Original Article

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Frequency of Maternal Risk Factors and Neonatal Complications of Premature Rupture of Membranes

H. Boskabadi (MD)[1], M. Zakeri Hamidi (PhD)*[2], G. Maamouri (MD)[1], A. Najafi (MD)[3]

1.Department of Pediatrics, Mashhad University of Medical Sciences, Mashhad, I.R.Iran
2.Department of Midwifery, Tonekabon Branch, Islamic Azad University, Tonekabon, I.R.Iran
3.Mashhad University of Medical Sciences (MUMS), Mashhad, I.R.Iran

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ABSTRACT

BACKGROUND AND OBJECTIVE: Premature rupture of membranes (PROM) is a serious complication during pregnancy, which is accompanied by prenatal, neonatal and maternal complications including premature delivery, infection and fetal death. The Purpose of this research is to study the frequency of maternal risk factors and neonatal complications of premature rupture of membranes.

METHODS: This cross-sectional study was conducted on 309 infants with premature rupture of membranes (more than 18 hours before delivery) from 2009 to 2015. After confirming premature rupture of membranes based on history and speculum examination, a questionnaire containing pregnancy information, delivery information and infant profile was completed and assessed.

FINDINGS: Maternal risk factors included diabetes (23 cases, 12.7%), hypertension (17 cases, 9.5%), smoking (16 cases, 8.9%), history of premature rupture of membrane (16 cases, 8.9%), urinary tract infection (13 cases, 7.2%), thyroid disorders (9 cases, 5%), previous premature birth (8 cases, 4.4%) and cerclage (7 cases, 3.8%). Delivery complications included cesarean (117 cases, 38.1%), oligohydramnios (61 cases, 33.9%), chorioamnionitis (14 cases, 11.6%), placental abruption (17 cases, 9.5%), fetal distress (6 cases, 3.3%), intrapartum fever (6 cases, 3.3%) and placenta praevia (5 cases, 2.8%). Neonatal complications included immaturity (165 cases, 73%), jaundice (108 cases, 59%), neonatal infection (94 cases, 52%), respiratory distress syndrome (65 case, 30.4%) and asphyxia (52 cases, 17%). There was a significant difference between infants with infection and without infection in terms of first and fifth minute Apgar scores, erythrocyte sedimentation, platelet and gestational age (p=0.000).

CONCLUSION: Results of the study demonstrated that diabetes and hypertension are the most frequent maternal risk factors of premature rupture of membranes. Immaturity, respiratory disorders, asphyxia and infection are the most serious associated problems. It may be possible to reduce neonatal problems with proper measures and management.

KEY WORDS: *Premature rupture of membranes, Infants, Risk factors, Infection*.

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***Corresponding author: M. Zakeri Hamidi (PhD)**
Address: Department of Midwifery, Tonekabon Branch, Islamic Azad University, Tonekabon, I.R.Iran
Tel: +98 11 54271105
E-mail: maryamzakerihamidi@yahoo.co.nz

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Introduction

Preterm premature rupture of membranes (PPROM) is defined as loss of amniotic fluid before the beginning of labor pains prior to the 37th week of gestation (1). PPROM occurs in 3 to 8% of pregnancies and preterm deliveries are the main cause of one third of them (2). PPROM occurs spontaneously and is under the influence of several factors. The major causes of PPROM include structural deficiency in fetal membranes due to lack of collagen or abnormality, weakness of fetal membranes due to enzymatic degradation in inflammatory or infectious processes, protrusion of fetal membranes due to cervical insufficiency and activation of catabolic enzymes such as collagenase and mechanical stress (3, 4).

The risk factors of PPROM include increased pressure inside the amnion, low BMI, multifetal pregnancy, polyhydramnios, trauma, placental abruption, history of STD, vaginal bleeding at any time during pregnancy, cervical insufficiency, placenta praevia, black race, smoking and using tobacco, history of preterm delivery, enzymatic and genetic abnormalities, urinary tract infections, genital infections, nutritional deficiencies, low socioeconomic status, cerclage and amniocentesis (4-7).

In preterm pregnancies, PROM causes preterm delivery and perinatal, neonatal and maternal complications (2, 8). Maternal complications of PPROM include increase in cesarean, placental abruption, disseminated intravascular coagulation, sepsis, Asherman's syndrome and delayed menstruation (9, 10).

