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Outcomes of expectantly managed pregnancies with multiple gestations and preterm premature rupture of membranes prior to 26 weeks

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Abstract

Objective—To determine obstetric and neonatal outcomes of expectantly managed multi-fetal pregnancies complicated by early preterm premature rupture of membranes (PPROM) prior to 26 weeks.

Study Design—A retrospective cohort of all multi-fetal pregnancies complicated by documented PPRM occurring before 26 0/7 weeks and managed expectantly by a single Maternal-Fetal Medicine practice between 7/4/2002 and 9/1/2013. Neonatal and maternal outcomes were assessed and comparisons made between the fetus with ruptured membranes and the first fetus to deliver with intact membranes.

Results—23 pregnancies (46 fetuses) were analyzed with a median gestational age at PPRM of 22.9 weeks; 74% experienced PPRM < 24 weeks gestation. A median latency of 11 days was achieved with expectant management. Of the 46 neonates, 20 (43%) survived to hospital discharge. Of these, 12 (60%) experienced severe neonatal morbidity defined as defined as grade III or IV intraventricular hemorrhage, bronchopulmonary dysplasia, pulmonary hypoplasia, necrotizing enterocolitis requiring surgical intervention, and/or grade 3 or 4 retinopathy of prematurity. Eight neonates survived to hospital discharge without severe neonatal morbidity. The multiple with ruptured membranes was more likely to experience intrauterine demise but

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Condensation: Among multiples with PPRM < 26 weeks who are expectantly managed, neonatal survival rates are low (43%), and only 17% survived without significant neonatal morbidity.

Disclosure: none

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otherwise had similar outcomes as the multiple with intact membranes. Maternal morbidity was considerable, with 7/23 (30%) pregnancies complicated by clinical chorioamnionitis, 12/23 (52%) delivering by cesarean, of which 3/12 (25%) were classical cesarean deliveries.

Conclusion—Overall, neonatal survival to hospital discharge was 43%, but only 17% survived without significant neonatal morbidity. These data provide a basis for counseling and management of women with multi-fetal gestation complicated by very early PPRM.

Keywords

latency; multiple gestation; neonatal morbidity; periviable; preterm premature rupture of membranes

Introduction

Preterm premature rupture of membranes (PPROM) complicates 3–4.5% of all pregnancies and accounts for approximately 30% of preterm births.¹ PPRM is defined as rupture of the fetal membranes prior to 37 weeks gestation and prior to the onset of labor. The frequency of PPRM is higher in multi-fetal gestations,^{2,3} with one study reporting this complication in 11% of twins, 19% of triplets, and 20% of quadruplets.³ Pakrashi et al reported that PPRM also occurs at an earlier gestational age among multiple gestations with 36% of twin PPRM, 28% of triplet PPRM, and 50% of quadruplet PPRM occurring at < 28 weeks.³

The earlier that PPRM occurs during pregnancy, the higher the risk for early preterm delivery, and therefore the poorer the prognosis for intact neonatal survival. Additionally, risks of maternal morbidity increase as the gestational age at the time of PPRM decreases. Women who experience PPRM less than 23–24 weeks (prior to fetal viability) without overt evidence of intrauterine infection at the time of diagnosis are generally offered termination of pregnancy or expectant management. Traditionally, expectant management of PPRM prior to viability has been associated with a poor chance of neonatal survival and a high rate of severe, long-term neonatal morbidity among survivors. However, recent advances in perinatal and neonatal medicine suggest improved outcomes; in a recent cohort study of 159 women with singletons pregnancies complicated by PPRM less than 24 weeks, neonatal survival was 56%, and 48% survived without major neonatal morbidity.⁴ While the fetus within the ‘ruptured sac’ may face risks roughly equivalent to those of a singleton fetus of equivalent gestational age with PPRM, the same may not be true for the other fetuses in multi-fetal pregnancies.

There are few studies with regards to obstetric and neonatal outcomes of multi-fetal gestations following PPRM, particularly at very early gestational age. Thus, the purpose of this study was to report obstetric and neonatal outcomes of expectantly managed multi-fetal pregnancies complicated by early PPRM prior to 26 weeks, and to compare outcomes between fetuses in the ruptured versus intact amniotic sac.

