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Maternal and Neonatal Outcomes in Cases of Premature Preterm Rupture of Membranes and the Effect of Latency Periods (Rupture of Membranes to Delivery) on Adverse Pregnancy Outcomes

Zahra Akbarian Rad[1], Shahla Yazdani[2], Mina Galeshi[3], Neda Eftekhari[2], Fatemeh Shafizadeh[4*]

1. *Department of Pediatrics, School of Medicine, Babol University of Medical Sciences, Babol, Iran*
2. *Department of Obstetrics and Gynecology, School of Medicine, Babol University of Medical Sciences, Babol, Iran*
3. *Student Research Committee, School of Nursing and Midwifery, Shahroud University of Medical Sciences, Shahroud, Iran*
4. *Department of Obstetrics and Gynecology, School of Medicine, Babol University of Medical Sciences, Babol, Iran*

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Corresponding Information:
Fatemeh Shafizadeh,
Department of Obstetrics and Gynecology, School of Medicine, Babol University of Medical Sciences, Babol, Iran
Email: Shafizadehfatemeh64@gmail.com

ABSTRACT

Background & Objective: Premature preterm rupture of membranes (PPROM) occurs in about 2-5% of singleton pregnancies and is known to cause one-third of preterm births. Our primary aim was to determine the maternal and neonatal outcomes in PPROM cases in mothers with a gestational age of less than 37 weeks.

Materials & Methods: In this prospective cross-sectional study, eligible singleton women between 24+0-37+6 weeks of gestation with the PPROM enrolled who had referred to Ayatollah Rouhani Hospital in Babol, Iran, during the years 2019-2020. Maternal and neonatal outcomes were obtained by the checklist.

Results: The mean age of the studied mothers was 29.3± 6.19 years, and their mean body mass index was 30.6 ±5. The incidence of chorioamnionitis at the gestational age of >32 weeks was more than that in women at gestational age equal to or over 32 weeks (P≤0.0001). Vaginal bleeding was almost more than twice as high in women with a gestational age of less than 32 weeks compared to those with a gestational age equal to or over 32 weeks (P≤0.0001). Neonatal morbidity was higher in all cases at less than 32 weeks of gestation (P≤0.0001). The neonatal mortality rate was 5.35%, but it was 25% at less than 32 weeks of gestation (P≤0.0001). The latency period greater than 7 days had more odds ratio for neonatal morbidity.

Conclusion: Due to the high incidence of maternal and neonatal outcomes in gestational age less than 32 weeks, it is suggested that appropriate instructional materials and proper proceeding should be taken to prevent preterm labor and preterm rupture of the membranes.

Keywords: Latency, Morbidity, Neonatal mortality, Preterm labor, Premature rupture of membranes

Introduction

Premature preterm rupture of membranes (PPROM) is the rupture of the amniotic sac before 37 weeks of gestation, which is a predisposing factor for preterm delivery **(1)**. Although this complication occurs in about 2-5% of singleton pregnancies, it is known to cause one-third of preterm births (PTB) **(2)**. The prevalence of recurrent PPROM has been reported to be 21-33% **(3)**. PTB is the cause of 75% of prenatal morbidity as well as more than half of the disabilities and developmental disorders in children worldwide **(4)**, and PPROM accounts for approximately 20% of prenatal morbidity **(5)**. Despite extensive studies on this issue and improved antenatal care, the incidence of PTB in advanced societies has not decreased significantly **(6)**. Several factors are involved in PPROM and infection is one of the most common causes of PTB **(7, 8)**. The cause of premature rupture of the amniotic sac is completely unknown. One study illustrated that 25-50% of PTBs occurred without a known cause **(9)**.

Many factors such as PTB history, genetic factors, smoking, increasing maternal age, antepartum hemorrhage, and infection have been considered as the causes of PPROM. Regardless of the etiological cause, gestational age is a determining factor in the management of PPROM cases.

