

Outcomes of Pregnancies Complicated by Preterm Premature Rupture of Membranes Before and After 24 Gestational Weeks: A Retrospective Analysis

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ABSTRACT Objective: Preterm premature rupture of membranes (PPROM) complicates 1-5% of pregnancies. Data regarding the outcomes and prognostic factors of pregnancies with pre-viable PPRM (before 24 weeks of gestation) are relatively limited and vary. Therefore, we aimed to evaluate outcomes of PPRM and compare outcomes before and after 24 weeks of pregnancy. **Material and Methods:** This is a retrospective cohort study that spanned September 1, 2018 to September 30, 2020 at a tertiary hospital. Pregnant women who experienced PPRM between 12 and 33 6/7 weeks were included. Data on maternal obstetric and clinical characteristics, fetal and neonatal characteristics were compared in PPRM occurred before (n=42) and after (n=92) 24 gestational weeks groups. **Results:** Demographic data were similar for both groups. There were no cases of maternal sepsis and death in either group. Intrauterine death, retention products, necrotizing enterocolitis (NEC), and bronchopulmonary dysplasia (BPD) rates were significantly higher in PPRM occurring before 24 weeks of gestation. A logistic regression analysis showed that significant predictors of survival at discharge were gestational age at diagnosis, corticosteroid prophylaxis for fetal lung maturation, and delivery route. Multivariable regression analysis showed that the only independent predictor for survival rate at discharge was gestational age at diagnosis (odds ratio: 1.34, 95% confidence interval: 1.13, 1.19, p=0.001). **Conclusion:** Expectant management in pregnancies complicated by PPRM between 12 and 23 6/7 weeks of gestation is associated with an overall neonatal survival rate of 33.3%, high risk of BPD and NEC among survivors, and does not carry severe maternal risks.

Keywords: Preterm premature rupture of membranes; pregnancy outcomes; pregnancy complications

Preterm premature rupture of membranes (PPROM) complicates 1-5% of pregnancies and is defined as spontaneous rupture of amniotic membranes before 37 weeks, also, it is an important clinical condition, responsible for one-third of preterm births.^{1,2} PPRM also exposes pregnant women to risks of chorioamnionitis, placental abruption, cord prolapse, and urgent delivery.¹

Before 24 weeks of gestation, also referred to as pre-viable PPRM, appears in 3.7 out of every 1,000 births.³ Beydoun and Yasin reported the survival rate of babies born before 25 weeks of gestation as 0%.⁴ However, perinatal survival rates have increased in the last thirty years due to advances in neonatal care

but studies have reported survival rates of 12-96%, and the difference is huge.^{5,6} If PPRM occurs before the previable week of pregnancy, pulmonary hypoplasia risk appears up to 70%.⁷ It is a significant complication with a high mortality rate. Pulmonary hypoplasia is related to the gestational age at which membrane rupture occurs and whether oligohydramnios is present or not. PPRM has also been shown to be associated with neurodevelopmental impairment and neonatal white matter damage.⁷

Data regarding the outcomes and prognostic factors of pregnancies with pre-viable PPRM are relatively limited and vary. Therefore, as clinicians, counselling these patients is still a challenge. Because

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Peer review under responsibility of Journal of Clinical Obstetrics & Gynecology.

Received: 16 Jul 2023

Received in revised form: 01 Nov 2023

Accepted: 14 Nov 2023

Available online: 16 Nov 2023

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of the conflicting outcomes of extremely preterm infants suffering from pre-viable PPRM, American College of Obstetricians and Gynecology suggests that women presenting with pre-viable PPRM should be counseled regarding the risks and benefits of expectant management versus immediate delivery.⁸

In this study, we aimed to evaluate the maternal, fetal, and neonatal results of pregnant women with PPRM before and after 24 weeks of gestation at our tertiary education and research hospital.