If PROM lasts more than 18 hours, the risk of neonatal infection increases by ten times (11). Fetal and neonatal complications of PPROM include prematurity, neonatal sepsis, neonatal respiratory distress syndrome, intraventricular hemorrhage, prolapsed umbilical cord, asphyxia and death. In addition, long-term oligohydramnios exacerbates the risk of abnormal development of the lungs (pulmonary hypoplasia), similar to Potter syndrome (10,12,13). The risks of PPROM are important from two aspects of infection and preterm delivery and their complications are generally more intense for fetus and infant than mother. Overall, PPROM complications depend on age of pregnancy and chorioamnionitis status (14).

Results of a study demonstrated that the most common complications of PROM are immaturity and its side effects. However, infection was the most important preventable complication (11). Neonatal complications in the study of Brumbaugh et al. included pulmonary hypoplasia (44.83%), pulmonary hypertension (37.5%) and pneumothorax (36.21%) (15). Since most neonatal complications of PPROM are associated with preterm delivery, prolonging the time between rupture of membranes and childbirth by appropriate interventions may decrease perinatal mortality and morbidity (16). A meta-analysis by Mercer et al. revealed that prophylactic antibiotic significantly prolongs pregnancy and decreases maternal and infant mortality (17). Various antibiotics have been used in different periods in several studies to reduce intrauterine infection. After erythromycin, clindamycin and metronidazole, β-lactam antibiotics are the most commonly used antibiotics (18). Expectant treatment with antibiotics and corticosteroids is currently done for the period before the 37th week of gestation. Considering the germicidal effects of amniotic fluid and its protective role against infection, it seems that reduction of amniotic fluid after rupture of membranes affects the patient's resistance against infection and increases the risk of infection (19). Incidence of PPROM before the fetus has reached full term (37 weeks) increases the specified morbidity and mortality risks for mother and fetus and this issue highlights the critical role of doctors in taking care of pregnant women and considering all risk factors and ultimately making decisions about timely termination of pregnancy or continuing pregnancy (12). Since the main cause of spontaneous rupture of fetal membranes is yet unknown, there are no effective measures for its prevention.

Therefore, quick identification of risk factors can help to reduce maternal and neonatal complications of PPROM and even if these complications take place, one can reduce the neonatal complications with appropriate control. This study was conducted to assess the maternal risk factors, delivery problems and neonatal complications of prolonged rupture of the water bag.

Methods

This cross-sectional study was conducted among 309 infants with premature rupture of membranes in Ghaem Hospital in Mashhad from 2009 to 2015. This study was approved by Research Committee of Mashhad University and a written informed consent was obtained from parents before patients entered the study. Only patients with spontaneous rupture of fetal membranes more than 18 hours before delivery entered the study (20).

All cases of amniotomy were excluded from the study. When prolonged rupture of the water bag was confirmed based on history and examination with a speculum, a researcher-made questionnaire containing mother's information (education, parity, abortion,

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taking antibiotics before delivery, maternal diseases including gestational diabetes, hypertension, eclampsia, thyroid disorders, urinary tract infections, genital infections during pregnancy and bleeding, history of preterm delivery, smoking, cerclage, fever, corticosteroid therapy, the interval between corticosteroid use and delivery, the frequency of corticosteroid therapy, type of delivery and gestation period), status of placenta (placental abruption, placenta previa) and infant's specifications (fetal distress, oligohydramnios, polyhydramnios, gender, neonatal diseases including cardiac, pulmonary and nervous system disorders, CRP, blood culture, cerebrospinal fluid culture, oxygen therapy, neonatal complications, immaturity, infection, IVH, ESR, PLT, WBC, first-minute Apgar and fifth-minute Apgar) was completed. Descriptive statistics and t-test were used to analyze the data and $p<0.05$ was considered significant.

Results

Studying mothers with PROM showed that most of them (56.7%) had high school education. 69.6% of mothers had history of delivery. 78.5% of mothers were multigravida. 78.5% of them were multiparous. 83.9% of mothers had history of two abortions. 54.2% of infants were at gestational age of 32-37 weeks. Maternal risk factors included diabetes in 23 patients (12.7%), hypertension in 17 patients (9.5%), smoking in 16 patients (8.9%), urinary infection in 13 patients (7.2%), thyroid disorders in 9 patients (5%), cerclage in 7 patients (3.8%), history of PROM in 16 patients (8.9%) and history of preterm delivery in 8 patients (4.4%). Antibiotic therapy and corticosteroid therapy were done for mothers with PPROM to decrease the complications of PPROM. Antibiotic therapy was done for 79.7% of mothers. Using a single-dose antibiotic was more common (29.4%).