Material and Methods

This is a retrospective cohort of all multi-fetal pregnancies complicated by documented PPROM occurring before 26 0/7 weeks and managed by a single group of perinatologists at the University of Utah and Intermountain Healthcare Hospitals between 7/4/2002 and 9/1/2013. These dates were selected based on the availability of centralized data of good quality. Cases were identified through ICD-9 searches, review of established obstetric databases, and chart review. Data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of Utah Center for Clinical and Translational Science.⁵

PPROM was confirmed if at least two of the following were present: pooling, ferning, nitrazine, visible fetal parts seen on speculum examination without overlying membrane, and/or deepest vertical pocket of fluid on ultrasound examination < 2 cm. The date and time of membrane rupture was reported by the patient. In cases where an exact time could not be recalled, the date and time of rupture was designated as time of rupture confirmation. Because of this limitation, latency period was rounded to the nearest half day. Women declining expectant management, delivering within 12 hours of PPROM, presenting with chorioamnionitis and/or fetal demise of one or more fetuses, carrying a pregnancy complicated by twin-twin transfusion syndrome, or carrying one or more fetuses with known major structural anomalies, polyhydramnios, and/or aneuploidy were excluded. Those in which an interval delivery was attempted and achieved > 48 hours of latency were also excluded. Multiples that spontaneously reduced in the first trimester were designated by their reduced state. Neonatal resuscitation was uniformly performed at 24 weeks gestation or greater. For neonates delivering at 23 0/7–23 6/7 weeks, the decision whether to resuscitate was decided by consensus between the woman, her family, and her provider(s). Neonates delivering less than 23 0/7 weeks are provided comfort care at our institutions but are not actively resuscitated.

Gestational age was determined by best obstetric estimate per standard criteria, using a combination of last menstrual period dating and ultrasonographic data as appropriate.⁶ Chorionicity was determined by ultrasonographic findings and confirmed with placental pathology whenever possible. Maternal and neonatal records were reviewed by a single physician researcher (L.F.W.). Data collection was de-identified and therefore informed consent was waived. This study was approved by the University of Utah and Intermountain Healthcare Institutional Review Boards.

Neonatal survival without major morbidities was the primary outcome. Composite severe neonatal morbidity was defined as grade III or IV intraventricular hemorrhage, bronchopulmonary dysplasia, pulmonary hypoplasia, necrotizing enterocolitis requiring surgical intervention, retinopathy of prematurity grade 3 or 4, or neonatal death. All morbidities were assessed only in live-born neonates. For higher order multiple gestations (e.g., triplets and greater), comparisons were made between the fetus with ruptured membranes and the first fetus to deliver with intact membranes.

Data were analyzed using STATA version 12.0 (College Station, TX) and followed a within-pregnancy sample approach. If data were available for both multiples of the same pregnancy, the comparison was done using ordinary statistical tests: McNemar test for binary variables, Wilcoxon signed rank for ordered categorical variables, and paired sample t-test for continuous variables. If data were missing for one of the paired multiples, such as hospital length of stay when one multiple died, a mixed effects regression model was used, with outcome nested within pregnancies. These models are identical to the ordinary paired sample statistical tests when no data are missing, but can still use the data on the non-missing multiple to refine the estimates when a portion of the data are missing.

We attempted to capture time-specific probability estimates of death (intrauterine demise and neonatal death), neonatal survival, and neonatal survival without major composite morbidity by stratifying outcomes from each PPRM gestational age group by outcomes during each subsequent 2-week increment divided by the number of patients still being followed. If there were no events (deaths or diagnoses of morbidity) during a specific time period, the probability from the earlier time interval was carried forward.

Results

We identified 40 multi-fetal pregnancies with documented PPRM occurring prior to 26 weeks that were managed expectantly. Seven pregnancies were excluded from analysis because of a successful attempt at delayed interval delivery (each pregnancy attained at least 48 hours of latency for the remaining fetuses following delivery of the presenting neonate). Ten pregnancies were excluded from analysis due to the presence of major congenital fetal anomalies/aneuploidy or suspected twin-twin transfusion syndrome. Thus, 23 pregnancies were analyzed, including 22 dichorionic-diamniotic twins and 1 set of trichorionic-quadamniotic quadruplets (Figure 1).

