced by those who did not receive the medication. Furthermore, the statistical comparison between patients who were administered rescue steroids and those who were not administered was impeded by the restricted number of patients. These data should be refined in larger prospective studies.

Conclusion

Our study showed that the rates of overall survival and survival without composite neonatal morbidity in the expectantly managed previable PPROM are 50% and 33%, respectively. A delicate equilibrium should be maintained between neonatal and maternal risks, although a prolonged latency period and subsequent delivery at advanced gestational ages improve neonatal outcomes, it seems to confer risk for chorioamnionitis. We believe that our data provides important information for clinicians when counseling parents about management strategies in previable PPROM.

Declarations
Acknowledgment: None.
Funding: The authors received no funding or grants.
Ethics approval and consent to participate: All participants

signed informed written consent before being enrolled in the study. The study was reviewed and approved by the ethics committee of Kocaeli University (Ethics approval reference number: KU GOKAEK-2023/13.21, date 10 August 2023). All procedures were performed according to the Declaration of Helsinki.

Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request.

Conflict of interest: The authors declare that they have no competing interests.

Authors' contributions: Concept: Y.D., Design: Y.D., Data Collection or Processing: E.K., M.D.E, Analysis, and Interpretation: Y.D., A.G., Literature Search: Y.D., E.K., Writing: Y.D., E.K., Critical Review: Y.D. All authors read and approved the final manuscript.

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