Active management of labor is generally applied at gestational age over 34 weeks and 7 days **(10)**. Though there is evidence to suggest that gestational age should be considered at 35 weeks of gestation because of increased neonatal benefit, there is no consensus on this **(11)**. Due to the increased rate of morbidity and mortality in mothers and fetuses with this complication, timely and accurate diagnosis of PPROM is very important in disease management **(1)**. In recent years, many studies have evaluated the effect of latency periods (rupture of membranes to delivery) on perinatal outcomes and reported conflicting results **(5, 10, 12-14)**. Therefore, the aim of this study was to determine the maternal and neonatal outcomes in PPROM cases in mothers with a gestational age over 37 weeks and investigate the adverse outcome of neonates with the latency periods.

Materials and Methods

This cross-sectional study was performed on eligible pregnant women with a gestational age of 24-37 weeks, who were hospitalized due to the PPROM and treated at Ayatollah Rouhani Hospital in Babol, Iran from July 2019 to December 2020.

Gestational age was calculated based on the date of the first day of the last menstrual period (LMP), and if menstruation was irregular, gestational age less than 20 weeks was calculated by ultrasound. If the results of the two methods differed for more than seven days, the results of ultrasound were accepted. In patients who had no ultrasound, the gestational age was determined via a new ultrasound and matching the fundal height and date of the LMP.

The women whose recent fetal ultrasounds showed no abnormalities were included in the study. Confirmed rupture of the amniotic sac was affirmed by one of the methods including leakage of amniotic fluid from the vagina on speculum examination or positive Fern test or Nitrazine test **(15)**. Mothers who were discharged with personal consent and mothers who entered the active phase of labor or had bleeding, as well as mothers with gestational hypertension, gestational diabetes, multiple pregnancies, intrauterine fetal growth retardation, fetal distress at the time of admission, and preeclampsia were excluded from the current study. Sample size was determined using census. In the present study, sampling was done since the approval of the proposal and obtaining the code of ethics until 17 months.

After obtaining approval from the Vice Chancellor of Research and Technology of Babol University of Medical Sciences, patients admitted to the maternity ward from July 8, 2019 to December 8, 2020 and those who met the inclusion criteria were selected. Then, the data were collected using a checklist of variables including age, gestational age, number of gravidity, history of internal diseases and surgery, history of infertility, history of PTB, variables related to a recent pregnancy (i.e., gestational age based on the date of the last normal menstrual period or based on ultrasound parameters <20 weeks, time of rupture of the amniotic sac, proving method of amniotic sac rupture), information on the time of maternal-neonatal hospitalization such as recording the symptoms of chorioamnionitis (fever, fetal heart tachycardia, uterine tenderness, maternal tachycardia, foul-smelling discharge), time and cause of termination of pregnancy and delivery method, intrauterine complications such as antepartum bleeding, postpartum fever, weight and gender of the infant, Apgar score at birth, need for resuscitation at birth, neonatal mortality, intraventricular hemorrhage, respirtory distress syndrome (RDS), and neonatal sepsis.

Diagnosis of clinical chorioamnionitis was based on the temperature rise equal to or over 38°C (oral temperature) with at least two other symptoms, uterine tenderness as maternal abdominal pain when touched in the absence of uterine contractions, leukocytosis (>15,000 cells per cubic millimeters), maternal tachycardia (>100 beats), fetal tachycardia (>160 beats), or foul-smelling and purulent vaginal discharge**(16)**.

Descriptive results of statistical analysis for quantitative and qualitative variables were presented as mean ± standard deviation and frequency, respectively.

Independent t-test was used to compare quantitative variables between the studied groups and Chi-square test was applied for qualitative variables. Furthermore, crude and adjusted logistic regression models were utilized to estimate the odds ratio and eliminate the intervening variables. Data were analyzed using SPSS version 22 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). The criterion for determining the relationship was the statistically significant differences, and the level of significance was considered less than 0.05.

Results

Totally, 360 mothers were included in the current study, from which 24 were excluded considering the exclusion criteria (i.e., intrauterine growth retardation, multiple births, entering the active phase of labor, fetal bleeding and distress at admission, early discharge due to the personal consent, hospitalization for the preeclampsia, and gestational diabetes). Hence, the analysis was performed on 336 pregnant women with PPROM (Figure 1).