Corticosteroid therapy was done for 57.8% of cases. In 66.7% of cases, the interval between corticosteroid use and delivery was 24 hours. The frequency of corticosteroid therapy in 67.9% of cases was two times (Fig 1).

54.9% of infants were males and 45.1% of them were females. 38.1% of infants were born using cesarean method. 54.9% of infants were males and 60.9% of them were single. Complications during delivery included placental abruption in 17 patients (9.5%), oligohydramniosin 61 patients (33.9%), placenta praevia in 5 patients (2.8%), fetal distress in 6 patients (3.3%), chorioamnionitis in 14 patients (11.6%), intrapartum fever in 6 patients (3.3%) and cesarean in 117 patients (38.1%) (Fig 2).

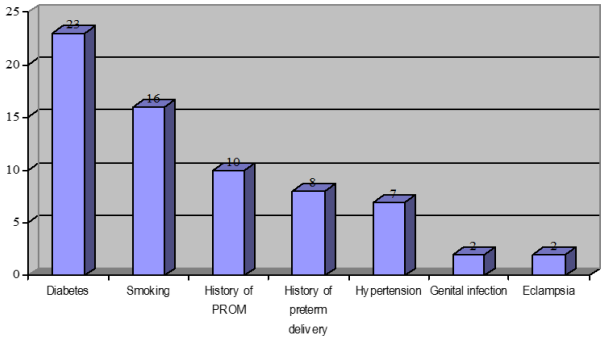


Figure 1. Frequency of maternal risk factors in premature rupture of membranes

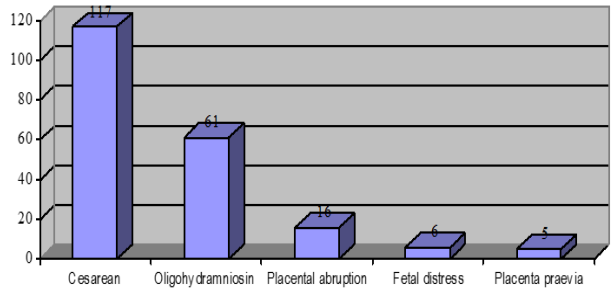


Figure 2. Frequency of delivery risk factors in premature rupture of membranes

Clinical symptoms observed in infants included immaturity in 165 patients (73%), respiratory symptoms in 65 patients (36%), CNS symptoms in 35 patients (19.4%) and cardiac symptoms in 21 patients (11.6%). Common lung problems (n = 42, 64.6%) among most infants in NICU included tachypnea, groaning and intercostal muscle retraction. 54.7% of infants suffered from reduced neural reflexes.

The most common heart problem (n=7, 10.9%) among infants was heart murmurs. Neonatal complications in this study included jaundice in 108 patients (59%), neonatal infection in 94 patients (52%), RDS in 65 patients (30.4%) and asphyxia in 52 patients (17%). Neonatal infections included meningitis in 13 patients (4.2%), sepsis in 18 patients (5.8%) and clinical infection in 62 patients (20.4%). CRP in 43.9% of infants, blood culture in 17.7% of infants and cerebrospinal fluid culture in 6.3% of infants were positive. Intubation was used for 23.1% of infants (Fig 3). Results of this study demonstrated that among all infants with PPROM, 33 infants (11.1%) suffered from infection (sepsis, meningitis, clinical infection) whereas the other 263 infants (88.9%) had no sign of infection. The difference between the two groups of infants with infection and infants without infection regarding the type of delivery was not statistically significant (p=0.563). The two groups were not statistically different in terms of chorioamnionitis (p=0.085), mortality (p=0.242) and

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IVH (p=0.620). CRP variable was statistically different between the two groups (p=0.000), which means positive CRP items were observed more in infants with infection. In the two groups of infants with infection and infants without infection, there was a significant difference between first-minute Apgar (p=0.000) and fifth-minute Apgar (p=0.000), which means infants with infection had lower first-minute Apgar and fifth-minute Apgar. There was a statistically significant difference between ESR (p=0.000) and PLT (p=0.000) in the two groups, which means the value of these two variables was higher among infants with infection. Infants' weight was significantly lower in the group of infants with infection (p=0.000).

