CEOG Clinical and Experimental Obstetrics & Gynecology
Original Research

Perinatal outcome of prolonged preterm premature rupture of membranes near the limit of fetal viability

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Summary

Purpose of investigation: The purpose of the present study is to evaluate the perinatal outcome of expectant management for prolonged preterm premature rupture of membranes (PPROM) near the limit of fetal viability. *Materials and Methods:* Pregnant women who delivered babies between January 2000 and March 2015 and had a history of PPROM at 22–23 weeks of gestation with a latency of one week or longer were included in the PPROM cohort. The control cohort included women who delivered babies within 24 hours after PPROM during the same period. Perinatal outcomes were compared between the two cohorts. *Results:* No differences were observed between the two cohorts in terms of survival to discharge from the NICU ($p = 0.43$) and respiratory complication at one year of corrected age ($p = 1.00$). *Conclusions:* Prolonged PPROM did not affect the rate of survival discharge from NICU and respiratory complication at one year of corrected age.

Key words: Premature rupture of membranes; Expectant management; Perinatal outcome; Fetal viability; Respiratory complication.

Introduction

Preterm premature rupture of membranes (PPROM) occurring before 37 weeks of gestation, occurs in approximately 3–4.5% of pregnancies [1]. A consensus has been reached regarding the guidelines for PPROM management at or after 24 weeks of gestation, which include expectant management with the administration of antibiotics and corticosteroids [2]. However, no consensus has been reached on guidelines for the treatment of PPROM before 24 weeks of gestation, and therefore, therapeutic approaches vary among institutions.

Waters *et al.* [3] performed a meta-analysis on mid-trimester PPROM and found that case membrane rupture occurred at or before 24 weeks of gestation had a pulmonary hypoplasia rate of 19.2% (23/120), bronchopulmonary dysplasia rate of 29.1% (30/103), and survival rate of 34.9% (38/109). Prolonged duration of membrane rupture or oligohydramnios is also associated with the development of pulmonary hypoplasia [3-5]. On the other hand, Brumbaugh *et al.* [6] reported that the survival rate was 90% (52/58) in cases of PPROM before 24 weeks of gestation, and that the mortality in such cases has dramatically decreased in recent years.

The present study focused on cases involving PPROM at 22–23 weeks of gestation, the limit of fetal viability, that were expectantly managed for one week or longer. These cases were matched at a ratio of one to one with control cases unaffected by prolonged PPROM in which neonates were delivered during the same period. The purpose of the present study is to elucidate the impact of mid-trimester PPROM by comparing perinatal outcomes between these cohorts.

Materials and Methods

Pregnant women who delivered babies at the Perinatal Center for Maternity and Neonate of Yokohama City University Medical Center between January 2000 and March 2015, and had a history of maternal rupture of membranes at 22–23 weeks of gestation, with a latency of one week or longer were included in the PPROM cohort. The control cohort included women who delivered babies within 24 hours after the rupture of membranes, without any effect of prolonged PPROM, at the present center during the same period. Women who delivered babies with congenital anomalies, those with multiple pregnancies, and those with an uncertain estimated date of delivery were excluded from both cohorts. The estimated date of delivery was determined by the last menstrual period and crown-rump length measured between seven and ten weeks of gestations at the discretion of the primary obstetrician and was used to calculate the gestational age. PPROM was diagnosed when continuous amniotic fluid leakage was macroscopically confirmed and when a positive result was obtained with either an alpha-fetoprotein test kit or a human insulin-like growth factor binding protein-1 test kit was positive. Cases in which the fetal membrane was resealed during the course of gestation after temporary membrane rupture due to amniocentesis or similar pro-

Revised manuscript accepted for publication April 10, 2017

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLVI, n. 1, 2019
doi: 10.12891/ceog4196.2019

7847050 Canada Inc.
www.irog.net

Published: 10 February 2019

Table 1. — *Characteristics of PPROM cohorts and control cohorts.*

		PPROM* (n=33)	control (n=33)	*p* value
Neonatal	Female sex	14 (42.4)	14 (42.4)	1.00
	Gestational age at birth (weeks)	26.6 (23.9-33.7)	26.3 (24.4-32.9)	0.66
	Birthweight (grams)	880 (626-1844)	910 (516-1938)	0.79
Maternal	Age (years)	32 (22-40)	33 (17-42)	0.55
	Primipara	18 (54.5)	20 (60.6)	0.80
	Completed betamethasone course more than 24 hours before delivery	33 (100)	33 (100)	1.00
	Completed betamethasone course more than 7 days before delivery	28 (84.8)	13 (39.4)	< 0.001
	Clinical chorioamnionitis	1 (3.0)	0 (0)	1.00
	Histological chorioamnionitis	20 (60.6)	14 (42.4)	0.22
	Maternal sepsis	1 (3.0)	0 (0)	1.000
	Preeclampsia	0 (0)	5 (15.2)	0.053
	Cesarean delivery	21 (63.6)	19 (57.6)	0.80
	Gestational age at first dose of betamethasone (weeks)	23.7 (22.3-26.6)	25.4 (22.0-31.1)	< 0.001
	Duration of betamethasone exposure to delivery (days)	20 (2-68)	4 (2-60)	< 0.001
	Oligohydramnios	21(63.6)	-	-