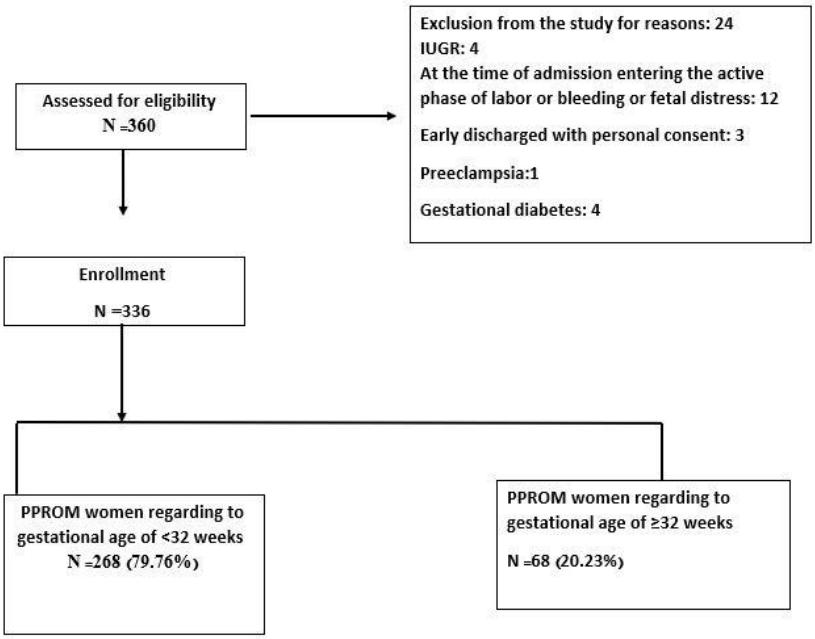

Figure 1. Evaluation of maternal and neonatal outcome in cases of preterm premature rupture of the bladder in 2019-2020

The mean age of the studied mothers was 29.3± 6.19 years, and their mean body mass index (BMI=kg /m2) was 30.6 ±5. In addition, the average birth weight of newborns was 2299±767 grams. In terms of neonatal gender, the number of boys born was 10.2% higher than that of girls. In the present study, the majority of pregnant women (72.2%) had no previous medical diseases, and the most common medical disease was hypothyroidism (16.1%) as well as thalassemia minor which was confirmed in 9.8% of pregnant women. The majority of women were primiparous (60.5%), and only 7.7% of mothers had a history of preterm delivery. Moreover, 2.4% of mothers were smokers and 1.8% of them had a history of alcohol drink. Overall, the most common adverse pregnancy outcomes were chorioamnionitis (8.6%), postpartum hemorrhage (6.8%), fetal distress (5.1%), and abruptio placenta (3.3%), respectively. The most common adverse neonatal outcomes were need for resuscitation (26.8%), admission to neonatal intensive care unit (23.8%), respiratory distress syndrome (18.7%), and neonatal mortality (5.4%), respectively.

Table 1 shows the adverse outcomes of pregnancy in PPROM women regarding the gestational age less than 32 weeks and equal to or over 32 weeks. It should be noted that the neonatal sepsis was found only in two infants at less than 32 weeks of gestational age.

Table 1. Comparison of the adverse outcome of pregnancy in PPROM women regarding to gestational age of <32 weeks and ≥32 weeks referred to Ayatollah Rouhani Hospital (number = 336)

Variable	GA <32 weeks (N=268)	GA ≥32 weeks (N=68)	Overall (N=336)	P-value
Bleeding	20(7.46)	10(14.70)	30(8.92)	0.05
clinical chorioamnionitis	4 (1.49)	25 (36.76)	29 (8.63)	0.001
Cesarean section	136 (50.74)	34 (50.00)	170 (50.59)	0.38
Fetal distress	12 (4.47)	5 (7.35)	17 (5.05)	0.01
APGAR score < 7	27(10.07)	28(41.17)	55(16.36)	0.0001
Need to resuscitation	62 (23.13)	28 (41.17)	90 (26.78)	0.003
Hospitalized in the NICU	20 (7.46)	48 (70.58)	80 (23.80)	0.0001
RDS	28 (10.44)	35 (51.47)	63 (18.75)	0.0001
Neonate mortality	1 (0.37)	17 (25.00)	18 (5.35)	0.0001

Table 2 illustrates the adverse outcomes of neonates with the latency periods. Women who gave birth in less than 3 days after amniotic sac rupture were considered as the reference group, and the crude and adjusted odds ratios of neonatal complications were associated with the gestational age in mothers who had delivery in 3-7 and less than 7 days after PPROM. Logistic regression method was used to estimate the odds ratio.

