Original Research

Neonatal Survival After Prolonged Preterm Premature Rupture of Membranes Before 24 Weeks of Gestation

Jane E. Brumbaugh, MD, Tarah T. Colaizy, MD, MPH, Nina Nuangchamnong, MD, Emily A. O'Brien, Diedre K. Fleener, RN, BSN, Asha Rijhsinghani, MD, and Jonathan M. Klein, MD

OBJECTIVE: To evaluate neonatal survival after prolonged preterm premature rupture of membranes (PROM) in the era of antenatal corticosteroids, surfactant, and inhaled nitric oxide.

METHODS: A single-center retrospective cohort study of neonates born from 2002–2011 after prolonged (1 week or more) preterm (less than 24 weeks of gestation) rupture of membranes was performed. The primary outcome was survival to discharge. Neonates whose membranes ruptured less than 24 hours before delivery (n=116) were matched (2:1) on gestational age at birth, sex, and antenatal corticosteroid exposure with neonates whose membranes ruptured 1 week or more before delivery (n=58). Analysis used conditional logistic regression for categorical data and Wilcoxon signed rank test for continuous data.

RESULTS: The prolonged preterm PROM exposed and unexposed cohorts had survival rates of 90% and 95%, respectively, although underpowered to assess the statistical significance (P=.313). Exposed neonates were more likely have pulmonary hypoplasia (26/58 exposed, 1/114 unexposed, P<.001), pulmonary hypertension (21/56 exposed, 10/112 unexposed, P<.001), and pulmonary air leak (21/58 exposed, 14/114 unexposed, P<.001). Gestational age at rupture (20.4 weeks exposed, 22.3 weeks unexposed, P=.189), length of rupture (3.7 weeks exposed, 6.4 weeks unexposed, P=.717), and lowest maximal vertical pocket before 24 weeks of gestation (0 cm exposed, 1.4 cm unexposed, P=.114) did not discriminate between survivors and nonsurvivors after exposure to prolonged preterm PROM.

CONCLUSION: With antenatal steroid exposure and aggressive pulmonary management, survival to discharge after prolonged preterm PROM was 90%. Pulmonary morbidities were common. Of note, the data were limited to women who remained pregnant 1 week or longer after rupture of membranes.

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Preterm birth affects over 11% of births in the United States, making prematurity a major public health concern.[1] Premature rupture of membranes (PROM) complicates 8% of all pregnancies with preterm PROM affecting 3% of pregnancies.[2,3] After rupture, preterm delivery frequently ensues in the subsequent week.[4,5] However, latency after rupture of membranes correlates inversely with gestational age at rupture.[6,7] The more preterm at the time of rupture, the longer the latency period is between rupture and delivery.

Accurate contemporary data describing neonatal outcomes after prolonged preterm premature rupture of membranes are critical for counseling women who experience second-trimester rupture of membranes. Before antenatal corticosteroid and postnatal surfactant administration, neonates exposed to preterm

From the Stead Family Department of Pediatrics, the Department of Obstetrics and Gynecology, and the College of Liberal Arts and Sciences, University of Iowa, Iowa City, Iowa.

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Corresponding author: Jane E. Brumbaugh, MD, 200 Hawkins Drive, 8805 JPP, Iowa City, IA 52242; e-mail: jane-brumbaugh@uiowa.edu.

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PROM before 24 weeks of gestation had 32% survival.[8] Kilbride et al[9] reported less than 10% survival for neonates exposed to oligohydramnios for more than 14 days after preterm PROM before 25 weeks of gestation. Finally, in this earlier era, Xiao et al[10] found less than 20% survival for neonates whose membranes ruptured before 22 weeks with subsequent delivery at or after 24 weeks of gestation.

