Neonatal Survivability following Previable PPROM after Hospital Readmission for Intervention

Felicia LeMoine, MD[1] Robert C. Moore, MS, MD[2] Andrew Chapple, PhD[3] Ferney A. Moore, MD[1] Elizabeth Sutton, PhD[2]

[1] Department of Obstetrics and Gynecology, Louisiana State University Health Science Center, Baton Rouge, Louisiana
[2] Department of Maternal-Fetal Medicine, Woman's Hospital, Baton Rouge, Louisiana
[3] Biostatistics Program, School of Public Health, Louisiana State University Health Sciences Center, New Orleans, Louisiana

Address for correspondence Felicia LeMoine, MD, Department of Obstetrics and Gynecology, Louisiana State University Health Science Center, 500 Rue de la Vie, Suite 404, Baton Rouge, LA 70817 (e-mail: fvenab@lsuhsc.edu).

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Abstract

Objective To describe our hospital's experience following expectant management of previable preterm prelabor rupture of membranes (pPPROM).

Study Design Retrospective review of neonatal survival and maternal and neonatal outcomes of pPPROM cases between 2012 and 2019 at a tertiary referral center in South Central Louisiana. Regression analyses were performed to identify predictors of neonatal survival.

Results Of 81 cases of pPPROM prior to 23 weeks gestational age (WGA), 23 survived to neonatal intensive care unit discharge (28.3%) with gestational age at rupture ranging from $18^{0/7}$ to $22^{6/7}$ WGA. Increased latency (adjusted odds ratio [aOR] = 1.30, 95% confidence interval [CI] = 1.11, 1.52) and increased gestational age at rupture (aOR = 1.62, 95% CI = 1.19, 2.21) increased the probability of neonatal survival. Antibiotics prior to delivery were associated with increased latency duration (adjusted hazard ratio = 0.55, 95% CI = 0.42, 0.74).

Conclusion Neonatal survival rate following pPPROM was 28.3%. Later gestational age at membrane rupture and increased latency periods are associated with increased neonatal survivability. Antibiotic administration following pPPROM increased latency duration.

Keywords
- previable
- preterm
- rupture of membranes
- mid-trimester PPROM

Preterm prelabor rupture of membranes (PPROM), defined as spontaneous rupture of membranes before 37 weeks gestational age (WGA) and onset of labor, is a leading cause of fetal and neonatal morbidity and mortality worldwide. Three per cent of pregnancies in the United States are estimated to be complicated by PPROM, with the majority of membrane rupture occurring when the fetus is considered viable (between $24^{0/7}$ and $36^{6/7}$ WGA).[1] In ~1% of pregnancies, rupture of membranes occurs near or prior to viability (termed previable PPROM or pPPROM).[1] Major contributors to neonatal morbidity and mortality following pPPROM are early gestational age at rupture and brief latency periods (i.e., the number of days from rupture of membranes to delivery). Reports have shown up to 50% of expectantly managed pregnancies affected by pPPROM deliver within 1 week of rupture, while other estimates report 22 to 34% of pPPROM-affected pregnancies have latency periods $\geq$ 1 month.[1,2] Though longer latency may result in more deliveries beyond the threshold of viability, earlier gestational ages at the time of rupture may still portend worse immediate and long-term neonatal outcomes.[1,3–9]

Clinical management of pPPROM may entail counseling patients to consider delivery versus expectant management considering poor neonatal prognosis and increased maternal risks associated with continued expectant management, especially prior to 20 WGA. Such maternal risks include

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chorioamnionitis, sepsis, placental abruption, endometritis, retained placenta, and hemorrhage.[1,3–9] However, advances in perinatal and neonatal practices have contributed to an uptrend in neonatal survival rates. Earlier studies published from 1984 to 2000 report a wide range of neonatal survival rates extending from 22 to 83% following PPROM at less than $26^{0/7}$ WGA.[3] In a recent study published in 2009, Manuck et al reported an overall neonatal survival rate of 56% following PPROM at less than 24 weeks, of which 27% survived without major neonatal morbidity.[7] These reports suggest a place for expectant management of pPPROM when no signs of labor, intrauterine infection, placental abruption, or fetal demise are present at the time of initial presentation.

When expectant management is pursued, close outpatient surveillance for labor, infection, and hemorrhage and surveillance of fetal status are prudent. With continued clinical stability throughout outpatient surveillance, hospital readmission would occur at viability, between $23^{0/7}$ and $24^{0/7}$ WGA (dependent on institutional practices). Following readmission, the standard interventions indicated for PPROM (latency antibiotics, a course of glucocorticoids for fetal lung maturity, and magnesium sulfate for fetal neuroprotection) are administered. Inpatient observation continues from the time of readmission until delivery either at $34^{0/7}$ WGA or when clinical evidence of maternal or fetal compromise is noted. Delivery of a viable infant is then attended by a neonatal intensive care specialist to provide full neonatal resuscitation.