Demographic and clinical characteristics are shown in Table 1. Approximately 44% of women were multiparous. Of these, none had a history of PPRM in a prior pregnancy. Two women had a history of cervical insufficiency: one had a prophylactic cerclage at 13 weeks with subsequent PPRM at 25.4 and the other had a physical exam indicated cerclage (due to the presence of amniotic membranes beyond the external os) at 19.0 weeks and subsequent PPRM at 21.4 weeks. Overall, the median gestational age at PPRM was 22.9 weeks (inter-quartile range [IQR]: 20.7–24.1 weeks); the majority (17/23, 74%) occurred prior to 24 weeks gestation. Three cases of PPRM occurred in the non-presenting multiple. Seventeen of 18 pregnancies reaching 23 weeks desired full resuscitation, 11 of these were delivered at 24 weeks or greater. The majority (15/17, 88.2%) received antenatal corticosteroids and 16/17 (94.1%) received latency antibiotics. One woman received magnesium sulfate for fetal neuroprophylaxis. The quadruplet pregnancy resulted in no surviving neonates following PPRM at 22 6/7 weeks and spontaneous labor with subsequent delivery at 23 3/7 weeks; neonatal resuscitation was not performed for any of the 4 neonates.

Overall neonatal outcomes are shown in Table 2. Of the 46 neonates, 4 experienced antepartum demise, 3 experienced an intrapartum demise, 9 suffered neonatal demise due to

severe prematurity without attempted resuscitation, and 10 died in the NICU. Thus, 20 (43%) survived to hospital discharge. Only 8 neonates (17%) survived to hospital discharge without severe neonatal morbidity. Of these 8 neonates, 5 had intact membranes and 3 had ruptured membranes.

Tables 3, 4, and 5 stratify outcomes by gestational age at PPRM and the current gestational age of the pregnancy. Generally, chances of death (intrauterine demise and neonatal death) decrease with increasing gestational age of PPRM and increasing latency (Table 3). Overall, the chance of a woman with PPRM at 18 0/7–19 6/7 having a surviving neonate is 37.5% and her chance of having a surviving neonate without major composite morbidity is 25.0%. While there is a significant improvement in the probability of neonatal survival with increasing gestational age at time of PPRM, the improvement in probability of a surviving neonate without composite morbidity is only modest (83.0% and 33.3% of women with PPRM at 24 0/7–25 6/7, respectively). Intact survival was more likely with increasing gestational age of delivery and occurred for 50% (5/10) of woman who remained undelivered with viable pregnancies at 28 weeks and 75% (3/4) of women who remained undelivered with viable pregnancies at 30 weeks.

When neonatal outcomes are stratified by membrane status, we found that neonates with rupture of membranes (ROM) were more likely to experience intrauterine demise (Table 6). Outcomes of the ruptured and un-ruptured neonate for the subset of 17 pregnancies reaching at least 23 0/7 weeks and desiring full resuscitation were similar (data not shown). For this subset, intrauterine demise or neonatal death complicated 8/17 multiples with ROM and 6/17 with intact membranes ($p=0.486$) and severe composite morbidity affected 11/14 multiples with ROM and 11/16 multiples with intact membranes ($p=0.144$). The median length of hospital stay for the surviving multiple with ROM was 98 days (IQR: 72–111 days) and 92 days (IQR: 46–139 days) for the surviving multiple with intact membranes, $p=0.579$.

There was also significant maternal morbidity. Approximately half (12/23, 52%) were delivered by cesarean section, including 3 classical uterine incisions and 2 deliveries complicated by umbilical cord prolapse prompting emergent cesarean delivery. There were two other cases of cord prolapse occurring at 23 weeks and were immediately brought to medical attention. Given periviable gestational age, both families opted for expectant management with fetal demise of the presenting twin in order to optimize outcomes for the second twin. Placental abruption was relatively rare (1/23, 4%). Infectious morbidity was also common; 7/23 (30%) pregnancies were complicated by clinical chorioamnionitis and 7/14 (50%) pregnancies had pathology confirmed chorioamnionitis or funicitis. In all 14 cases, pathology specimens were available for both placentas, and all had concordant pathologic findings for no inflammation or chorioamnionitis/funicitis.