Beyond survival, neonatal and maternal morbidities after preterm PROM merit attention. Pulmonary hypoplasia consists of dysplastic lung parenchyma and altered pulmonary vasculature.[11–14] This feared complication occurs in an estimated 10–20% of neonates after preterm PROM.[2] There are also infectious concerns for both the mother and the neonate in the setting of preterm PROM. Expectant management may result in prolonged latency, a risk factor for maternal chorioamnionitis.[7] Indeed, chorioamnionitis is the most common indication for delivery after preterm PROM.[8]

In the past two decades, there has been a dramatic improvement in neonatal outcomes after preterm birth as a result of the use of antenatal corticosteroids.[15–17] During this era, groups in Australia, Germany, and Belgium have reported neonatal survival as high as 70% after preterm PROM.[18–20] With the data continuing to evolve, second-trimester preterm PROM remains a challenge for both obstetricians and neonatologists counseling expectant mothers.

Management recommendations for preterm PROM at 24 weeks of gestation or greater includes expectant management; antibiotics to prolong latency, if no contraindications; a course of corticosteroids; and group B streptococci prophylaxis, if indicated.[2] However, evidence is lacking to guide management of preterm PROM before 24 weeks of gestation. To appropriately address this question, updated analysis of the neonatal morbidities and mortality after second-trimester preterm PROM is needed. The aim of this study was to evaluate contemporary neonatal outcomes after expectant management of preterm PROM before 24 weeks of gestation with a latency 7 or more days.

MATERIALS AND METHODS

We conducted a single-center retrospective analysis of a cohort of neonates born at the University of Iowa Hospitals and Clinics in Iowa City, Iowa. The center averages 1,800 deliveries and 700 neonatal intensive care unit admissions per year. We collected data on all neonates born between January 2002 and December 2011 who had a history of maternal rupture of membranes before 24 weeks of gestation with a latency of 1 week or longer. These preterm PROM–exposed neonates were identified by gestational age at rupture of membranes and gestational age at birth in the University of Iowa Neonatal Admissions Registry. Unexposed neonates, matched by gestational age at birth, sex, and antenatal corticosteroid exposure, experienced maternal rupture of membranes less than 24 hours before delivery. We conducted two-to-one matching of neonates unexposed to preterm PROM for each preterm PROM–exposed neonate. Neonates were matched by gestational age at birth (±1 week), sex, and any antenatal corticosteroid exposure, three variables known to affect neonatal outcomes. For each preterm PROM–exposed neonate, the two next born unexposed neonates meeting criteria were matched to the exposed neonate. We excluded outborn neonates, higher-order multiples (triplet or more), neonates with major congenital anomalies, and neonates with birth weights less than 400 g. A total of 58 neonates met the inclusion and exclusion criteria for the preterm PROM–exposed cohort, and the neonates were matched to 116 unexposed neonates. All data were abstracted from maternal and neonatal medical records. Two of the authors (N.N. and D.K.F.) were responsible for the abstraction of maternal records. Two of the authors (J.E.B. and E.A.O.) were responsible for the abstraction of neonatal records. The University of Iowa institutional review board approved the study with a waiver of consent.

Data collected included gestational age at rupture of membranes, gestational age at birth, survival to discharge, pulmonary hypoplasia, pulmonary hypertension, air leak, and bronchopulmonary dysplasia. Estimated date of delivery was determined by last menstrual period or ultrasound examination at the primary obstetrician's discretion and then was used to calculate gestational age. Chorioamnionitis was diagnosed clinically or histologically in the medical record. Rupture of membranes confirmation methods included visualization of amniotic fluid pooling in the vagina, ferning, ultrasound documentation of a reduction in amniotic fluid volume, amniocentesis dye infusion, and AmniSure. Antenatal ultrasound data consisted of maximal vertical pocket measurements of amniotic fluid for the preterm PROM–exposed cohort only. The frequency of antenatal ultrasound monitoring after confirmation of rupture of membranes varied.