MATERIAL AND METHODS

This study was performed as a retrospective observational study that spanned September 1, 2018 to September 30, 2020 at a tertiary education and research hospital with an annual number of approximately 5,000 births. It was identified that 141 cases of PPRM occurring at the gestational age between 12+0 and 33+6 weeks. Written informed consent was obtained from all patients. Ethics approval was obtained from the Health Sciences University Ümraniye Training and Research Hospital Ethics Committee (date: September 17, 2020, no: 22131). The study was conducted in accordance with the Helsinki Declaration principles. Cases presented with iatrogenic rupture of membranes and congenital anomalies were excluded. Both singleton and multiple pregnancies were included. Before 24 weeks of gestation seven pregnant women opted termination of pregnancy. The clinical records of 134 pregnant women and neonates were evaluated. Viability was defined as being at or after 24 weeks of gestation or having an estimated fetal weight of 500 gr and above. To assess the surviving neonates' short-term outcomes we investigated, intraventricular hemorrhage [(IVH), Grade 3, 4], bronchopulmonary dysplasia (BPD), retinopathy of prematurity [(ROP), Stage 3 or higher], necrotizing enterocolitis (NEC), and contracture deformities rates.

PREGNANCY MANAGEMENT

The gestational week of the patients was calculated with the last menstrual period and first -trimester ultrasonography findings. It was observed that each patient underwent a sterile speculum examination for

PPROM confirmation. Diagnosis of membrane rupture was made when direct water leakage was observed or when placental alpha microglobulin-1 protein marker test (AmniSure ROM Test; QIAGEN Sciences, AmniSure GMBH, Gießen, Germany) was positive. Each patient was evaluated by ultrasonography for fetal well-being, and it was observed that amniotic fluid volume and fetal anomaly screening were also performed.

The family was given counselling about perinatal outcomes. Termination option was offered to all patients with pre-viable PPRM. The expected treatment was performed for the patients that had no symptoms which met Gibbs' clinical criteria for chorioamnionitis. Gibbs' criteria include a temperature of at least 37.8 °C, as well as two or more of the following: fetal tachycardia, maternal tachycardia, uterine sensitivity, bad smell of amniotic fluid, and maternal leukocytosis. Expectantly managed pregnancies were followed as inpatients at the beginning.⁹ When we were sure of the maternal and fetal reassuring, the patients were followed up weekly as outpatients. After two days of intravenous ampicillin (2 grams every 6 hours), oral amoxicillin was administered for five days. Pregnants were monitored by daily vital signs and body temperature, twice weekly C-reactive protein, and leukocytes. Fetal well-being was monitored by daily non-stress test and weekly assessment of amniotic fluid index. To check for signs of cervicitis, the patients also received vaginal and cervical swabs.

A single course of antenatal corticosteroids was administered to all pregnant women who were considered to have reached the viable gestational week. The choice of administration after 22 completed gestational weeks in pre-viable PPRM patients varied due to the attending doctor's discretion. Tocolytics were also administered to enable the use of steroids to promote lung maturity. Continued to be expected management unless there were chorioamnionitis, uncontrollable painful uterine contractions by tocolysis, and abnormal fetal heart rate pattern. Indications for a caesarean section included suspected fetal distress, previous uterine surgery, fetal malpresentation, and placental abruption.

STATISTICAL ANALYSIS

Data were analysed using the SPSS ver. 22.0 (SPSS, IBM, Chicago, IL). The Kolmogorov-Smirnov test was used to analyse the normality of the data. Qualitative variables were expressed as counts and percentages, and quantitative variables were expressed as mean±SD or interquartile range, as suitable. The data were analysed by using the Pearson χ^2 -test or the Fisher's exact test and continuous variables using the Mann-Whitney U test and the Student's t-test, as appropriate. Multivariable logistic regression analyses were also performed controlling for confounding variables. Statistical significance was considered with p value ≤ 0.05 .