Comment

Neonatal outcomes among babies delivered as a part of a multi-fetal gestation following early PPRM less than 26 weeks were poor. Although women achieved a median of 1.6 weeks of latency following PPRM, the median delivery gestational age was still very

premature (23.7 weeks gestation). Overall, 44% of neonates survived to hospital discharge. However, 60% of surviving neonates had at least one major neonatal morbidity, and 38/46 (83%) of all neonates either died or had at least one major neonatal morbidity. Outcomes were marginally improved among the subset of pregnancies reaching 23 weeks or greater and desiring full intervention, where overall survival to hospital discharge was 59%; 29% of these did not suffer severe neonatal morbidity. However, chances of neonatal survival without major morbidity were markedly improved for the small group of women who still remained pregnant at 28 and 30 weeks (50% and 75%, respectively).

We identified only one difference in neonatal outcome by membrane status: the neonate with ruptured membrane was more likely to experience intrauterine fetal demise. All other outcomes including neonatal death, severe composite neonatal morbidity, and days the neonate was hospitalized did not differ by membrane status, although conclusions are limited by small sample size.

Our average latency period of 11 days is longer than what has previously been reported. Hsieh et al reported a median latency of 4.8 days for twins with PPROM between 20 and 30 weeks, Mercer et al² reported a median latency of 1.6 days in a subanalysis of twins with PPROM between 19 and 26 weeks, and Bianco et al⁷ reported a median latency of 27.6 hours in a subanalysis of twins with PPROM between 20 and 30 weeks. These differences may be explained by the earlier gestational age at PPROM of our study population (18 to 26 weeks), and the fact that there is an inverse relationship between latency and gestational age at PPROM in multi-fetal pregnancies as there is in singletons.^{7,8} We also routinely used latency antibiotics (87%) while Bianco et al⁷ reported latency antibiotic administration in only 14% (antibiotic use was not addressed in the studies by Mercer et al² or Hsieh et al⁸). Lastly, we excluded those women who delivered within 12 hours of presentation, which biases our results towards those most likely to achieve some degree of latency.

The rate of chorioamnionitis (30.4%) in this cohort was also higher than what was reported by older studies; Bianco et al⁷ reported a chorioamnionitis rate of 16.4% and endometritis rate of 8.6%, while Myles et al⁹ reported a chorioamnionitis rate of 8.7%. However, this is lower than what was reported in a cohort of singletons with PPROM < 24 weeks from our institutions (49.3%).⁴ This finding raises the possibility that the cause of PPROM in multiples may differ from singletons, and that infection in these patients may be secondary to PPROM rather than causal of PPROM or preterm labor. Our data also suggests that the multiple with intact membranes carries a similar risk of infection as the multiple with ruptured membranes in the setting of expectantly managed PPROM. All 14 cases where pathology evaluation was performed had concordant pathologic findings, with no evidence of inflammation, chorioamnionitis, or funisitis. This is in contrast to the Northwestern Twin Chorionicity Study which reported a significantly lower frequency of chorioamnionitis for dichorionic twins.¹⁰ However, this study included all twins in which a full pathologic evaluation was available and made no exclusion or distinction with regards to obstetric complications or delivery indication. It is possible that the protective effect seen with dichorionicity is short-lived and lost with any prolongation of latency in the setting of PPROM.

When comparing our neonatal outcomes to those of singleton pregnancies complicated by PPROM at a similar gestational age as reported by Manuck et al, we found that multiples generally had worse outcomes.⁴ In our cohort of multiples, 15% experienced an intrauterine demise after PPROM while only 4% of singletons complicated by PPROM < 24 weeks experienced an intrauterine demise. For those with PPROM at 18 0/7–19 6/7 weeks, we found that 2/8 (25%) of live-born multiples and 7/25 (20%) of singletons survived to hospital discharge without severe composite morbidity. No multiples and 7/23 (23%) singletons with PPROM at 20 0/7–21 6/7 weeks survived without severe composite morbidity and 3/16 (17%) of multiples and 26/68 (38%) singletons with PPROM at 22 0/7–23 6/7 weeks survived without severe composite morbidity. The disparity in outcomes is likely attributable to the significantly shortened latency period found in multiples as compared to singletons.^{7,9,11} Meaningful comparisons for specific neonatal morbidities cannot be made as they were not assessed in a portion of live-born neonates who died shortly after delivery. Hence our reported number of pulmonary hypoplasia, IVH, and other morbidities among live-born neonates is likely an underestimation.