**PPROM: preterm premature rupture of membranes.*

cedures were also excluded. All women were hospitalized for management. Non-stress tests (NSTs) were performed twice daily for fetal monitoring. Biophysical profile scores were determined daily if the attending physician determined the NST assessment to be insufficient. Moreover, ultrasonographic fetal growth assessments and amniotic fluid index measurements were performed two or three times per week. Based on the physical findings and leucocyte/C-reactive protein values, intravenous tocolytic and/or antibiotic therapies were administered on a case-by-case basis at the discretion of the attending obstetrician. When delivery was expected to occur within one week, betamethasone was administered at a dosage of 12 mg twice per 24-hour period. Fetal conditions were assessed during expectant management, and immediate vaginal or cesarean delivery was performed for women with a non-reassuring fetal status.

The institutional perinatal database was used for a retrospective review of the included women's medical charts. This study was approved by the ethics committee of the Yokohama City University Medical Center (D1509019).

Thirty-three women met the inclusion criteria for the PPROM cohort. Because all had delivered a baby 24 hours or more after the administration of betamethasone, the control cohort included 192 women who had also delivered a baby 24 hours or more after the administration of betamethasone. The PPROM and control cohorts were matched (one to one) with regards to characteristics such as gestational age at birth (within ± seven days), birthweight (within ± 100 grams), and sex. Maternal and neonatal characteristics and neonatal outcomes were compared between the two cohorts.

The evaluated maternal and neonatal characteristics were neonatal sex, gestational age at birth, birthweight, maternal age, proportion of primipara, proportion of cases completed betamethasone course more than seven days before delivery, clinical chorioamnionitis (C-CAM), histological chorioamnionitis (H-CAM), maternal sepsis, preeclampsia, cesarean delivery, gestational age at the first dose of betamethasone, and duration from betamethasone exposure to delivery.

The evaluated neonatal outcomes were survival to discharge from the neonatal intensive care unit (NICU), grade III or IV intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA) without spontaneous closure, retinopathy of prematurity, oxygen requirement at 28 days of postnatal age, 40 weeks of postmenstrual age and one year of corrected age, and respiratory complication at one year of corrected age.

H-CAM was diagnosed according to the Blanc classification [7]. Using the criteria proposed by Lencki *et al.* as reference [8], C-CAM was diagnosed in women with maternal fever (≥ 38 °C) when any of the following criteria were met: 1) maternal tachycardia (≥ 100 bpm), 2) uterine tenderness, 3) foul-smelling vaginal discharge and amniotic fluid, and 4) maternal leukocytosis (≥ 15,000/μL). In women without maternal fever, C-CAM was diagnosed when all four of the above criteria were met. Maternal sepsis was defined as a positive result from a maternal blood culture during hospitalization. IVH was assessed according to the Papile classification [9]. Grade III IVH was defined as IVH with ventricular dilatation, and grade IV IVH as that with parenchymal hemorrhage. PVL was defined as cyst formation around the lateral ventricle, based on assessment of the coronal and sagittal brain echography images. NEC was defined based on characteristic clinical signs and symptoms, as well as plain abdominal radiographic findings such as pneumatosis intestinalis, pneumoperitoneum, and portal air. PDA was diagnosed using echocardiography and defined as a case without spontaneous closure in which indomethacin administration or surgery was required for closure. Retinopathy of prematurity was defined as a case requiring laser photocoagulation. Respiratory complication was defined as a case requiring oxygen therapy or respiratory management at one year of corrected age. Oligohydramnios was defined as a condition in which the amniotic fluid index was < 5 cm or the amniotic fluid pocket was < 2 cm [10].

The data are presented as medians (ranges) or frequencies (percentages). SPSS 24 statistical software was used for the statistical analyses. The Mann–Whitney U-test was used to analyze continuous variables, and Fisher's exact test was used to analyze intergroup differences in categorical data. The level of statistical significance was set at $p < 0.05$.