The primary neonatal outcome was survival to hospital discharge. Secondary outcomes included pulmonary hypoplasia, bronchopulmonary dysplasia, air leak, early-onset sepsis, intraventricular hemorrhage, and periventricular leukomalacia. Pulmonary hypoplasia was defined by the clinical team based on radiologic findings

and respiratory support requirements. Pulmonary hypertension was defined clinically with echocardiographic confirmation when available. Pulmonary air leak was defined as pneumothorax, pneumomediastinum, or pulmonary interstitial emphysema on chest radiograph. Neonates who required supplemental oxygen or positive pressure ventilation at 36 weeks postmenstrual age were defined as having bronchopulmonary dysplasia. Tension pneumothorax was defined as pneumothorax requiring evacuation by needle thoracentesis or chest tube placement. Early-onset culture-positive sepsis was defined as a positive blood culture obtained within the first 3 days of life. Screening cranial ultrasound scans were performed at approximately 1 week chronological age and 36 weeks postmenstrual age. Intraventricular hemorrhage detected by cranial ultrasonography was graded 1–4 based on the Papile classification.[21] Periventricular leukomalacia was defined by white matter injury on cranial ultrasonography. Patent ductus arteriosus was defined by presence on echocardiogram. Necrotizing enterocolitis was defined as stage 2 or greater based on Bell's criteria.[22]

Data analysis was performed using SAS 9.3. Descriptive statistics were performed to compare the cohort of neonates exposed to preterm PROM with the unexposed cohort. The Wilcoxon sign rank test was used for matched continuous data. Stratified exact logistic regression was used to compare categorical variables between preterm PROM–exposed and unexposed neonates accounting for both the matching design and the sample size. Statistical significance was set at $P<.05$.

RESULTS

By design, neonatal sex and gestational age at birth were similar for the preterm PROM–exposed and unexposed cohorts (Table 1). The cohorts differed by gestational age at rupture of membranes (median [interquartile range] 22.3 [19.7–23.1] weeks for the preterm PROM exposed, 26.8 [25.0–29.9] weeks for the unexposed, $P<.001$) and by latency (median [interquartile range] 6.2 [2.9–9.3] weeks for the preterm PROM exposed, 0 [0–0.1] weeks for the unexposed, $P<.001$). Of the 18 neonates exposed to ruptured membranes before 20 weeks of gestation, 15 survived to discharge; one neonate survived after rupture of membranes at 13 weeks of gestation. Latency for the preterm PROM–exposed cohort ranged from 7 to 121 days. The nine neonates with the longest latencies (74–121 days) in this cohort all survived to discharge.

Maternal complications differed for the two cohorts (Table 1). Histologic chorioamnionitis was more common in the preterm PROM–exposed cohort (odds ratio [OR] 6.02, 95% confidence interval [CI] 2.40–17.80, $P<.001$). There were no cases of maternal culture-positive sepsis. Preeclampsia was more common among the unexposed mothers (unable to calculate OR as a result of no incidence in the preterm PROM–exposed cohort, $P<.001$). Twin gestation was also more common in the unexposed cohort (OR 0.13, 95% CI 0.02–0.46, $P<.001$).

For the preterm PROM–exposed neonates, the survival rate was 90% (95% CI 0.91–0.99), whereas for the unexposed neonates, the survival rate was 95% (95% CI 0.82–0.97) (Table 2). The two cohorts had similar rates of survival to discharge (OR 0.42, 95% CI 0.08–1.87, $P=.313$) and composite poor outcome of death, grade 3 or 4 intraventricular hemorrhage, or periventricular leukomalacia (OR 1.13, 95% CI 0.44–2.82, $P=.930$). However, the cohorts differed in the incidence of neonatal pulmonary morbidities. Clinical diagnoses of pulmonary hypoplasia (unable to calculate OR as a result of the low incidence in the unexposed cohort, $P<.001$), pulmonary hypertension (OR 11.11, 95% CI 3.24–58.82, $P<.001$), and pulmonary air leak (OR 5.29, 95% CI 1.99–16.39, $P<.001$) were all more common in the preterm PROM–exposed cohort. In addition, the preterm PROM–exposed cohort was more likely to be supported with high-frequency ventilation (OR 6.94, 95% CI 2.25–28.57, $P<.001$), to receive inhaled nitric oxide (OR 18.18, 95% CI 4.41–166.67, $P<.001$), and to be discharged on pulmonary medications (OR 5.28, 95% CI 1.94–14.32, $P=.001$). None of the neonates required tracheostomy or home ventilatory support. Data were missing for up to 13% of the data for the individual outcomes. This data loss was primarily secondary to competing outcomes, ie, death or transfer to other hospitals before discharge limiting availability of later measures, including bronchopulmonary dysplasia and discharge-related measures.