RESULTS

Demographic and obstetric outcome data of pregnancies with pre-viable (before 24 weeks of gestation) and viable (after 24 weeks of gestation) PPRM

(n=134) are presented in Table 1. Of the cases, 121 were singleton and 13 were twin pregnancies. The fetus identified as having PPRM was included in the analyses for each twin pregnancy. There was no statistically significant difference between singleton and twin pregnancies in terms of demographic data and median gestational ages at PPRM. The common maternal demographic and clinical data were similar in pre-viable and viable PPRM groups (Table 1).

The rate of being anhydramnios at initial was higher in the pre-viable PPRM group than the viable PPRM group (45.2% vs. 14.1% p=0.003, respectively). The rate of administration corticosteroids for fetal lung maturation was higher in the viable PPRM group than the pre-viable PPRM group in relation to the prophylaxis protocol applied. Caesarean section and neonatal intensive care unit (NICU) admission rates were higher in the viable

TABLE 1: Demographic and obstetric outcomes of patients with pre-viable (before 24 weeks of gestation) and viable (after 24 weeks of gestation) PPRM.

	Pre-viable PPRM (n=42)	Viable PPRM (n=92)	p value
Maternal age (years)	28 (26-32)	30 (25-34)	0.547 ^a
Gravida	2 (1-4)	2 (1-3)	0.936 ^a
Parity	1 (0-2)	1 (0-2)	0.985 ^a
Cervical length (mm)	0 (0-30)	23 (0-35)	0.479 ^a
History of PPRM	1 (2.4)	1 (1.1)	0.523 ^b
Smoking	3 (7.1)	3 (3.3)	0.372 ^b
Multiple pregnancy	4 (9.5)	9 (9.8)	>0.99 ^b
Gestational age at PPRM (week)	19.1 (16.8-21.6)	29.5 (26.6-32.3)	<0.001 ^a
Latency (day)	5 (2-34)	4 (1-19)	0.131 ^a
Antenatal steroid	17 (40.4)	74 (80.4)	<0.001 ^b
Being anhydramnios at initial	19 (45.2)	13 (14.1)	0.003 ^b
Gestational age at birth (week)	22.1 (18.2-26.2)	32.4 (29.5-33.5)	<0.001 ^a
Birthweight (gram)	552 (200-870)	1,758 (1,200-2,158)	<0.001 ^b
APGAR 1'	0 (0-5)	7 (5-8)	<0.001 ^a
APGAR 5'	0 (0-7)	8 (7-10)	<0.001 ^a
Live birth	29 (69.0)	90 (97.8)	<0.001 ^b
Caesarean section	8 (27.5)	60 (65.2)	<0.001 ^b
NICU admission	15 (51.7)	79 (87.7)	0.003 ^b
Chorioamnionitis	2 (4.9)	3 (3.3)	0.644 ^b
Placental abruption	0 (0)	3 (5.1)	0.812 ^b
Retained POC	17 (40.4)	2 (2.2)	<0.001 ^b
Maternal sepsis	0 (0)	0 (0)	-
Maternal death	0 (0)	0 (0)	-

Data presented as fraction (%) and interquartile range as appropriated; ^aMann-Whitney U test; ^bChi-squared test; PPRM: Preterm premature rupture of membranes; NICU: Neonatal intensive care unit; POC: Products of conception.

PPROM group than the pre-viable PPRM group (65.2% vs 27.5% $p<0.001$ and 87.7% vs 51.7% $p=0.003$, respectively). APGAR scores were higher, neonatal exitus rates were lower in the viable PPRM group. There were no neonatal contracture deformities in the groups. Maternal adverse outcomes such as placental abruption, and chorioamnionitis were not significantly different in the pre-viable and the viable PPRM groups. There were no cases of maternal sepsis and death in either group. Retained products of conception (POC) rate was higher in pre-viable PPRM group than in viable PPRM group (40.4% vs 2.2% $p<0.001$, respectively). Delivery and survival outcomes are summarized in Figure 1. BPD and NEC rates were higher in the pre-viable PPRM group than in the viable PPRM group (13.8% vs 1.2% $p<0.001$ and 6.9% vs 0.0% $p=0.032$, respectively). Neonatal sepsis, IVH, and ROP rates were

not found statistically different. While the overall survival to discharge rate based on the total number of expected managed pregnancies was 33.3% (14/42) in pre-viable PPRM group it was 93.4% (86/92) in the viable PPRM group ($p<0.001$).