Results

Table 1 presents the neonatal and maternal characteristics. In the PPROM cohort, 21 women (63.6%) developed oligohydramnios during expectant management. No dif-

Table 2. — *Comparison of neonatal outcome between PPROM cohorts and control cohorts.*

Neonatal outcomes	PPROM* (n=33)	control (n=33)	P value	OR (95% CI)
Stillbirth	0 (0)	0 (0)	1.00	-
Survival to discharge	31 (93.9)	28 (84.8)	0.43	0.36 (0.065, 2.01)
Grade 3 or 4 intraventricular hemorrhage	2 (6.1)	2 (6.1)	1.00	1.00 (0.13, 7.56)
Periventricular leukomalacia	1/31 (3.2)	1/28 (3.6)	1.00	0.90 (0.054, 15.10)
Patent ductus arteriosus	5/31 (16.1)	8/28 (28.6)	0.35	0.48 (0.14, 1.70)
Necrotizing enterocolitis	0/31 (0)	1/29 (3.4)	0.48	0.97 (0.90, 1.03)
Retinopathy of prematurity with laser photocoagulation	4/31 (12.9)	1/28 (3.6)	0.36	4.00 (0.42, 38.15)
Oxygen requirement at 28 days of postnatal age	21/31 (67.7)	18/29(62.1)	0.79	1.28 (0.44, 3.72)
Oxygen requirement at 40 weeks of postmenstrual age	10/31 (32.3)	7/28 (21.4)	0.39	1.75 (0.54, 5.66)
Oxygen requirement at one year of corrected age	1/31 (3.2)	0/28 (0)	1.00	-
Respiratory complication‡	2/31 (6.5)	1/28 (3.6)	1.00	1.86 (0.16, 21.7)

**PPROM: preterm premature rupture of membranes.*

‡Respiratory complication was defined as requirement of oxygen therapy or respiratory management at one year of corrected age.

ferences were observed between the PPROM and control cohorts in terms of the matched characteristics of birthweight, gestational age at birth, and neonatal sex. Concerning betamethasone exposure, all cases in both cohorts completed the betamethasone course at least 24 hours before delivery. However, because betamethasone course was started at a significantly earlier time point in the PPROM cohorts, the duration from betamethasone exposure to delivery was significantly longer ($p < 0.001$), and the proportion of the cases who completed the betamethasone course seven days before delivery was significantly higher in this cohort than in the controls ($p < 0.001$). There were no differences in the incidence of maternal sepsis, H-CAM, and C-CAM.

Table 2 presents the neonatal outcomes in the PPROM and control cohorts. The rates of survival to discharge from the NICU were 93.9% in the PPROM cohort and 84.8% in the control cohort, and this difference was not significant ($P = 0.43$). Although no intrauterine fetal deaths or stillbirth occurred in either cohort, two neonates in the PPROM cohort and five in the control cohort died in the NICU. In the PPROM cohort, one neonate died of early-onset sepsis and IVH at one day of age, and the other died of IVH and circulatory failure at 43 days of age. In the control cohort, two neonates died of early-onset sepsis at four days and six days of age, respectively, and one neonate died of late-onset sepsis at 28 days of age. In addition, one neonate died of short-bowel syndrome after surgery for NEC, and another neonate died of pneumonia at 176 days of age after long-term respiratory management. No differences were observed between the two cohorts in terms of IVH, PVL, and PDA requiring treatment, retinopathy of prematurity with laser photocoagulation, oxygen requirement at 28 days of postnatal age, 40 weeks of postmenstrual age, and at one year of corrected age, and respiratory complication at one year of corrected age. In the PPROM cohort, two infants developed respiratory complications at one year of corrected age. One of these infants was delivered at 23 weeks and six days of gestation and had not been exposed to oligohydramnios, requiring continuous oxygen therapy. The other infant was delivered at 24 weeks and two days of gestation and had been exposed to oligohydramnios for only two days before delivery, requiring tracheotomy and respiratory management because of laryngomalacia. On the other hand, in the control cohort, one infant who was delivered at 27 weeks and six days of gestation, developed respiratory complications requiring tracheotomy because of laryngomalacia.

Discussion

Infant with prolonged PPROM at 22–23 weeks of gestation had a favorable rate of survival to discharge from NICU (93.9%). No difference was observed in the rate of survival to discharge from NICU between PPROM and control cohorts. Moreover, there was no difference in respiratory outcomes between infants with and those without prolonged PPROM at 22-23 weeks of gestation.