While our study is limited by the retrospective nature and small number of cases, it is one of the largest series of expectantly managed multiples with very early PPROM. In a smaller study, Mercer et al² reported outcomes for 17 multiples with PPROM at < 26 weeks. Other studies have reported outcomes for PPROM among multiples < 30 weeks.^{7,8,11,12} Since our hospitals are tertiary referral centers, it is possible that there were other cases of multi-fetal pregnancy complicated by very early PPROM not captured by our study. However, these were likely to be cases that were not eligible for, or did not elect expectant management. It is also possible that those who were referred to our health care system and those who opted for expectant management may have had PPROM at a later gestational age and be deemed by their primary provider to have a higher probability of successful outcomes. These biases would skew results towards a more favorable outcome and thus our findings may be overly optimistic. However, the cultural climate in Utah, where rates of pregnancy termination are historically low, likely encourages expectant management of even those pregnancies predicted to have poor outcomes (such as those complicated by early PPROM). Lastly, we are unable to extrapolate outcomes when PPROM occurs <18 gestation, but presume that outcomes would be worse with PPROM at extremely early gestational ages.

This study is unique in that it presents both obstetric and neonatal outcomes for one of the largest cohorts of expectantly managed multi-fetal pregnancies complicated by PPROM at less than 26 weeks. Our results are notable for an overall neonatal survival to hospital discharge rate of nearly 50%. However, less than one in 5 neonates overall survived without significant neonatal morbidity. The duration and cost of neonatal care is substantial, and long-term outcomes for these neonates are unknown. These findings provide a basis for counseling and management of women with multi-fetal gestation complicated by very early PPROM.

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Figure 1. Study enrollment

GA=Gestational age

IQR=Inter-quartile range

LOS=Length of stay

Table 1

Maternal demographics (N=23 pregnancies).

Maternal age, y (mean $\pm$ SD)	32.5 $\pm$ 6.9
Caucasian	19/22 (86.4%)
Married	16/20 (80.0%)
Private Insurance	11/13 (47.8%)
Primiparous	13/23 (56.5%)
History of PPRM	0/23 (0.0%)
History of cervical insufficiency	2/23 (8.7%)

Table 2

Overall neonatal outcomes.

Neonatal characteristics and outcomes	All multiples N=46	Multiples delivered 23 0/7 weeks with planned resuscitation N=34
Median gestational age at PPROM (IQR), weeks	22.9 (20.7–24.1)	23.3 (21.7–24.3)
Median gestational age at delivery (IQR), weeks	23.7 (23.0–27.7)	26.6 (23.4–28.3)
Median latency (IQR), days	11 (3–30)	15 (3–35)
Median birth weight (IQR), grams	670 (492–970)	890 (550–990)
Male gender	28/40 (70.0%)	24/34 (70.6%)
Death	26/46 (56.5%) [42.3–69.8]	14/34 (41.2%) [26.4–57.8]
Intrauterine demise	7/46 (15.2%) [7.6–28.3]	4/34 (8.8%) [4.7–26.7]
Neonatal death	19/39 (48.7%) [33.9–63.8]	10/30 (33.3%) [19.2–51.2]
Severe composite morbidity*	31/39 (79.5%) [64.4–89.2]	22/30 (73.3%) [55.6–86.8]
IVH		
None [†]	11/39 (28.2%) [16.6–43.8]	10/30 (33.3%) [19.2–51.2]
Grade I, II [†]	8/39 (20.5%) [10.8–35.5]	8/30 (26.7%) [14.2–44.5]
Grade III, IV [†]	5/39 (12.8%) [5.6–26.7]	5/30 (16.7%) [7.3–33.6]
Pulmonary hypoplasia [†]	1/39 (2.6%) [0.5–13.2]	0/30 (0.0%) [0.0–11.4]
Bronchopulmonary dysplasia [†]	14/39 (35.9%) [22.7–51.6]	13/30 (43.4%) [27.4–60.8]
Joint contractures [†]	2/39 (5.1%) [1.4–16.9]	2/30 (6.7%) [1.9–21.3]

(%), [95% confidence interval]

* For all live-born neonates

[†] Findings were not assessed in a portion of live-born neonates who died shortly after delivery

Table 3

Probability of perinatal death occurring prospectively based on gestational age at time of rupture and gestational age of ongoing latency.