The American College of Obstetricians and Gynecologists, per Practice Bulletin No. 188, recommends thorough counseling regarding the risks and benefits of expectant management following pPPROM, including "a realistic appraisal of neonatal outcomes."[10] The bulletin specifically states "attempts should be made to provide parents with the most current and accurate information as possible."[10] Despite this recommendation, the reported rates of neonatal survivability are widely variable throughout literature, and these inconsistencies lend much difficulty in formulating accurate recommendations and proposed maternal and neonatal prognoses during patient counseling.[2,3,10] In an effort to contribute to this body of literature and, more importantly, to aid in institution-specific maternal counseling, we reviewed the neonatal and maternal outcomes within our institution following previable membrane rupture (rupture at less than $23^{0/7}$ WGA) with readmission for full neonatal resuscitation at viability (defined as $23^{0/7}$ WGA) between 2012 and 2019.

Methods

Study Design

Woman's Hospital (Baton Rouge, LA) is a tertiary referral center for South Central Louisiana providing care for both low- and high-risk patients and performing ~8,000 deliveries per year. The Level III neonatal intensive care unit (NICU) provides care for nearly 750 neonates per year. We performed a retrospective, hospital medical record review of patients admitted to Woman's Hospital for PPROM between January 2012 and July 2019. This time frame was chosen to reflect current management practices, notably magnesium sulfate administration for preterm delivery at less than $32^{0/7}$ WGA for fetal neuroprotection. Institutional Review Board (IRB) approval and waiver of Health Insurance Portability and Accountability Act authorization were obtained from both Woman's Hospital Foundation IRB and Louisiana State University Health Sciences Center, New Orleans IRB prior to study initiation. Patients with singleton gestations receiving care at Woman's Hospital for pPPROM prior to $23^{0/7}$ WGA were included. pPPROM was diagnosed on physical examination by one, or a combination of the following: (1) visualization of amniotic fluid passing from the cervical canal and pooling in the vagina via sterile speculum examination, (2) a basic pH (i.e., positive nitrazine) test of vaginal fluid, (3) arborization (ferning) of dried vaginal fluid identified via microscopic examination, or (4) an amniotic fluid index (AFI) of less than 4 cm with a patient-reported history indicating significant loss of vaginal fluid prior to $23^{0/7}$ WGA. Patients with multiple gestations, fetuses with known fetal anomalies, recent intervention (amniocentesis, cerclage placement, or chorionic villus sampling), desire for medical termination, indication for termination (i.e., fetal demise, chorioamnionitis, active labor, active placental abruption), or with no desire for neonatal resuscitation following delivery were excluded. All patients included in this study were admitted for an initial observation period (length of observation varied pending provider preference) followed by outpatient observation if no signs of labor, chorioamnionitis (i.e., maternal temperature $\geq$ 39°C or maternal temperature 38.0 to 38.9°C associated with at least one of the following: maternal leukocytosis, purulent cervical drainage, or fetal tachycardia), placental abruption (i.e., separation from the placenta from its implantation site before delivery), or nonreassuring fetal status (i.e., category III fetal heart tracing or intrauterine fetal demise) were noted. Outpatient management continued until $23^{0/7}$ WGA (point of viability as determined by Woman's Hospital) at which point the patient would be readmitted for inpatient management until delivery. Corticosteroids for fetal lung maturity (i.e., 12 mg intramuscular administered every 24 hours for a total of two doses) and magnesium sulfate for fetal neuroprotection (i.e., 6 g loading dose, 6 g in 100 mL infused over 15 to 20 minutes, followed by maintenance dose of 2 g/h at the rate of 50 mL/h of 20 g/500 mL for a minimum of 12 hours) were administered in all patients at readmission. Tocolytic agents were not administered in any patients studied. Antibiotic administration (yes/no), antibiotic class, timing of antibiotic administration, route of antibiotic administration, and duration of antibiotic administration all varied among providers given no current literature to support recommendations for administration of latency antibiotics following rupture of membranes in the previable period. Latency antibiotics (i.e., erythromycin 500 mg orally every 8 hours for 7 days with 48-hour course of ampicillin 2 g intravenously every 6 hours followed by amoxicillin 500 mg orally every 9 hours for 5 days) were administered to all patients who had not received antibiotics prior to viability ($23^{0/7}$ WGA). Fetal monitoring varied widely prior to viability (i.e., less than $23^{0/7}$ WGA). After $23^{0/7}$ WGA, fetal monitoring varied by gestational age, but at minimum, weekly sonographic fluid evaluation and twice daily fetal heart rate assessment were

performed. Delivery of the fetus occurred at clinical signs of chorioamnionitis (as defined earlier), placental abruption, preterm labor, nonreassuring fetal status, or at 34 WGA. Prior to $23^{0/7}$ WGA, all deliveries occurred vaginally. After $23^{0/7}$ WGA, delivery route was determined by routine obstetric indications.

