

Outcomes of Extremely Preterm Infants Exposed to Prolonged Preterm Prelabor Rupture of Membranes Before 24 Weeks of Gestation



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Introduction

Preterm prelabor rupture of membranes (PPROM) before or near the limit of viability is associated with serious maternal and neonatal complications, including chorioamnionitis, extremely preterm (EPT) birth, and pulmonary hypoplasia.

- Objectives:**
- Describe contemporary outcomes of EPT infants exposed to prolonged PPRM at <24 weeks’ gestation.
 - Identify perinatal factors associated with survival and survival without severe neurodevelopmental impairment (NDI).

Methods

- Clinical cohort:**
- Infants born <27 weeks’ gestational age admitted to NICHD Neonatal Research Network centers, 2012-2018, in 2 groups:
- Infants born to mothers with prolonged (≥120 hours) PPRM, with rupture of membranes (ROM) before 24 weeks’ gestation (perivable), or
 - Infants of mothers with ROM within 18 hours of delivery
- Excluded cases with ROM >18 to <120 hours prior to delivery and infants who did not receive active treatment (surfactant, intubation, ventilatory support, parenteral nutrition, chest compressions, or epinephrine)

- Outcomes at 22-26 months’ corrected age:**
- Survival
 - Survival without Severe Neurodevelopmental Impairment (NDI), defined as any of the following: severe cerebral palsy, Gross Motor Function Classification level 4-5, Bayley-III cognitive composite <70, severe bilateral vision or hearing loss

- Analysis:**
- Regression models to compare outcomes of infants exposed to prolonged PPRM and unexposed infants, adjusting for birth gestational age, sex, multiple gestation, receipt of antenatal steroids, small for gestational age (SGA), mother’s insurance, and center
 - Separate regression models to identify factors associated with survival and survival without severe NDI among infants exposed to prolonged PPRM

Results

- Maternal and infant characteristics:**
- Perinatal characteristics of infants exposed to prolonged, perivable PPRM (n=609) differed from unexposed infants (n=4,489) (**Table 1**):
- Lower gestational age at birth
 - Higher rates of chorioamnionitis and antenatal steroids
 - Lower rates of cesarean delivery, multiple gestations, and SGA infants

Table 1. Maternal and Neonatal Characteristics		
	Prolonged PPRM N=609	ROM ≤18 hours N=4489
Birth gestational age, completed weeks	24 (24-25)	25 (24-26)*
Gestational age at rupture, weeks	22.3 (21.3-23.1)	25 (24.0-26.0)*
Latency between ROM and birth, hours	317.2 (205.3-504.0)	0 (0-0.02)*
Private insurance	252 (41)	1938 (43)
Clinical chorioamnionitis	210 (35)	475 (11)*
Antenatal steroids	591 (97)	3900 (87)*
Cesarean delivery	346 (57)	2987 (67)*
Multiple gestation	124 (20)	1288 (29)*
Birth weight, g	720 (600-840)	705 (590-835)
Small for gestational age	20 (3)	460 (10)*
Male sex	324 (53)	2311 (52)

Median (IQR) presented for continuous variables; N (%) presented for categorical variables
*P<0.05 by Wilcoxon test (continuous variables) or Chi-square test (categorical variables)

- Neonatal morbidities and treatments differed between groups (**Table 2**):
- Infants exposed to PPRM had higher rates of pneumothorax, high-frequency ventilation (HFV), inhaled nitric oxide (iNO) therapy, and early-onset sepsis.
 - Unexposed infants had higher rates of severe intraventricular hemorrhage, spontaneous intestinal perforation, and patent ductus arteriosus treatment.

Table 2. Neonatal Treatments and Morbidities		
	Prolonged PPRM	ROM ≤18 hours
Surfactant	547 (90)	4066 (91)
High frequency ventilation	334 (60)	2332 (54)*
Pulmonary interstitial emphysema	89 (16)	629 (15)
Pneumothorax	66 (12)	324 (8)*
Inhaled nitric oxide	131 (23)	509 (12)*
Bronchopulmonary dysplasia (BPD)	364 (81)	2507 (65)
Severe (Grade 3) BPD	61 (14)	372 (11)
Postnatal steroids for BPD	161 (31)	1077 (27)
Patent ductus arteriosus, treated	148 (29)	1547 (40)*
Severe intraventricular hemorrhage	96 (18)	920 (22)*
Periventricular leukomalacia	34 (6)	252 (6)
Early-onset sepsis	24 (4)	100 (2)*
Late-onset sepsis	155 (29)	1106 (27)
Necrotizing enterocolitis, surgical	30 (5)	236 (6)
Spontaneous intestinal perforation	26 (5)	305 (7)*
Retinopathy of prematurity (ROP), treated	118 (26)	854 (25)

N (%) presented for each variable.
*P<0.05 adjusted for birth gestational age, sex, multiple gestation, antenatal steroids, SGA, and center.