Gestational Age at PPROM		Current Gestational Age						
		18 0/7–19 6/7	20 0/7–21 6/7	22 0/7–23 6/7	24 0/7–25 6/7	26 0/7–27 6/7	28 0/7–29 6/7	30 0/7–31 6/7
18 0/7–19 6/7	N=8	5/8 (62.5%) [30.6–86.3]	5/8 (62.5%) [30.6–86.3]	3/6 (50.0%) [18.8–81.2]	1/4 (25.0%) [4.6–69.9]	1/4 (25.0%) [4.6–69.9]	0/2 (0.0%) [0.0–65.8]	0/2 (0.0%) [0.0–65.8]
20 0/7–21 6/7	N=10	N/A	9/10 (90.0%) [59.6–98.2]	6/7 (85.7%) [48.7–97.4]	1/2 (50.0%) [9.5–90.6]	1/2 (50.0%) [9.5–90.6]	1/2 (50.0%) [9.5–90.6]	–
22 0/7–23 6/7	N= 12 *	N/A	N/A	6/12 (50.0%) [25.4–74.6]	2/4 (50.0%) [15.0–85.0]	2/4 (50.0%) [15.0–85.0]	2/4 (50.0%) [15.0–85.0]	1/2 (50.0%) [9.5–90.6]
24 0/7–25 6/7	N=12	N/A	N/A	N/A	2 /12 (16.7%) [4.7–44.8]	1/8 (12.5%) [2.2–47.1]	0/2 (0.0%) [0.0–65.8]	–

The data are number of neonates from each PPROM gestational age group that experienced intrauterine or neonatal death during each subsequent 2-week interval / the number of neonates still being followed, (%).

* Does not include outcomes for the quadruplet pregnancy complicated by PPROM at 22 6/7 and subsequent delivery at 23 3/7 with plan for no resuscitation

Table 4

Probability of neonatal survival to hospital discharge occurring prospectively based on gestational age at time of rupture and gestational age of ongoing latency.

Gestational Age at PPROM		Current Gestational Age						
		18 0/7–19 6/7	20 0/7–21 6/7	22 0/7–23 6/7	24 0/7–25 6/7	26 0/7–27 6/7	28 0/7–29 6/7	30 0/7–31 6/7
18 0/7–19 6/7	N=8	3/8 (37.5%) [13.7–69.4]	3/8 (37.5%) [13.7–69.4]	3/6 (50.0%) [18.8–81.2]	3/4 (75.5%) [30.0–95.4]	3/4 (75.5%) [30.0–95.4]	2/2 (100.0%) [34.2–100]	2/2 (100.0%) [34.2–100.0]
20 0/7–21 6/7	N=10	N/A	1/10 (10.0%) [1.8–40.4]	1/7 (14.3%) [2.6–51.3]	1/2 (50.0%) [9.5–90.6]	1/2 (50.5%) [9.5–90.6]	1/2 (50.0%) [9.5–90.6]	–
22 0/7–23 6/7	N = 12 *	N/A	N/A	6/12 (50.0%) [25.4–74.6]	2/4 (50.0%) [15.0–85.0]	2/4 (50.0%) [15.0–85.0]	2/4 (50.0%) [15.0–85.0]	1/2 (50.0%) [9.5–90.6]
24 0/7–25 6/7	N=12	N/A	N/A	N/A	10/12 (83.3%) [55.2–95.3]	7/8 (87.5%) [5.3–97.8]	2/2 (100.0%) [34.2–100.0]	–

The data are number of neonates from each PPROM gestational age group that survive to discharge during each subsequent 2-week interval / the number of neonates still being followed, (%), [95% confidence interval].

* Does not include outcomes for the quadruplet pregnancy complicated by PPROM at 22 6/7 and subsequent delivery at 23 3/7 with plan for no resuscitation

Table 5

Probability of neonatal survival to hospital discharge without severe composite morbidity occurring prospectively based on gestational age at time of rupture and gestational age of ongoing latency.