A logistic regression analysis demonstrated that significant predictors of neonatal survival rate at discharge were gestational age at diagnosis, corticosteroid prophylaxis for fetal lung maturation, and route of delivery. Multivariable regression analysis demonstrated that the only independent predictor for survival rate at discharge was gestational age at diagnosis [odds ratio (OR): 1.34, 95% confidence interval (CI): 1.13, 1.19, $p=0.001$] (Table 2). Twenty two weeks' cut-off would be most relevant to being alive at discharge in the receiver operating characteristic (ROC) curve analysis (AUC: 0.82, 95% CI: 0.71, 0.93).

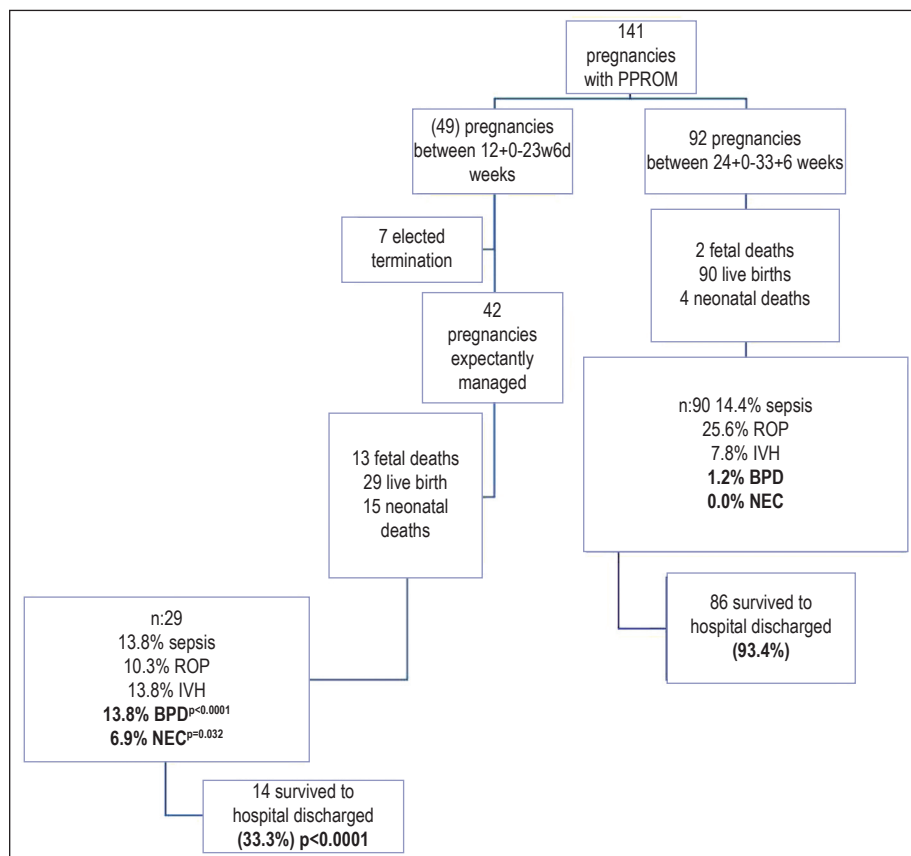


FIGURE 1: Flow chart with summary of outcomes of PPRM cases.

PPROM: Preterm premature rupture of membranes; ROP: Retinopathy of prematurity; IVH: Intraventricular hemorrhage; BPD: Bronchopulmonary dysplasia; NEC: Necrotizing enterocolitis.