Data Collection

Maternal data collected include age, race, ethnicity, body mass index (BMI), gravida, parity, history of tobacco use, and history of preterm delivery. Obstetric data collected include WGA at rupture of membranes, WGA at delivery, latency (defined as number of days from time of rupture of membranes to time of delivery), receipt of antibiotics prior to delivery (defined as administration of any antibiotic regimen from the time of membrane rupture diagnosis to delivery), route of delivery, chorioamnionitis, maternal sepsis, cord prolapse, and maternal length of stay (defined as the cumulative number of days the patient was admitted to the hospital, including the initial observation, readmission, delivery, and postpartum inpatient care). Neonatal data included intrauterine fetal demise, neonatal birth weight, 1- and 5-minute Apgar scores, admission to NICU, and length of NICU stay. Neonatal survival parameters included admission to NICU with survival until discharge, admission to NICU but neonatal death prior to discharge, or death without NICU admission. Neonatal diagnoses at the time of NICU discharge (pulmonary hypoplasia, bronchopulmonary dysplasia, respiratory distress, intraventricular hemorrhage [grades I–IV], periventricular leukomalacia, necrotizing enterocolitis, neonatal sepsis, limb deformities, and retinopathy of prematurity) were also noted.

Survival Rate

Overall survival rate was defined as a proportion of neonates who survived to NICU discharge relative to the total number of gestations that met eligibility criteria for this study. To compare maternal characteristics of early versus late pPPROM patients, subjects were stratified into early pPPROM (less than $21^{0/7}$ WGA at rupture) and late pPPROM ($21^{0/7}$–$23^{0/7}$ WGA at rupture). Similar to the overall survival rate, survival rate in each of the aforementioned groups was determined.

Statistical Analysis

Maternal characteristics were compared between the mothers of neonatal survivors and mothers of neonatal nonsurvivors using Wilcoxon's signed-rank tests for continuous variables and Fisher's exact tests for categorical variables. Similarly, neonatal characteristics were compared between early pPPROM survivors and late pPPROM survivors using Wilcoxon's signed-rank tests for continuous variables and Fisher's exact tests for categorical variables.

Mean gestational ages at rupture and delivery and mean latency periods were compared between the early and late pPPROM groups using Wilcoxon's signed-rank tests. Best subset selection was used to identify two covariates best fitting for the logistic regression model which ultimately included latency time and gestational age at rupture of membranes. Only two covariates were included in the best subset selection following the suggestion that 10 cases and controls be included for each covariate included in a logistic regression.[11] Multivariable Cox's regression was then performed for latency using the following variables to determine which factors most influenced latency length: race, nulliparity, history of preterm delivery, smoking status, BMI, gestational age at rupture of membranes, and receipt of antibiotics prior to delivery.

Results

Population Demographics

Between January 2012 and July 2019, we identified 480 patients admitted to Woman's Hospital for management of PPROM from which 81 met eligibility criteria for our study. Of those meeting eligibility criteria, the majority were of African American race (67%), nonsmoking (93%), and obese (mean BMI $32.2 \pm 9.6\ kg/m^2$) with an average age of 29 ± 6 years (►**Table 1**). The gestational age at rupture of membranes ranged from $15^{5/7}$ to $22^{6/7}$ WGA in all patients. There was no significant difference in age, BMI, race, or history of preterm delivery in mothers of the surviving neonates compared with the mothers of nonsurviving neonates (►**Table 1**).

Rate of Neonatal Survival following pPPROM

Overall survival rate for neonates following pPPROM prior to 23 WGA was 28.4% ($n = 23$). Gestational age at rupture ranged from $18^{0/7}$ to $22^{6/7}$ WGA in the survivors. Of the surviving neonates, 7 were of the early pPPROM group, while 16 were of the late pPPROM group. Of the nonsurviving neonates, 33 were of the early pPPROM group, while 25 were of the late pPPROM group.

Obstetrical Characteristics of Mothers of Surviving versus Nonsurviving Neonates

Compared with mothers of nonsurviving neonates, mothers of surviving neonates had a significantly greater gestational age at rupture (150 ± 12 vs. 142 ± 13 days, respectively, $p = 0.005$), greater gestational age at delivery (186 ± 25 vs. 150 ± 14 days, respectively, $p < 0.001$), and a longer latency period (36 ± 35 vs. 8 ± 15 days, respectively, $p < 0.001$). A significantly higher proportion of mothers of surviving neonates received antibiotics prior to delivery when compared with the mothers of nonsurviving neonates (100 vs. 59%, $p < 0.001$).

Maternal length of hospital stay was significantly longer in the mothers of surviving neonates as compared with the mothers of the nonsurviving neonates (22 ± 17 vs. 5 ± 5 days, $p < 0.001$). The overall rate of chorioamnionitis was 28% ($n = 23$), and mothers of surviving neonates had a significantly lower rate of chorioamnionitis when compared with mothers of nonsurviving neonates (9 vs. 36%, $p = 0.014$). There were no significant differences in the rates of cord prolapse and placental abruption between the surviving and nonsurviving neonates (►**Table 1**). Of the nonsurvivors, three of the neonatal deaths were intrauterine fetal deaths.