- Outcomes at 22-26 months’ corrected age:**
- Odds of survival and survival without severe NDI were not significantly different between groups (**Table 3**).
 - Prolonged PPRM was associated with lower odds of survival without severe BPD, while odds of survival without serious respiratory morbidity at 22-26 months’ corrected age were not significantly different between groups.

Table 3. Infant Outcomes				
	Prolonged PPRM N=609	ROM ≤18 hours N=4489	Adjusted OR (95% CI)	P
Neonatal outcomes, n (%)				
Survival to discharge	444 (73)	3285 (73)	0.84 (0.68-1.05)	0.12
Survival without severe (Grade 3) BPD	382 (64)	2916 (67)	0.81 (0.67-0.99)	0.04
Survival without severe neonatal morbidity*	252 (42)	1818 (42)	1.07 (0.89-1.30)	0.47
Outcomes at 22-26 months’ corrected age, n (%)				
Survival without severe NDI	298 (56)	2212 (57)	0.91 (0.75-1.12)	0.37
Survival without serious respiratory morbidity**	294 (54)	2308 (57)	0.83 (0.68-1.01)	0.06
Outcomes among surviving infants at 22-26 months’ corrected age, n (%):				
Severe NDI	71 (19.2)	503 (18.5)	0.99 (0.74-1.33)	0.96
Moderate or severe NDI	171 (46.3)	1176 (43.3)	1.10 (0.87-1.39)	0.43
Moderate or severe cerebral palsy	35 (9.4)	267 (9.5)	0.96 (0.65-1.41)	0.84
Oxygen use	32 (8.5)	168 (5.9)	1.44 (0.94-2.19)	0.09
Ventilator or CPAP	11 (2.9)	62 (2.2)	1.44 (0.73-2.84)	0.29

*Defined as severe BPD, surgical necrotizing enterocolitis, cystic periventricular leukomalacia, severe intraventricular hemorrhage, or severe ROP
**Defined as tracheostomy; continued hospitalization for respiratory reasons at or beyond 50 weeks’ PMA; use of supplemental oxygen, respiratory support, or respiratory monitoring (e.g., pulse oximeter, apnea monitor) at follow-up, or ≥2 rehospitalizations for respiratory reasons before follow-up

- Higher gestational age at birth and at ROM were associated with higher odds of survival without severe NDI, while SGA infants had lower odds of survival without severe NDI (**Table 4**).

Table 4. Factors Associated with Survival without Severe NDI among Infants Exposed to Prolonged PPRM				
	Survival		Survival without severe NDI	
	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Birth gestational age, weeks	1.60 (1.30-1.96)	<0.001	1.37 (1.13-1.67)	0.001
Gestational weeks at rupture	1.57 (1.39-1.78)	<0.001	1.44 (1.26-1.63)	<0.001
Antenatal steroids	4.07 (1.13-14.61)	0.03	2.91 (0.68-12.40)	0.15
Female sex	1.26 (0.82-1.92)	0.29	1.57 (1.06-2.34)	0.03
Clinical chorioamnionitis	0.98 (0.62-1.55)	0.94	1.11 (0.73-1.68)	0.64
Cesarean delivery	1.10 (0.71-1.72)	0.66	0.90 (0.60-1.34)	0.59
Small for gestational age	0.25 (0.08-0.78)	0.02	0.14 (0.04-0.51)	0.003

Conclusions

- The majority of actively treated EPT infants born to mothers with prolonged, perivable PPRM survived without severe NDI at 22-26 months’ corrected age.
- Odds of survival without severe NDI were not significantly different from unexposed infants, but decreased with earlier gestational age at ROM.
- These data may be useful to inform counseling of families affected by PPRM before 24 weeks’ gestation.
- Higher rates of HFV, iNO, and pneumothorax in the PPRM group suggest that care teams should be prepared to have access to these therapies and strive to minimize lung injury from admission.

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