There was no statistically significant difference between the two groups in terms of Initial Total Bilirubin (p=0.080). Gestational age was statistically different in the two groups (p=0.000), which means gestational age in the group of infants with infection was lower. The interval between PROM and delivery was significantly higher in the group of infants with infection (p=0.003) (table 1).

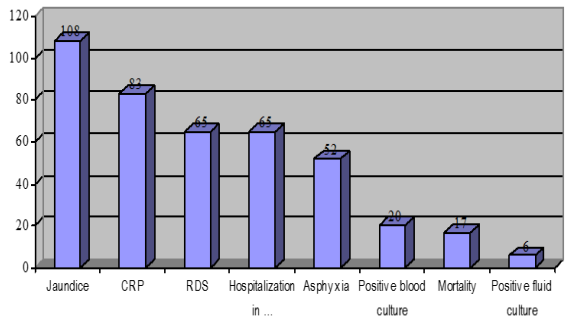


Figure 3. Frequency of neonatal complications in premature rupture of membranes

Table 1. Comparison of mean clinical and laboratory parameters among infants in the group of infants with infection and the group of infants without infection

Variable / Group	With infection Mean±SD	Without infection Mean±SD	P-Value
First-minute Apgar	1.53±6.78	0.89±8.33	0.000
Fifth-minute Apgar	1.22±7.35	0.69±9.11	0.000
ESR	6.44 7.03	0.00±1	0.000
PLT (g/dl)	14330±16156	12400±330000	0.000
Birth weight (g)	427.85±1396.42	500.80±2647.73	0.000
Initial total bilirubin (mg/dl)	2.19±11.35	1.99±9.90	0.080
Gestational age (weeks)	3.19±3063	2.99±36.04	0.000
Time of PROM (days)	4.40±4.98	2.52±2.50	0.003

Discussion

According to the results of this study, 78.5% of mothers were multigravida and 78.5% of them were multiparous. Similarly, the occurrence of PPROM in the first pregnancy was the most frequent according to the study of Okeke et al. (2). In the study of Stuart et al., 67.1% of mothers with PROM were multigravida and 29.1% of them were experiencing their first pregnancy (21). In the study of Yang et al., 41.1% of mothers with PPROM were nulliparous (22). In this study, 83.9% of mothers had history of two abortions. The study of Dadkhah et al. revealed that cases of threatened abortion increase as spontaneous preterm birth and PROM increase (23).

Study of Hackenhaar et al. demonstrated that there is a relationship between cases of threatened abortion and PPROM (24). In this study, the maternal risk factors included diabetes (12.7%), hypertension (9.5%), smoking (8.9%), urinary tract infection (7.2%), thyroid disorders (5%), cerclage (3.8%), history of PROM (8.9%) and history of preterm delivery (4.4%). The maternal morbidity in the study of Hackenhaar et al. was 20% (24).

According to the study of Caughy et al., history of PROM, smoking, anemia, low BMI and abdominal trauma were among the maternal risk factors of PPROM (3). In the study of Yang et al., the maternal risk factors of PPROM included history of PROM (11%), cerclage (4.1%), tobacco use (17.8%) and history of preterm delivery (9.6%) (22). The maternal risk factors in the study of Boskabadi et al. included history of PROM (10%), addiction (8%), urinary tract infection (5.3%), diabetes (4.7%), placental abruption (4.7%), preeclampsia (3.3%) and cerclage (2 %) (11). One of the maternal risk factors in this study was mothers' diabetes, observed in 12.7% of cases. Results of a study by Al Riyami et al. demonstrated that 11.4% of mothers with PPROM suffer from diabetes (25). In this study, hypertension as a risk factor of PPROM was observed in 9.5% of mothers. Results of a study by Kaya et al. confirmed the hypertension of mother to be a risk factor of PPROM (26).