Predictors of Neonatal Survival following pPPROM

Using the best subset logistic regression model, more advanced gestational age at the time of rupture (adjusted odds

Table 1 Maternal demographic and obstetric characteristics

Maternal characteristics	All $n = 81$	Surviving neonates $n = 23$	Nonsurviving neonates $n = 58$	*p*-Value
Age, y	28.8 ± 5.7	30.3 ± 5.6	28.2 ± 5.7	0.190
BMI, kg/m^2	32.2 ± 9.6	30.8 ± 6.5	32.7 ± 10.6	0.737
Current smoker	6 (7%)	3 (13%)	3 (5%)	0.345
Race				
African American	54 (67%)	12 (52%)	42 (72%)	0.151
Caucasian	25 (31%)	11 (48%)	14 (24%)	
Other	2 (2%)	0 (0%)	2 (3%)	
Parity				
Nulliparous	38 (47%)	8 (35%)	30 (52%)	0.219
Multiparous	43 (53%)	15 (65%)	28 (48%)	
History of preterm delivery	19 (23%)	7 (3%)	12 (21%)	0.390
Gestational age at rupture, wk	20.6 ± 1.9	21.4 ± 1.7	20.3 ± 1.9	0.005
Gestational age at delivery, wk	22.9 ± 3.4	26.6 ± 3.6	21.4 ± 2.0	<0.001
Latency, d	16 ± 26	36 ± 35	8.2 ± 15	<0.001
Cesarean delivery	18 (22%)	12 (52%)	6 (10%)	<0.001
Receipt of antibiotics prior to delivery	57 (70%)	23 (100%)	34 (59%)	<0.001
Maternal cumulative length of stay, d	10 ± 13	22 ± 17	5 ± 5	<0.001
Chorioamnionitis	23 (28%)	2 (9%)	21 (36%)	0.014
Maternal sepsis	0 (0%)	0 (0%)	0 (0%)	
Cord prolapse	3 (4%)	0 (0%)	3 (5%)	0.554
Placental abruption	4 (5%)	3 (13%)	1 (2%)	0.067

Abbreviation: BMI, body mass index.
Notes: Data are reported as mean (standard deviation) and by frequency (%) for continuous and categorical variables, respectively; *p*-value compares survivors versus nonsurvivors. Body mass index = self-reported height and weight at the time of admission for PPROM. Latency = number of days between gestational age at delivery minus gestational age at PPROM.

ratio [aOR] = 1.62, 95% confidence interval [CI] = 1.19, 2.21) and longer latency periods (aOR = 1.30, 95% CI = 1.11, 1.52) were associated with increased probability of neonatal survival.

►**Fig. 1** displays the estimated neonatal survival probability as a function of latency duration for an average gestational age at rupture (►**Fig. 1A**) and as a function of gestational age at rupture for an average latency duration (►**Fig. 1B**) based on our data. ►**Fig. 1A** illustrates that at the average gestational age of rupture of 21 weeks, the estimated probability of survival for a neonate with 30 latency days is 41% (95% CI = 14–76%), with 40 latency days is 91% (95% CI = 53–99%), and with 50 latency days is 99% (95% CI = 81–100%). Among the 15 patients with latency periods more than 30 days, 67% ($n = 10$) survived. ►**Fig. 1B** illustrates that at the average latency duration of 16 days, the estimated probability of survival was 8% (95% CI = 1–34%) at 21 weeks, and 72% (95% CI = 45–89%) at 22 weeks. ►**Fig. 2** illustrates the relationship between latency duration and gestational age at rupture in a scatterplot overlaid with neonatal survival status. Longer latency times were, in general, associated with increased survival rates; however, shorter latency times with a greater gestational age at rupture had several surviving neonates.

Predictors of Latency following pPPROM

Considering the finding that longer latency, that is, increased time to delivery from rupture, increased the probability of neonatal survival and that latency is a potentially modifiable variable in clinical practice, a post hoc fit, multivariable Cox's regression model was performed to investigate factors influencing latency in our cohort. Here, smaller hazard ratios indicate a longer latency period. African American race (adjusted hazard ratio [aHR] = 1.36, 95% CI = 1.02, 1.82) and increased gestational age at rupture (aHR = 1.61, 95% CI = 1.23, 2.10) were associated with a significantly decreased latency duration and, therefore, an increased hazard of early delivery (►**Fig. 3**). Administration of antibiotics prior to delivery was associated with a significantly increased latency duration and, therefore, a decreased hazard of early delivery (aHR = 0.55, 95% CI = 0.42, 0.74) (►**Fig. 3**).

Neonatal Outcomes of Surviving Neonates following pPPROM

Of all surviving neonates, the mean birth weight was 1,018 ± 559 g, mean Apgar scores at 1- and 5-minutes were 4 ± 2 and 7 ± 2, respectively, and the mean neonatal length of stay was 100 ± 62 days (►**Table 2**). These neonatal