No difference was observed in the rate of survival to discharge from the NICU between the PPROM and control cohorts (93.9% *vs*. 84.8%, $p = 0.43$). Several studies have investigated the mid-trimester rupture of membranes [11-15]. Waters *et al.*, who conducted a meta-analysis of cases of expectantly managed rupture of membranes at or before 24 weeks of gestation, reported a survival rate of 34.9% (38/109) among evaluated infants [3]. The prognosis for the expectant management of rupture of membranes at less than 24 weeks of gestation is known to be poor. However, Brumbaugh *et al.* [6] reported in 2014 that the rate of survival to discharge from NICU was 90% for infants with prolonged PPROM (at least one week) before the gestational age of 24 weeks. The authors reported that perinatal outcomes had improved dramatically in comparison to the outcomes 20 years earlier and that the causes for the discrepancy between theirs and previous reports were exposed to antenatal betamethasone and improvements in the respi-

ratory management of neonates [6]. In the study conducted by Brumbaugh *et al.* [6], however, selection bias may have been introduced by the termination of pregnancy when an adverse perinatal outcome was expected. In Japan, expulsion of a fetus at or after 22 weeks and 0 days of gestation is considered premature birth, rather than abortion, from a legal perspective, and therefore induced abortion is not legally allowed at or after 22 weeks of gestation. Therefore, in the present study, there is no bias towards pregnancy termination when poor prognosis is expected. The present results, which were not affected by such bias, are consistent with the results reported by Brumbaugh *et al.* and support the validity of expectant management for cases involving the rupture of membranes at 22–23 weeks of gestation. In the present study, the rate of survival to discharge from NICU was lower in the control cohort than in the PPROM cohort. Neonatal deaths due to sepsis occurred in both cohorts. In the PPROM cohort, one neonate died of early-onset sepsis. In the control cohort, one neonate died of early-onset of sepsis and two neonates died of late-onset sepsis. There was no difference in occurrence of early-onset sepsis associated with chorioamnionitis. In the present study, betamethasone course was started significantly earlier in the PPROM than in the control cohort. In addition, the proportion of the cases who completed the betamethasone course seven days before, delivery was significantly higher in the PPROM cohort than in the control cohort. These differences may have affected the neonatal outcomes. Moreover, there was no difference in respiratory outcomes between infants with and those without prolonged PPROM at 22-23 weeks gestation. Increased morbidity, particularly postnatal pulmonary hypoplasia, and bronchopulmonary dysplasia are challenges encountered during the expectant management of patients with midtrimester rupture of membranes [4, 11-16]. In fact, Waters *et al.* reported that the rupture of membranes at or less than 24 weeks of gestation resulted in pulmonary hypoplasia in 19.2% (23/120) of infants and bronchopulmonary dysplasia in 29.1% (30/103) of infants [3]. In the present study, oxygen requirements at three time points—28 days of postnatal age, 40 weeks of postmenstrual age, and one year of corrected age — and respiratory complication at one year of corrected age were assessed to determine the impact on the fetal lungs; no difference was observed between the PPROM and control cohorts at any time point.

Most infants with respiratory complications gradually improve with a decrease in oxygen requirement. In the present study, the rate of oxygen requirement dramatically decreased from 67.7% at 28 days of postnatal age to 3.2% at one year of corrected age.

Two infants with respiratory complications in the PPROM cohort were delivered at gestational ages of 23 weeks and six days and 24 weeks and two days, respectively. These cases were delivered at an extremely early gestational age (23.9-33.7 weeks) in these infants. In the infant who required oxygen therapy at one year of corrected age, no oligohydramnios was noted.

Although the development of fatal pulmonary hypoplasia is inevitable in the context of early mid-trimester oligohydramnios, as seen in Potter syndrome [17], this finding suggests that the rupture of membranes at or after 22 weeks of gestation does not cause pulmonary hypoplasia with a fatal impact on the fetal respiratory organs. Neonatal respiratory complications may not be affected by the duration of oligohydramnios, or the presence or absence of oligohydramnios, but affected by the gestational age at birth.

The present study had several limitations. First, it was a single-center retrospective study with a small sample size in which decisions regarding the administration of antibiotics, selection of tocolytic agents, and dosing regimens of these agents were dependent on the discretion of attending obstetricians. Second, given the long study period (2000–2015), changes in the respiratory management of neonates might have affected the results. Third, because the neonates were followed up to one year of age to observe infant outcomes, future studies of long-term outcomes may reveal differences. Despite these limitations, it is noteworthy that prolonged PPROM near the limit of fetal viability may not affect the long-term respiratory outcomes. The additional accumulation of cases and studies with long-term follow-up are needed in the future to determine the effects of prolonged PPROM near the limit of fetal viability on respiratory function.

Conclusion

Prolonged rupture of membranes near the limit of fetal viability (22–23 weeks of gestation) does not exert fatal effects on the neonatal respiratory function at one year of corrected age. This finding suggests that cases involving the rupture of membranes at 22–23 weeks of gestation are candidates for expectant management.

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