Over the course of neonatal hospitalization, there were two deaths attributed to pulmonary hypoplasia, two to sepsis (*Escherichia coli* and coagulase-negative *Staphylococcus* infection), and two to complications of extreme prematurity in the preterm PROM–exposed cohort. In the unexposed cohort, there were two deaths attributed to complications of extreme prematurity, one to sepsis (*E coli*), one to hepatic rupture, one to necrotizing enterocolitis, and one to bronchopulmonary dysplasia. Although there were no deaths in the delivery room, three neonatal deaths occurred within 1 hour of birth (one preterm PROM–exposed neonate; two unexposed neonates).

For the exposed cohort, the lowest maximal vertical pocket measured throughout gestation was

Table 1. Neonatal and Maternal Characteristics

Characteristic	Preterm PROM–Exposed (n=58)	Unexposed (n=116)	*P*
Neonatal*			
Female sex	30 (52)	60 (52)	1.000†
Gestational age at birth (wk)	26.6 (25.0–29.9)	26.8 (25.0–29.9)	.734‡
Gestational age at rupture (wk)	22.3 (19.7–23.1)	26.8 (25.0–29.9)	<.001‡
Length of rupture (wk)	6.2 (2.9–9.3)	0 (0–0.1)	<.001‡
Birth weight (g; n=172)	878 (672–1,382)	939 (696–1,350)	.733‡
SGA (n=172)	6 (11)	15 (13)	.831†
Maternal			
Age (y)	26.5 (23–32)	26.0 (22–32)	.551‡
Antenatal steroid exposure	58 (100)	116 (100)	1.000†
Gestational age at first dose of steroid (wk)	23.7 (23.4–24.0)	25.9 (24.5–28.6)	<.001‡
Completed steroid course more than 24 h before delivery	56 (97)	65 (56)	<.001†
Completed steroid course more than 7 d before delivery	35 (60)	26 (22)	<.001†
Steroid administration less than 12 h before delivery	2 (3)	22 (19)	.014†
Rescue steroid course	18 (31)	8 (7)	<.001†
Antenatal antibiotics	57 (98)	60 (52)	<.001†
Clinical chorioamnionitis	21 (36)	7 (6)	<.001†
Histologic chorioamnionitis (n=166)	42 (76)	42 (38)	<.001†
Preeclampsia§	0 (0)	26 (22)	<.001†
Twin gestation	4 (7)	34 (29)	<.001†
Cesarean delivery	34 (59)	81 (70)	.188†

PROM, premature rupture of membranes; SGA, small for gestational age.
Data are n (%) or median (interquartile range) unless otherwise specified.
* n=174 unless noted.
† Stratified exact logistic regression.
‡ Wilcoxon signed rank test.
§ One case of eclampsia in unexposed.

1.2 (0–2.0) cm (median [interquartile range]). The lowest maximal vertical pocket measured before 24 weeks of gestation was 1.4 (0.9–2.2) cm. The last maximal vertical pocket measured before delivery was 1.6 (0.9–5.6) cm. Neither survival to discharge nor the composite poor outcome of death, grade 3 or 4 intraventricular hemorrhage, or periventricular leukomalacia was predicted by ultrasound amniotic fluid measures for the preterm PROM–exposed cohort (Tables 3 and 4). The point estimate for the maximal vertical pocket was consistently lower, albeit not statistically different, for the preterm PROM–exposed neonates who died compared with the preterm PROM–exposed neonates who survived to discharge (Table 3).

DISCUSSION

In this cohort of preterm neonates exposed to prolonged (7 or more days) preterm (less than 24 weeks of gestation) rupture of membranes, there was a 90% survival rate. The preterm PROM–exposed cohort was more likely to have pulmonary hypoplasia, pulmonary hypertension, and pulmonary air leak, but not bronchopulmonary dysplasia. Our study expands the gestational age at rupture and latency for neonatal survival after preterm PROM in the era of antenatal corticosteroids, surfactant, and inhaled nitric oxide.[23–25] With the low mortality rate, we lacked the power to model predictors of death, and Tables 3 and 4 should be interpreted with caution.