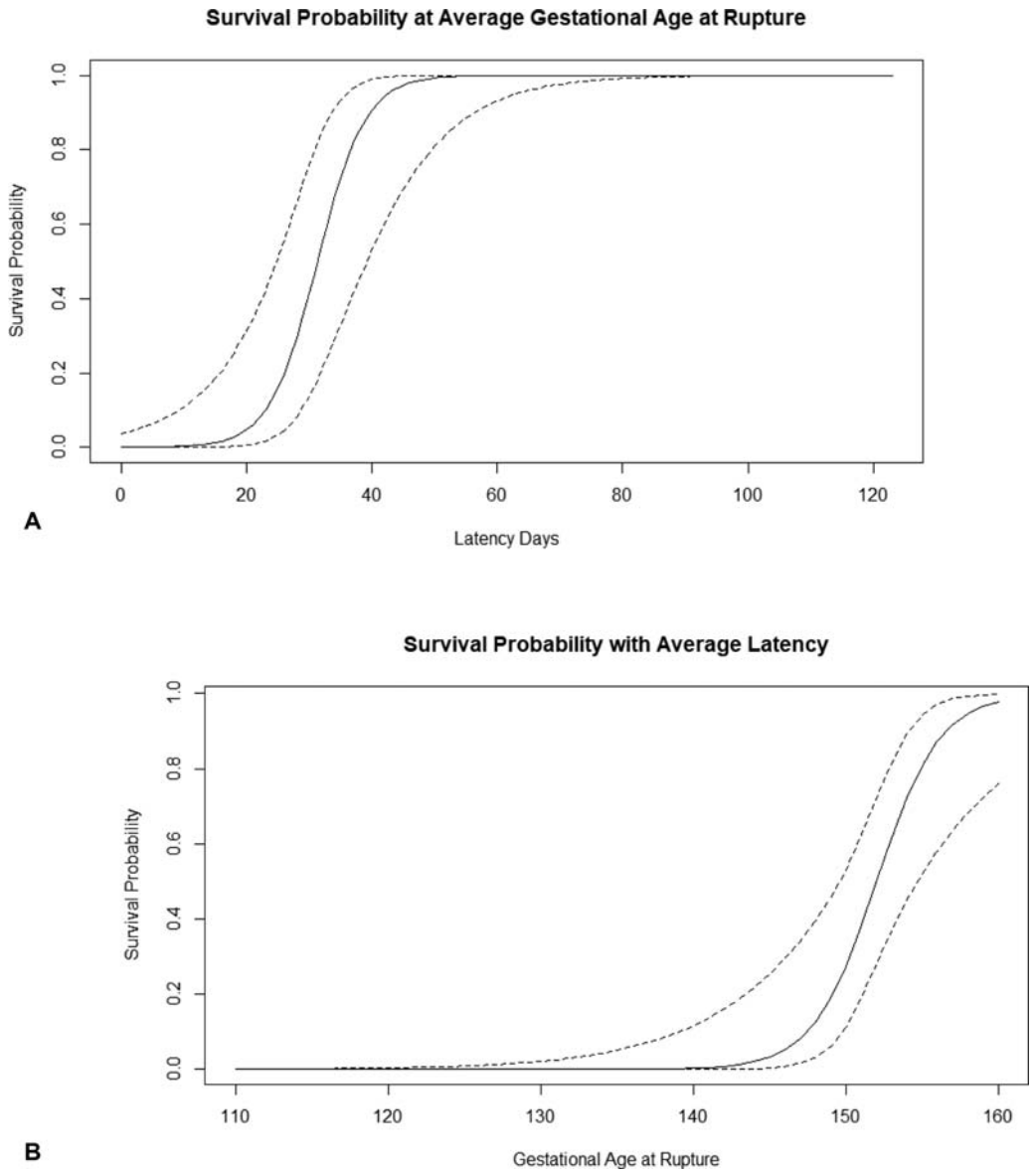

Fig. 1 (**A**) Estimated neonatal survival probability and 95% confidence interval as a function of latency duration for an average gestational age at rupture. (**B**) Estimated neonatal survival probability and 95% confidence interval as a function of gestational age at rupture for an average latency duration.

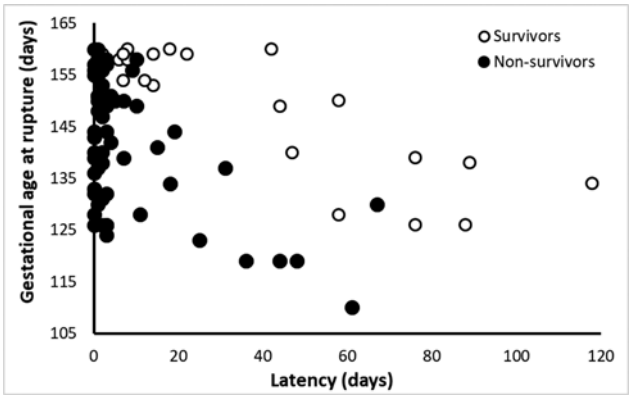

Fig. 2 Neonatal survival as a function of latency duration and gestational age at rupture.

characteristics were compared between the survivors of the early pPPROM and late pPPROM groups. When compared with the late pPPROM group, the mean neonatal birth weight was significantly greater in the early pPPROM group ($1{,}573 \pm 652$ vs. 775 ± 285 g, $p = 0.002$). There was no significant difference in mean 1- and 5-minute Apgar scores between the early and late pPPROM groups ($p = 0.119$ and $p = 0.120$, respectively). There was no significant difference in the mean neonatal length of stay between the early and late pPPROM groups (69 ± 73 vs. 114 ± 53 days, $p = 0.061$).