According to this study, smoking was one the maternal risk factors among 8.9% of mothers. In a study by Arnildo et al. in 2014, the relationship between smoking and PPROM was confirmed (24). The urinary tract infection in mothers with PPROM was 7.2%. This frequency was 3.1% in the study of Emechebe et al. in 2015 (27). 3.8% of mothers have undergone cerclage operation. In the study of Yang et al., 4.1% of mothers have undergone cerclage operation (22). 8.9% of the infants in our study had history of PPROM. According to the study of Caughey et al., the risk of PPROM increases in the cases of

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having history of PPROM and low body mass index (3). History of preterm delivery in the study of Yang et al. was 11% (22). 4.4% of cases had history of preterm delivery. Results of a study by Mercer et al. demonstrated that there is a significant relationship between PPROM and uterine contractions during mothers' first trimester (28). The study of Hackenhaar et al. confirmed the relationship between PPROM and treatment of pregnancies at risk of preterm delivery. Uterine contraction in threatened preterm delivery weakens the amniotic membranes (24). History of preterm delivery in the study of Yang et al., which investigated the maternal and fetal outcomes of PPROM, was 9.6% (22). Antibiotic therapy was carried out on 79.7% of mothers. Using single-dose antibiotic was more common (29.4%). Study of Egarter et al. demonstrated that using preventive antibiotics decreases maternal morbidity (29). A trial by Amon et al. using prophylactic ampicillin in PPROM revealed lower risk of delivery and neonatal infection among patients receiving ampicillin (30).

Results of a study, which compared the two methods of antibiotic therapy with cefotaxime and ampicillin demonstrated that definite infection, high ESR, positive CRP, need for hospitalization and infant mortality was higher in the group of infants receiving ampicillin (31). Corticosteroid therapy was used for 57.8% of cases. In 66.7% of cases, the interval between corticosteroid use and delivery was 24 hours. The frequency of corticosteroid therapy was twice in 67.9% of cases. Harding et al. showed that corticosteroid use before the 34th week of gestation decreases perinatal morbidity and mortality due to decresed risk of IVH, RDS and necrotizing enterocolitis (NEC) (32). Perinatal complications include placental abruption (9.5%), oligohydramnios (33.9%), placenta praevia (2.8%), fetal distress (3.3%), chorioamnionitis (19.6%), intrapartum fever (3.3%) and cesarean (38.1%).

One of the perinatal complications in this study was placental abruption, occurring in 9.5% of cases. In the study of Caughy et al., prenatal bleeding was associated with PPROM and placental abruption was the cause of PROM in 10-15% of cases (3). Oligohydramnios was observed in 33.9% of PPROM cases. Due to germicidal effect of amniotic fluid and its anti-infective role, oligohydramnios after PPROM affects the resistance of the body against infection and increases the risk of infection (33). 3.3% of the studied infants suffered from fetal distress. In the study of Movahedi et al., fetal distress was observed in 21% of infants at 28 to 34 weeks' gestational age with PPROM (34). Respiratory distress syndrome (RDS) was observed in 30.4% of infants. In the study of Sims et al., respiratory distress syndrome was observed in 17% of infants with PPROM (35). All infants (100%) in the study of Yang et al. suffered from respiratory distress syndrome (22). 19.6% of mothers with PROM suffered from chorioamnionitis. In the study of Yang et al., chorioamnionitis was observed in 37% of mothers. In addition, placental examination indicated histologic chorioamnionitis in 67.1% of cases (22). Intrapartum fever was observed in 3.3% of mothers. Fever was observed in 95% of mothers with PPROM in the study of Movahedi et al. (34).

One may attribute the different statistics of intrapartum fever to proper and timely use of antibiotics in the present study. 38.1% of infants were born by caesarean. In the study of Sirak et al., 23.2% of infants with PPROM were born by caesarean (36). In a study by Osmanagaoglu et al., 21% of PPROM cases were associated with caesarean (37). In the study of Yang et al., this percentage was 31.5% (22). According to Movahedi et al., rate of cesarean delivery was 52.7% (34). The clinical symptoms in infants included immaturity (73%), respiratory symptoms in 65 patients (36%), CNS symptoms in 35 patients (19.4%) and cardiac symptoms in 21 patients (11.6%). The common pulmonary problems (64.6%) among most infants in NICU included tachypnea, groaning and intercostal muscle retraction. 54.7% of infants suffered from reduced neural reflexes. Heart murmur was the most common heart disease among infants (10.9%). In the present study, immaturity was the most common clinical symptom (73%) among infants. Results of another study also reported immaturity to be the most common (67%) neonatal complication (11). One of the clinical symptoms among infants survived from PPROM was respiratory disorder, observed in 36% of infants.