TABLE 2: Single variable and multivariable regression analysis of maternal risk factors affecting neonatal survival rate at discharge.

	Single variable regression analysis		Multivariable regression analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Gestational age at diagnosis	1.34, (1.11-1.58)	0.001	1.34, (1.12-1.58)	0.001
Corticosteroid prophylaxis	0.25, (0.07-0.83)	0.024	0.32, (0.08-2.02)	0.62
Being anhydramnios at initial	0.44, (0.12-1.60)	0.21		
Route of delivery	1.06, (1.03-1.74)	0.016	0.95, (0.89-1.78)	0.27
Latency period	0.98, (0.96-0.99)	0.04	0.99, (0.97-1.00)	0.23
Birth week	1.02, (0.92-1.13)	0.65	1.06, (0.98-1.14)	0.103
Birth weight	1.00, (0.99-1.00)	0.503	1.00, (1.00-1.00)	0.65

OR: Odds ratio; CI: Confidence interval.

TABLE 3: Clinical characteristics and neonatal survival and morbidity outcomes of pregnant women with PPRM before 24 weeks of gestation.

	12-20 w PPRM	20-24 w PPRM	p value
GA at PPRM	17.0 (15.9-18.0)	22.4 (21.6-23.0)	<0.001^a
Latency, day	5.5 (1.0-59.5)	12.0 (3.0-34.0)	0.951 ^a
Cervix, mm	0 (0-40)	11 (0-36)	0.974 ^a
Birth week	19.5 (16.6-26.1)	24.0 (23.3-28.6)	0.061 ^a
Birth weight, gram	269 (150-800)	758 (555-1030)	0.043^a
Being anhydramnios at initial n, %	11/21, 55.0%	8/21, 38.1%	0.968 ^b
TOP n, %	4/25, 16.0%	3/24, 12.5%	0.865 ^b
IUFD n, %	9, 42.8%	4, 19.1%	0.116 ^b
Neonatal death n, %	7/12 58.3%	8/17 47.0%	0.550 ^b
<24 h	5/7, 71.4%	5/8, 62.5%	
24 h-7 d	1/7, 14.2%	1/8, 12.5%	
>7 d	1/7, 14.2%	2/8, 25.0%	
Sepsis	1/12, 8.3%	3/17, 17.6%	0.622 ^c
NEC n, %	1/12, 8.3%	1/17, 5.8%	>0.99 ^c
IVH n, %	2/12, 16.6%	2/17, 11.7%	>0.99 ^c
ROP n, %	1/12, 8.3%	2/17, 11.7%	>0.99 ^c
BPD n, %	1/12, 8.3%	3/17, 17.6%	0.622 ^c
Survival at discharge n, %	5/21, 23.8%	9/21, 42.8%	0.190 ^b

Data presented as fraction (%) and interquartile range as appropriated; ^aMann-Whitney U test; ^bChi-squared test; ^cFisher exact; PPRM: Preterm premature rupture of membranes; TOP: Termination of pregnancy; IUFD: Intrauterine fetal demise; NEC: Necrotizing enterocolitis; IVH: Intraventricular hemorrhage; ROP: Retinopathy of prematurity; BPD: Bronchopulmonary dysplasia.

The pregnancies with pre-viable PPRM were stratified again based on gestational age into (12.0-19.6 weeks), and (20.0-23.6 weeks) PPRM groups. Median values of gestational ages, latency periods, cervix lengths, and birth weeks were not found significantly different (Table 3). Median birth weight was found lower in 12.0-19.6 weeks than in 20.0-23.6 weeks close to the statistical significance ($p=0.043$). Amniotic fluid amount at initial, fetal death, neonatal

death, postnatal adverse outcome rates, and the incidence of survival at discharge were not found significantly different between these subgroups.