The rates of neonatal outcomes among all neonatal survivors are noted in ►**Table 2**.There was a higher rate of bronchopulmonary dysplasia in the surviving neonates of the late pPPROM group when compared with the neonatal survivors of the early pPPROM group (88%, $n = 14$ and 43%, $n = 34$, respectively; $p = 0.045$). There were no differences in rates of pulmonary hypoplasia, respiratory distress syndrome,

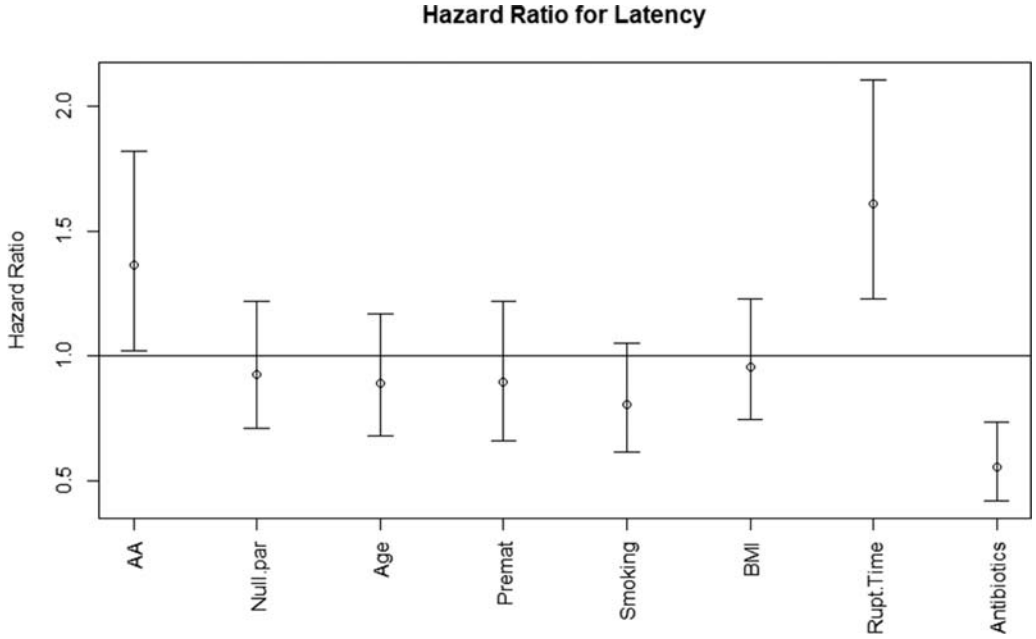

Fig. 3 Multivariable Cox's regression model for early latency duration. AA, African American race; BMI, body mass index; Null.par, nullparity; Premat, history of premature delivery; Rupt.Time, gestational age at rupture.

intraventricular hemorrhage (grades I/II and III/IV), periventricular leukomalacia, retinopathy of prematurity, necrotizing enterocolitis, neonatal sepsis, or limb deformities between the neonatal survivors of the early and late pPPROM groups.

Discussion

The aim of this study was to examine the survival rate of neonates following pPPROM, defined as spontaneous rupture of membranes at less than $23^{0/7}$ WGA. Of the 81 clinically confirmed cases of pPPROM that were managed expectantly, 28.4% of pregnancies resulted in the delivery of a neonate who survived to NICU discharge. More advanced gestational ages at the time of membrane rupture and at the time of delivery were associated with higher rates of neonatal survival. An increased latency period also correlated with an increased probability of neonatal survival. These findings suggest that spontaneous rupture at an earlier gestational

Table 2 Neonatal outcomes of surviving neonates

	All $n = 23$	Early pPPROM $n = 7$	Late pPPROM $n = 16$	*p*-Value
Birth weight, g	1,018 ± 559	1,573 ± 652	775 ± 285	0.002
Apgar				
1-min Apgar	4.1 ± 2.4	2.7 ± 3.3	4.8 ± 1.7	0.119
5-min Apgar	6.8 ± 1.6	6 ± 2	7.1 ± 1.4	0.120
Neonatal NICU length of stay, d	100 ± 62	69 ± 73	114 ± 53	0.061
Pulmonary hypoplasia	0 (0%)	0 (0%)	0 (0%)	1.000
Bronchopulmonary dysplasia	17 (74%)	3 (43%)	14 (88%)	0.045
Respiratory distress syndrome	15 (65%)	3 (43%)	12 (75%)	0.182
IVH grade III/IV	0 (0%)	0 (0%)	0 (0%)	0.684
IVH grade I/II	1 (4%)	0 (0%)	1 (6%)	0.480
Periventricular leukomalacia	0 (0%)	0 (0%)	0 (0%)	1.000
Retinopathy of prematurity	19 (83%)	4 (57%)	15 (94%)	0.067
Necrotizing enterocolitis	5 (22%)	1 (14%)	4 (25%)	1.000
Limb deformities	0 (0%)	0 (0%)	0 (0%)	1.000
Neonatal sepsis	3 (13%)	1 (14%)	2 (12%)	1.000

Abbreviations: IVH, intraventricular hemorrhage; NICU, neonatal intensive care unit; pPPROM, previable preterm prelabor rupture of membranes.
Note: Data are reported as mean ± standard deviation and by frequency (%) for continuous and categorical variables, respectively; *p*-value compares early pPPROM with late pPPROM.

age requires a longer latency period to reach a more advanced gestational age thereby increasing the probability of survival. Moreover, administration of antibiotics prior to delivery may promote extended latency periods and, indirectly, increase the probability of neonatal survival.