It must be acknowledged that expectant management of preterm PROM poses risks for the pregnant woman because maternal sepsis is reported to occur in 1% of cases.[3] There were no cases of maternal sepsis in our sample. However, neonates exposed to preterm PROM were at higher risk of exposure to histologic chorioamnionitis. Although infection is often presumed in neonates after preterm PROM, we found no difference in the incidence of neonatal early-onset sepsis, and only 5% of the preterm PROM–exposed cohort had positive cultures.

Neonatal pulmonary morbidities are of particular interest after preterm PROM. Application of the physiologic definition of bronchopulmonary dysplasia that was developed during the study interval may have lowered the high rates of bronchopulmonary dysplasia for both cohorts.[26,27] The high incidence of pulmonary hypoplasia after preterm PROM in this sample reflects the use of a clinical definition rather than pathology-based tissue criteria as well as the

Table 2. Neonatal Outcomes

Outcome	Preterm PROM–Exposed	Unexposed	*P*
Survival to discharge	52/58 (90)	110/116 (95)	.313*
Respiratory distress syndrome	58/58 (100)	102/114 (90)	.012*
Pulmonary hypoplasia	26/58 (45)	1/114 (<1)	<.001*
Clinical pulmonary hypertension	21/56 (38)	10/112 (9)	<.001*
Echocardiogram pulmonary hypertension	5/43 (12)	6/81 (7)	.584*
Pulmonary air leak	21/58 (36)	14/114 (12)	<.001*
Bronchopulmonary dysplasia	43/48 (90)	84/106 (79)	.076*
Early-onset sepsis culture–positive	3/57 (5)	5/115 (4)	1.000*
Intraventricular hemorrhage	8/54 (15)	25/114 (22)	.337*
Grade 3 or 4 intraventricular hemorrhage	4/58 (7)	14/116 (12)	.447*
Periventricular leukomalacia	4/52 (8)	4/111 (4)	.420*
Composite poor outcome†	11/58 (19)	20/116 (17)	.930*
Ventilator length (d)	36 (9–60)	27 (2–59)	.287‡
Conventional ventilator	48/55 (87)	96/112 (86)	1.000*
High frequency ventilator	45/57 (79)	61/113 (54)	<.001*
Surfactant doses	2 (1–3)	1 (1–4)	.359‡
Inhaled nitric oxide	26/56 (46)	14/112 (11)	<.001*
Length of stay (d)	92 (72–124)	83 (53–111)	.138‡
Discharge supplemental oxygen	38/49 (78)	68/104 (65)	.055*
Chronologic age off supplemental oxygen (mo)	9.3 (6.8–17.8)	8.6 (6.1–12.4)	.165‡
Discharge pulmonary medications	24/49 (49)	23/103 (22)	.001*
Patent ductus arteriosus	22/54 (41)	55/112 (49)	.334*
Necrotizing enterocolitis	1/52 (2)	9/111 (8)	.535*
Retinopathy of prematurity with laser photocoagulation	3/52 (6)	12/110 (11)	.399*

PROM, premature rupture of membranes.
Data are n/N (%) or median (interquartile range) unless otherwise specified.
* Stratified exact logistic regression.
† Death, grade 3 or 4 intraventricular hemorrhage, or periventricular leukomalacia.
‡ Wilcoxon signed rank test.

duration of latency. We speculate that one reason for the improved survival associated with pulmonary hypoplasia is recognition that these neonates may have reversible pulmonary hypertension responsive to nitric oxide.[28,29]

This retrospective cohort study has two primary strengths. The first is its relatively robust sample size with 58 neonates exposed to preterm PROM for 7 or more days before 24 weeks of gestation. The second strength is the matching process that accounted for gestational age at birth (±1 week), sex, and antenatal corticosteroid exposure. Gestational age at birth rather than gestational age at rupture or latency is the key predictor of survival after preterm PROM.[4,5] We matched the preterm PROM–exposed neonates with the next-born unexposed neonates to control for any historical variation in practice over the study period. By matching the cohorts, we were able to address differences in survival and morbidities specifically related to preterm PROM.