The most common pulmonary problem was tachypnea, groaning and intercostal muscle retraction (64.6%). According to the study of Yang et al., 68.4% of infants who survived from PROM, suffered from long-term pulmonary complications in the form of bronchopulmonary dysplasia (BPD) (22). The neonatal complications of this study included jaundice in 108 patients (59%), neonatal infection in 94 patients (52%), RDS in 65 patients (30.4%) and asphyxia in 52 patients (17%). Neonatal complications in the study of Al-Riyami et al. included immaturity (46%), RDS (79%), sepsis (50%) and low birth weight (46%) (38). The most common neonatal complications in the study of Emechebe et al. included jaundice (23.4%), asphyxia (16.2%), sepsis (13%) and death (8.3%) (27). PROM-associated neonatal complications in another study included immaturity (67.3%), RDS (22.6%), asphyxia (8.6%), meningitis (5.2%), sepsis (4%),

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pneumonia (1.3%) and death (4.6%) (11). Investigating the infection problems of infants with PROM showed meningitis in 13 patients (4.2%), sepsis in 18 patients (5.8%) and clinical infection in 62 patients (20.4%). Fetal and maternal infection does not occur before PPROM.

In fact, it is one the complications of PPROM. As the interval between PROM and delivery is prolonged (34 to 37 weeks), the risk of fetal and maternal infection increases, compared with term pregnancies (39). Results of a study by Noor et al. demonstrated that 16.47% of mothers PPROM experience infection, whereas 28.2% of infants experience infection and will require antibiotics (40). Neonatal sepsis was observed in 5.8% of survived infants. However, it was reported to be 42.1% in the study of Yang et al. (22). In the study by Movahedi et al., sepsis was observed in 3% of infants with PPROM (34).

In this study, IVH was present in 6.5% of infants. In the study of Yang et al., severe IVH (grade 3 or 4) was observed in 7.9% of the survived infants (22). 5.5% of infants died according to the results of the present study. Perinatal mortality rate in the study of Okeke et al. was reported to be 7% (2). This rate was reported to be 67.7% in the study of Moretti et al. (41). In a study by Nihal et al., of 44 preterm infants who were admitted to ICU ward, 7 infants (16%) died (38). Results of the study by Movahedi et al. demonstrated that 1.75% of infants with PPROM died (34). Of all infants with PPROM, 33 infants (11.1%) were with infection and other 263 infants (88.9) were without infection. In another study, 12 infants (7.7%) suffered from a recognized infection (meningitis, sepsis and pneumonia) (11). Based on results of the present study, maternal risk factors during pregnancy included Diabetes, hypertension, history of PROM, smoking, urinary tract infection, thyroid disorders, history of immaturity and cerclage, respectively. Problems during delivery included cesarean, oligohydramnios, chorioamnionitis, placental abruption, fetal distress, fever and placenta praevia, respectively. Clinical symptoms in infants included immaturity, respiratory distress, CNS symptoms and cardiac symptoms, respectively. The common pulmonary problems among most infants in NICU included tachypnea, groaning and intercostal muscle retraction. The common neurological problem was reduced neural reflexes. The most common heart problem among infants was heart murmur. The neonatal problems in this study included jaundice, infection, RDS and asphyxia, respectively.

The common infection problems in infants with PROM included clinical infection, sepsis and meningitis, respectively. Overall, PPROM is a serious complication during pregnancy and if this problem occurs, there is no effective measure to prevent it and perinatal morbidity and mortality (particularly preterm delivery and infection) increases because of this problem. Therefore, since the risk factors of PPROM can be identified, identification of infants at risk before their birth and following the susceptible infants is suggested to reduce neonatal complications. Identification of maternal risk factors of PPROM and if possible, preventing these factors or proper management of some of them such as diabetes and hypertension may reduce their complications. On the other hand, proper measures during delivery such as using antibiotics and corticosteroids can reduce neonatal problems. Although the most common complication of premature rupture of membranes is immaturity, respiratory problems, asphyxia and infection are the most serious associated problems.

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