Mothers of surviving neonates had a greater cumulative length of hospital stay than mothers of the nonsurviving neonates. This is likely attributable to increased latency. There was no difference in maternal sepsis, cord prolapse, or placental abruption between the mothers of the surviving and nonsurviving neonates. Interestingly, the rates of chorioamnionitis were significantly higher in the mothers of the nonsurviving neonates than the mothers of the surviving neonates. Considering that surviving neonates had longer latency and increased latency is a risk factor for chorioamnionitis, one may anticipate rates of chorioamnionitis to be higher in the mothers of the surviving neonates. A possible explanation could be mothers presenting with clinical signs and symptoms of chorioamnionitis following rupture of membranes would undergo delivery regardless of gestational age at presentation, per standard of care practices. If chorioamnionitis was diagnosed prior to viability, there is a lesser probability of survival in these neonates.

Among the surviving neonates, respiratory complications (bronchopulmonary dysplasia and respiratory distress syndrome) and retinopathy of prematurity were the most prevalent. Of all neonatal outcomes addressed, only bronchopulmonary dysplasia rates were significantly greater in the late pPPROM group as compared with the early pPPROM group. This may be explained by the more advanced gestational ages at delivery and increased latency periods within the early pPPROM group. The extended latency periods allow for continued lung maturation, potentially resulting in decreased oxygen requirements following delivery. However, within our study, this is most likely the result of small sample size within the early pPPROM group as compared with the late pPPROM group. The significantly greater birth weight for the neonates of the early pPPROM groups is, also, likely explained by the more advanced gestational ages at delivery for those of the early pPPROM group when compared with the neonates of the late pPPROM group.

Current literature reports a wide range of neonatal survival rates following PPROM, particularly "mid-trimester PPROM" (i.e., prior to $26^{0/7}$ WGA) and pPPROM.[1,2,4,6,7,12,13] The survival rate obtained within this study falls on the lower end of the previously reported range (22–83%).[1,2,4,6,7,12,13] In review of those previous studies, pregnancies with rupture of membranes occurring as high as $26^{0/7}$ WGA were included. These more advanced gestational ages (as compared with those included within this study) portend a more favorable neonatal outcome on the basic concept of increased fetal maturity, most notably, fetal lung maturity. This is supported by the findings that the mean gestational age at rupture of membranes within this study (for both surviving and nonsurviving neonates) was 144 versus 147 to 206 days noted in previous studies.[2,6,7,12,14] These findings, along with a high-risk patient population, contribute to the relatively lower survival rate found within our study. Our rates of obstetrical and neonatal outcomes were similar to those reported in previous studies.[1,2,7,12]

The results of our study are not only pertinent for patient counseling within our institution but also describe maternal characteristics and neonatal outcomes following pPPROM in a diverse, contemporary cohort. Additionally, advances in optimization of neonatal care (e.g., surfactant, antenatal corticosteroids for fetal lung maturity, and magnesium sulfate for fetal neuroprotection) have prompted the consideration for a new definition of viability reaching below the previous 24 to 28 WGA, perhaps, as low as 22 WGA. These findings contribute to the understanding of maternal and fetal outcomes associated with obstetrical events surrounding this new period of viability.

Strengths of the study include the setting and the contemporary population studied. As mentioned previously, this study was conducted after a string of improvements in antenatal and neonatal care, most notably, antenatal magnesium sulfate administration for fetal neuroprotection and standardized postnatal feeding protocols, to optimize preterm fetal outcomes.[15] This study was also conducted within a tertiary care center, focused primarily on obstetrical and neonatal care, with 62,930 deliveries occurring within our studied time frame. As a tertiary referral center, the patient population studied includes a more contemporary cohort, representing an older and overweight patient population.

However, these patient profiles serve as a limitation of our study as increased age and BMI are associated with higher risks of adverse obstetrical outcomes potentially skewing results to reflect a lower overall survival rate. Selection bias is also a limitation. Patients who were not candidates for expectant management were not included, biasing results toward higher neonatal survival rates and lower rates of adverse maternal outcomes. Conversely, patients opting for labor induction or pregnancy termination were not candidates for this study, potentially biasing toward a lower than anticipated overall survival neonatal rate. Other limitations include small sample size secondary to the low incidence of pPPROM, the lack of uniformity in antibiotic administration (timing and route of administration and antibiotic[s] of choice), and the lack of data on long-term morbidity and mortality.