Table 2. The adverse outcome of neonates with the latency periods referred to Ayatollah Rouhani Hospital (number = 336)

Neonatal complication	Latency	Unadjusted OR	CI 95%		P-value	Adjusted OR	CI95%		P-value
			Lower	Upper			Lower	Upper	
NICU	<3	Reference 1.00							
	3-7 days	5.52	2.95	10.31	0.0001	3.56	1.78	7.10	0.0001
	>7	33.33	12.51	88.80	0.0001	10.08	3.34	30.44	0.0001
RDS	<3	Reference 1.00							
	3-7 days	6.93	3.50	13.70	0.0001	5.002	2.43	10.26	0.0001
	>7	19.00	7.97	45.26	0.0001	7.58	2.79	20.55	0.0001
Low APGAR score	<3	Reference 1.00							
	3-7 days	0.93	0.43	1.99	0.85	0.38	0.15	0.97	0.04
	>7	2.70	1.17	6.23	0.20	0.50	0.17	1.46	0.01
Resuscitation	<3	Reference 1.00							
	3-7 days	1.33	0.73	2.44	0.34	1.19	0.63	2.25	0.01
	>7	4.14	1.91	8.96	0.57	3.08	1.23	7.69	0.01
Neonatal death	<3	Reference 1.00							
	3-7 days	1.68	0.49	5.77	0.40	0.33	0.08	1.34	0.12
	>7	6.78	2.17	21.12	0.0001	0.53	0.14	1.94	0.33

Discussion

One-third of the PTBs occur as a result of PPROM. PPROM remains the leading cause of PTB and adverse neonatal outcomes. The main cause of PPROM is still unknown **(17)** and delivery strategies for PPROM treatment remain controversial. In the absence of other cases, labor induction is not recommended for women with PPROM during 28-34 gestational weeks due to the increase of neonatal morbidity and cesarean section **(18)**. Expectant management is a classic approach to PPROM management before 34 weeks of gestation, which includes hospitalization as well as prescribing corticosteroids and broad-spectrum antibiotics to prevent infection **(19)**. Rapid delivery in women with PPR-OM is essential in cases of intrauterine infection, abruption, and non-reassuring fetal status **(20)**. In the present study, the PPROM management as a conservative one before the 37th week of pregnancy based on the guidelines of Iran was accompanied by the administration of corticosteroids and broad-spectrum antibiotics.

Labor induction or cesarean section is recommended when symptoms of chorioamnionitis or other maternal and fetal complications develop. Conservative managment and prolongation of pregnancy protect the fetus from prematurity, however the risk of infection increases so that the use of antibiotics such as prophylaxis reduces the risk of chorioamnionitis, endometritis, and neonatal infection **(21)**.

In different studies, the incidence of chorioamnionitis was reported from 7.5% to 37.5% **(22-25)**. In this study, the overall incidence of chorioamnionitis was 8.63% due to the use of antibiotics. Similar to our study, Dagklis *et al.* (2013) in a ten-year retrospective study reported that the incidence of clinical chorioamnionitis was 7.5% in women with PPROM between 24+0 and 36+6 weeks of gestation **(25)**. However, in the study of Yu *et al.* (2015), the incidence of clinical chorioamnionitis was 17.8% in pregnancies with PPROM at less than 34 weeks of gestation. In their study as our study, the diagnosis of chorioamnionitis was based only on clinical signs, and the histopathological examination of the placenta was impossible for diagnosis of chorioamnionitis **(17)**.