DISCUSSION

The principle findings demonstrated that the only factor that was significantly related to survival at discharge was gestational age at PPRM diagnosis in this study. Expectant management in pre-viable

PPROM does not increase severe maternal morbidity and mortality. In pre-viable PPRM patient group, the average live birth and baby take-home rates were 69% and 33%, respectively. In the subgroup analysis of pre-viable PPRM patients, this study could not show a significant difference in severe neonatal morbidity, neonatal mortality, and survival discharge rates.

There are limited data regarding pre-viable PPRM outcomes in the recent literature. Similar outcomes to ours have been reported for PPRM before viability in recent literature.¹⁰⁻¹⁶ Accumulated data shows that there is still a high risk of short and long-term severe morbidity among survivors. Unfortunately, no clinical evidence has been demonstrated to reliably predict pregnancy outcomes at the time of initial diagnosis of pre-viable PPRM so far.

In the present study, neonatal outcome was not influenced by the amount of amniotic fluid or severity of oligohydramnios. However, in a recent review by Ladella et al. on 117 PPRM patients, they showed that the development of oligohydramnios after PPRM is associated to lower Apgar scores and longer hospitalization in the NICU.¹⁷ Another study demonstrated that there is a statistically significant relationship between neonatal survival and the severity of oligohydramnios.¹⁸ Although it was reported between 3.7% to 29.4% rate, we found no contracture deformities in this PPRM cohort.^{12,19} These reports have also demonstrated that a longer latency period and a later gestational age at membrane rupture are significantly associated with a high survival rate. In a study in which 104 patients with PPRM at 20-23 6/7 weeks of gestation were included and 51 neonates continued to survive, no severe neonatal morbidity was observed in 52.9% of the survivors, and prolongation of the latency period and an increase in the gestational week at birth were associated with increased survival. In particular, PPRM at 22 gestational weeks or beyond (adjusted OR: 12.2, 95% CI: 3.3, 44.8) and a latency period of 7 days or more (adjusted OR: 10.1, 95% CI: 3.2, 31.6) were statistically significantly associated with overall survival. The same two variables were statistically significantly associated with neonatal survival with no

severe morbidity.¹² In a study by Sorano et al., which included 66 patients who developed PPRM between gestational weeks of 20-23 6/7, it was found that the per-one day increase in gestational age at which rupture occurs and the per one-day increase in latency period increase neonatal survival without significant neonatal morbidity (adjusted OR: 1.37, 95% CI: 1.03, 1.83 and adjusted OR 1.11, 95% CI 1.02, 1.21, respectively).¹⁹ However, in multivariate analysis, it was found that only the gestational age at membrane rupture maybe predict survival at discharge as a neonatal outcome (adjusted OR: 1.34 95% CI: 1.13, 1.59). In the ROC curve analysis, it was demonstrated that 22 weeks' cut-off would be most relevant to being alive at discharge (AUC: 0.82, 95% CI: 0.71, 0.93).

Esteves et al. claimed that having more than 750 g birthweight was associated with a lower mortality rate for newborns and a lower risk of developing at least one serious morbidity at birth over to 917 g and 27 weeks.¹⁵ We could not find an association between birth weight and adverse neonatal outcome. In our results, this lack of the association between neonatal outcome and all risk factors such as latency period, amniotic fluid amount, and birthweight, could be explained by the small sample size and the higher perinatal losses, especially for the PPRM before 24 weeks. Although our results were such, based on our general clinical observation, and we think that prolonging intrauterine stay will better the neonatal outcome.

Termination of pregnancy is a legal situation according to Türkiye law. In our clinic following the initial diagnosis of pre-viable PPRM, patients are counselled extensively and they could decide whether to continue or not the pregnancy. It is a controversial issue because neonatal survivals have been reported very differently (20-80%) in studies and there is a great difference in morbidity among survivors (30-100%).^{5,19-22} In our findings, live birth rate was 69%, survival rate at discharge was 33% for pre-viable PPRM patients. After birth, 44.8% of neonates experienced severe morbidity. The rates of BPD, IVH, ROP, and NEC were 13.8%, 13.8%, 10.3%, and 6.9%, respectively. In their review, Waters and Mercer reported an overall survival rate of