Future studies of interest should address the limitations as previously mentioned. A prospective, longitudinal, multicenter study of maternal outcomes as well as both short- and long-term neonatal outcomes following pPPROM would be ideal. Further studies should aim to identify reliable prognostic factors and methods to enhance the probability and effect of these factors. For example, antibiotics given beyond $24^{0/7}$ WGA have been shown to increase latency resulting in improved neonatal outcomes.[16] Future studies exploring the effects of latency antibiotics at earlier, previable gestational ages would be of consideration. Also, prior studies have described an effect on AFI on neonatal outcomes.[17,18] Given lack of uniformity in AFI assessment and reassessment, these data were not available for analysis within this study;

however, future prospective studies addressing amniotic fluid assessment and fetal lung morphology following pPPROM via various imaging techniques would be of interest as well.[19]

In conclusion, despite the limited sample size of our study, the neonatal survival rate following pPPROM within our institution is consistent with previous literature and provides institution-specific, data-driven rates that allow for more informed patient counseling. Also, as supported by previous literature, factors that increased the likelihood of neonatal survival within our study included more advanced gestational age at rupture and longer latency periods. Future studies should be aimed at identifying variables that optimize these three factors so as to increase the probability of a surviving neonate. As supported by prior studies, our study shows a positive association between antibiotic administration prior to delivery and latency period; therefore, there is a need for future studies to assess if antibiotic administration during the previable gestational period will increase rates of viable neonates. As the gestational age of neonatal viability continues to trend downward with the advances in obstetric and neonatal medical practices, continued research evaluating maternal and neonatal outcomes following preterm deliveries are necessary to aid in patient counseling and management.

Authors' Contribution

F.A.M., R.C.M., and F.L. conceptualized and designed the study. F.L. collected the data. A.C. analyzed the data. F.L. and E.S. interpreted data and drafted the manuscript. All authors were involved in the review, revision, and editing of the final manuscript.

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Conflict of Interest

None declared.

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References

1 Mercer BM. Preterm premature rupture of the membranes. Obstet Gynecol 2003;101(01):178–193
2 Muris C, Girard B, Creveuil C, Durin L, Herlicoviez M, Dreyfus M. Management of premature rupture of membranes before 25 weeks. Eur J Obstet Gynecol Reprod Biol 2007;131(02):163–168
3 Kilbride HW, Thibeault DW. Neonatal complications of preterm premature rupture of membranes. Pathophysiology and management. Clin Perinatol 2001;28(04):761–785
4 Yeast JD. Preterm premature rupture of the membranes before viability. Clin Perinatol 2001;28(04):849–860
5 Birth P. Obstetric Care Consensus No. 6 Summary: periviable birth. Obstet Gynecol 2017;130(04):926–928
6 Waters TP, Mercer BM. The management of preterm premature rupture of the membranes near the limit of fetal viability. Am J Obstet Gynecol 2009;201(03):230–240
7 Manuck TA, Eller AG, Esplin MS, Stoddard GJ, Varner MW, Silver RM. Outcomes of expectantly managed preterm premature rupture of membranes occurring before 24 weeks of gestation. Obstet Gynecol 2009;114(01):29–37
8 Wong LF, Holmgren CM, Silver RM, Varner MW, Manuck TA. Outcomes of expectantly managed pregnancies with multiple gestations and preterm premature rupture of membranes prior to 26 weeks. Am J Obstet Gynecol 2015;212(02):215.e1–215.e9
9 Manuck TA, Varner MW. Neonatal and early childhood outcomes following early vs later preterm premature rupture of membranes. Am J Obstet Gynecol 2014;211(03):308.e1–308.e6
10 Kuba K, Bernstein PS. ACOG practice bulletin no. 188: prelabor rupture of membranes. Obstet Gynecol 2018;131(06):1163–1164
11 Agresti A. Categorical Data Analysis, 2nd ed. New York: Wiley; 2002
12 Sim WH, Araujo Júnior E, Da Silva Costa F, Sheehan PM. Maternal and neonatal outcomes following expectant management of preterm prelabour rupture of membranes before viability. J Perinat Med 2017;45(01):29–44
13 Hibbard JU, Hibbard MC, Ismail M, Arendt E. Pregnancy outcome after expectant management of premature rupture of the membranes in the second trimester. J Reprod Med 1993;38(12):945–951
14 Manuck TA, Maclean CC, Silver RM, Varner MW. Preterm premature rupture of membranes: does the duration of latency influence perinatal outcomes? Am J Obstet Gynecol 2009;201(04):414.e1–414.e6
15 Khan Z, Morris N, Unterrainer H, Haiden N, Holasek SJ, Urlesberger B. Effect of standardized feeding protocol on nutrient supply and postnatal growth of preterm infants: a prospective study. J Neonatal Perinatal Med 2018;11(01):11–19
16 Mercer BM, Miodovnik M, Thurnau GR, et al; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Antibiotic therapy for reduction of infant morbidity after preterm premature rupture of the membranes. A randomized controlled trial. JAMA 1997;278(12):989–995
17 Lee JY, Ahn TG, Jun JK. Short-term and Long-term postnatal outcomes of expectant management after previable preterm premature rupture of membranes with and without persistent oligohydramnios. Obstet Gynecol 2015;126(05):947–953
18 Park JS, Yoon BH, Romero R, et al. The relationship between oligohydramnios and the onset of preterm labor in preterm premature rupture of membranes. Am J Obstet Gynecol 2001;184(03):459–462
19 van Teeffelen AS, Van Der Heijden J, Oei SG, et al. Accuracy of imaging parameters in the prediction of lethal pulmonary hypoplasia secondary to mid-trimester prelabor rupture of fetal membranes: a systematic review and meta-analysis. Ultrasound Obstet Gynecol 2012;39(05):495–499