Our study had limitations. This retrospective analysis included only those cases of preterm PROM

Table 3. Neonatal Outcomes Predicted by Antenatal Ultrasound Examination: Death

	Preterm PROM–Exposed Cohort		
Findings Among Deceased and Surviving Neonates	Deceased (n=6)	Survived to Discharge (n=52)	*P**
Gestational age at rupture (wk)	20.4 (18.1–22.7)	22.3 (19.8–23.2)	.189
Gestational age at birth (wk)	24.7 (23.9–26.1)	26.8 (25.4–30.0)	.035
Length of rupture (wk)	3.7 (3.3–10.3)	6.4 (2.6–8.8)	.717
Lowest MVP (cm)	0 (0–0.9)	1.3 (0–2.1)	.138
Lowest MVP (cm) before 24 wk	0 (0–1.3)	1.4 (1.1–2.2)	.114

PROM, premature rupture of membranes; MVP, maximal vertical pocket.
Data are median (interquartile range) unless otherwise specified.
* Wilcoxon signed rank test.

Table 4. Neonatal Outcomes Predicted by Antenatal Ultrasound Examination: Composite Poor Outcome

Findings Among Neonates With and Without Composite Poor Outcome*	Preterm PROM–Exposed Cohort		
	Deceased (n=11)	Survived to Discharge (n=47)	$P^{\dagger}$
Gestational age at rupture (wk)	22.7 (19.7–23.1)	22.3 (19.7–23.1)	.796
Gestational age at birth (wk)	25.1 (24.0–26.0)	27.1 (25.4–30.1)	.003
Length of rupture (wk)	3.3 (1.6–6.1)	6.7 (3.3–9.4)	.049
Lowest MVP (cm)	0.9 (0–1.8)	1.2 (0–2.0)	.665
Lowest MVP (cm) before 24 wk	1.4 (0–2.7)	1.4 (1.0–4.0)	.806

PROM, premature rupture of membranes; MVP, maximal vertical pocket.
Data are median (interquartile range) unless otherwise specified.
* Death, grade 3 or 4 intraventricular hemorrhage, or periventricular leukomalacia.
† Wilcoxon signed rank test.

managed expectantly at a single center. Data were not available for pregnancies that ended with termination (elective or medically indicated) or fetal demise after preterm PROM. As a result, there was a potential for selection bias. This study was not adequately powered to state there was no difference in survival between the preterm PROM–exposed and unexposed or to provide population estimates of neonatal outcomes after preterm PROM. However, the survival rate of 90% in the preterm PROM–exposed cohort suggests second-trimester preterm PROM may result in manageable neonatal lung disease with lung growth not halted indefinitely.

Because of the differences in pregnancy complications, the window of threatened preterm delivery in which to administer antenatal corticosteroids differed for the two cohorts. With second-trimester preterm PROM, women were more likely to complete their corticosteroid course more than 24 hours before delivery. Preeclampsia was more frequent in mothers of the preterm PROM–unexposed cohort. Not infrequently women with preeclampsia delivered before completion of the antenatal corticosteroid course. The higher completion rate of corticosteroid administration more than 24 hours before delivery in the preterm PROM cohort may have favorably influenced the neonatal outcomes for the preterm PROM–exposed cohort. Finally, the larger percentage of multiple gestations in the unexposed cohort could have adversely affected the neonatal outcomes for the unexposed cohort.

These data suggest that neonatal survival is possible after second-trimester preterm PROM in a center offering expectant maternal management, routine administration of antenatal corticosteroids, and a neonatal team prepared to aggressively manage the ensuing neonatal lung disease. Despite improved survival over the past two decades, neonates exposed to preterm PROM still require increased resources, including high-frequency ventilation, inhaled nitric oxide therapy, and pulmonary therapies at discharge. The improved neonatal survival rate may alter counseling and referral practice for health care providers caring for women who experience second-trimester preterm PROM, are interested in continuation of pregnancy, and remain pregnant for 1 week or more after rupture of membranes. Future work should incorporate a multicenter design, larger sample size, and long-term neurodevelopmental follow-up to further inform counseling and referral practice.

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