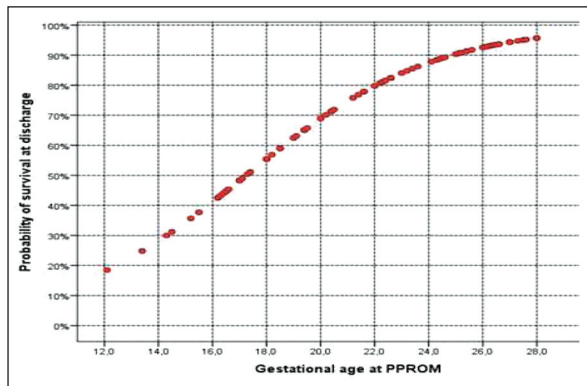


FIGURE 2: Probability chart shows probability of survival at discharge according to the gestational age at PPROM diagnosis.

PPROM: Preterm premature rupture of membranes.

44%, based on findings of different pre-viable PPRM studies.³ In the same review, they reported the rates of BPD, IVH, ROP and, NEC were 29.1%, 5%, 4.6%, and 4%, respectively.³ This wide variation may be associated with improvements in neonatal care over the years. Another factor is that due to the low incidence of pre-viable PPRM, some studies have a wide range of gestational age at the diagnosis of PPRM, as in our study. In the present study, a probability chart that shows probability of survival at discharge according to the gestational age at PPRM diagnosis between 12.0 and 28.0 weeks of gestation was presented (Figure 2). It may be helpful in daily clinical practice while counselling the parents in this clinical condition. We think that patients should also be given a prognosis based on gestational age at the time PPRM occurred especially in the second trimester.

In our study group, there was no maternal sepsis and death. Clinical chorioamnionitis rates were similar before and after 24 weeks of PPRM groups. The only difference was found for retained POC as a maternal complication. Gunes et al reported in their recent study that the most common complication was chorioamnionitis (24.48%) and other maternal complications were placental abruption, sepsis, caesarean hysterectomy, and postpartum abdominal abscess.¹⁸ In a recent systematic review, it was reported that the rate of chorioamnionitis was 47% and complications such as retained POC and curettage were more common in PPRM before 20 weeks.¹¹

There are several strengths in our study. Our study group was a relatively homogeneous group. All patients were evaluated and managed by a single perinatologist group and had well-characterized perinatal outcomes. The limitations of the present study included retrospective design, small sample determined by the low frequency of pre-viable PPRM and, lack of long-term outcomes.

CONCLUSION

Finally, expectant management appears to be a more acceptable option for patients with PPRM due to efforts that focused on prolonging intrauterine life without causing severe maternal complications. The present study showed that expectant management in 42 pregnancies complicated by PPRM before 24 weeks of gestation is associated with a live birth rate of 69%, a survival at a discharge rate of 33%, a high risk of BPD and NEC among survivors, and carries low maternal risks. Despite the limitations, this study will be helpful to discuss the perinatal outcome while we are counselling the parents in PPRM situation.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Ayşegül Özel, Ayşegül Çakmak, Cem Yalçınkaya, Canan Satır Özel, Murat Muhcu; **Design:** Ayşegül Özel, Ayşegül Çakmak, Murat Muhcu; **Control/Supervision:** Ayşegül Özel, Murat Muhcu; **Data Collection and/or Processing:** Ayşegül Özel, Ayşegül Çakmak, Cem Yalçınkaya; **Analysis and/or Interpretation:** Ayşegül Özel, Murat Muhcu; **Literature Review:** Ayşegül Özel, Ayşegül Çakmak, Cem Yalçınkaya, Canan Satır Özel; **Writing the Article:** Ayşegül Özel; **Critical Review:** Ayşegül Özel, Murat Muhcu; **Materials:** Ayşegül Özel, Ayşegül Çakmak, Cem Yalçınkaya, Canan Satır Özel.

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