In the present study, the incidence of chorioamnionitis at gestational age of less than 32 weeks was 36.76%, which agrees with that of Ehsanipour *et al.* (2012) who reported that the incidence of chorioamnionitis at gestational age of less than 32 weeks was 23.2% and 9.8% in singletons and twins, respectively. However, through histological examination of placenta, they stated that these rates were 35.9% and 67.7% in twins and singletons, respectively **(26)**. In the present study, the incidence of chorioamnionitis was only 1.49% at gestational age of more than 32 weeks, which was quite different from that in the gestational age of less than 32 weeks.

In the current study, another adverse maternal outcome was vaginal bleeding, which was almost more than twice as high in women with gestational age of less than 32 weeks compared to those with gestational age equal to or over 32 weeks, and this difference was statistically significant (P-value=0.05). These results are in line with those of Yu (2015). In his study, women with vaginal bleeding also had a lower gestational age **(17)**.

PPROM is a serious pregnancy complication that causes 28% of complications and neonate morbidity worldwide **(27)**. In the present study, the neonate mortality rate was 5.35%, but it was 25% at less than 32 weeks of gestational age.

In a study conducted by Goya (2013), the NMR was 7.41% at gestational age less than 34 weeks. They concluded that the NMR reduced with an increase in gestational age **(28)**.

In the current study, women with PPROM with a latency period greater than 7 days had more odds ratio for NMR, but when measured by other risk factors especially gestational age in logistic regression, the adjusted odds ratio for NMR with an increasing duration of rupture of membrane was not significantly different from that in the reference group (<3 days from the membrane rupture to delivery).

In several studies, the results related to the effect of latency period of managed PPROM cases until delivery on the occurrence of perinatal complications were significantly different. Manuck *et al.* (2009) and Baser *et al.* (2020) reported that there was an increase in perinatal complications in PPROM at gestational age of less than 34 weeks, but perinatal complications had no relationship with the duration of the latency per-iod **(29, 30)**. Nevertheless, Melamed *et al.* (2011) show-ed the increased neonatal composite complications in PPROM cases with a latency period of more than 8 days in 280+0-336+6 weeks **(24)**. In the current study, the odds ratio for neonatal complications including neonatal intensive care unit (NICU), respiratory distress syndrome (RDS), Apgar score less than 7 in the fifth minute, and needing resuscitation in neonates with a latency period of more than 7 days was higher in all cases.

The purpose of the expectant approach in PPROM management is to improve neonatal outcomes without increasing the risk for mother and fetus. However, the optimal expectant time for PPROM is unclear in terms of neonatal complications **(31)**. It has been suggested that the best neonatal outcomes in PPROM cases with a latency period of 9 days are before 28 weeks of gestation **(32)**. Nevertheless, in another study, the 1-7-day latency period at the gestational age of 24-34 weeks was appropriate **(31)**. In the current study, the most common adverse neonatal outcomes in PPROM were need for resuscitation at birth, hospitalization in NICU, RDS, and NMR. In the study of Noor *et al.*, similar results were obtained in that the most common neonatal outcomes in PPROM were low birth weight, hospitalization in NICU, and NMR **(33)**.

One of the strengths of the present study was that the women were homogeneous, and all patients were evaluated by a gynecologist and pediatrician in a tertiary specialty hospital. The limitations of the present study were that a small number of patients had a latency period of more than 14 days; hence women with more than 7-day latency period were evaluated. Another limitation of this study was the inability to make long-term evaluation of the nervous system of the infants born to mothers with longer latency periods.

Conclusion

Generally, it can be concluded that PPROM can increase neonatal composite complications except for neonatal death in PPROM cases with a latency period of more than 7 days in 24+0 - 36+6 weeks. Moreover, it was concluded that PPROM can increase neonatal morbidity depending on the gestational age especially that of less than 32 weeks. Therefore, expectant management should be performed even in tertiary centers that have NICUs. It is recommended that a similar study with a larger sample size with a latency period of more than 14 days from membrane rupture to delivery should be conducted in terms of complications and neonatal morbidity.

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Conflict of Interest

The authors declared no conflict of interest.

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