Gestational Age at PPROM		Current Gestational Age						
		18 0/7–19 6/7	20 0/7–21 6/7	22 0/7–23 6/7	24 0/7–25 6/7	26 0/7–27 6/7	28 0/7–29 6/7	30 0/7–31 6/7
18 0/7–19 6/7	N=8	2/8 (25.0%) [7.2–59.1]	2/8 (25.0%) [7.2–59.1]	2/6 (33.3%) [9.7–70.0]	2/4 (50.0%) [15.0–85.0]	2/4 (50.0%) [15.0–85.0]	2/2 (100.0%) [34.2–100.0]	2/2 (100.0%) [34.2–100.0]
20 0/7–21 6/7	N=10	N/A	0/10 (0.0%) [0.0–27.8]	0/7 (0.0%) [0.0–35.4]	0/2 (0.0%) [0.0–65.8]	0/2 (0.5%) [0.0–65.8]	0/2 (0.0%) [0.0–65.8]	–
22 0/7–23 6/7	N = 12 *	N/A	N/A	2/12 (16.7%) [4.7–44.8]	1/4 (25.0%) [4.6–69.9]	1/4 (25.0%) [4.6–69.9]	1/4 (25.0%) [4.6–69.9]	1/2 (50.0%) [9.5–90.6]
24 0/7–25 6/7	N=12	N/A	N/A	N/A	4/12 (33.3%) [13.8–60.9]	4/8 (50.0%) [21.5–78.5]	2/2 (100.0%) [34.2–100.0]	–

Data are the number of neonates from each preterm premature rupture of membranes gestational age group without major morbidity during each subsequent 2-week interval / the number of neonates still being followed, (%), [95% confidence interval].

* Does not include outcomes for the quadrupelet pregnancy complicated by PPROM at 22 6/7 and subsequent delivery at 23 3/7 with plan for no resuscitation

Table 6

Outcomes by membrane status.

Neonatal characteristics and outcomes	PROM multiple N=23	Non-PROM multiple N=23	p-value
Median gestational age at delivery (IQR), weeks	23.7 (23.0–27.7)	23.7 (23.0–27.7)	0.157*
Median latency (IQR), days	11 (3–30)	11 (3–30)	> 0.99
Median birth weight (IQR), grams	670 (485–960) N=19	695 (496–997.5) N=14	0.097
Cesarean delivery	11/23 (47.8%)	12/23 (52.2%)	0.144
Male gender	13/21 (61.9%)	15/20 (75.0%)	0.280
Death	14/23 (60.9%) [40.8–77.8]	12/23 (52.2%) [33.0–70.8]	0.484
Intrauterine demise	6/23 (26.1%) [12.6–46.5]	1/23 (4.4%) [0.8–21.0]	0.001
Neonatal death	8/17 (47.1%) [26.2–69.0]	11/22 (50.0%) [30.7–68.3]	0.880
Severe composite morbidity [†]	14/17 (82.4%) [59.0–93.8]	17/22 (77.3%) [56.6–89.9]	0.148
IVH			
None [‡]	3/17 (17.6%) [6.2–41.0]	8/22 (36.4%) [19.7–57.0]	n/a [§]
Grade I, II [‡]	4/17 (23.5%) [9.6–47.3]	4/22 (18.2%) [7.3–38.5]	n/a [§]
Grade III, IV [‡]	3/17 (17.7%) [6.2–41.0]	2/22 (9.1%) [2.5–27.8]	n/a [§]
Pulmonary hypoplasia [‡]	1/17 (5.9%) [1.1–27.0]	0/22 (0.0%) [0.0–14.9]	n/a [§]
Bronchopulmonary dysplasia [‡]	6/17 (35.3%) [17.3–58.7]	8/22 (36.4%) [19.7–57.0]	n/a [§]
Joint contractures [‡]	2/17 (11.8%) [3.3–34.3]	0/22 (0.0%) [0.0–14.9]	n/a [§]

(%), [95% confidence interval]

* Reflects hourly variation in delivery gestational age which was recorded by units of hours

[†] For all live-born neonates[‡] Findings were not assessed in a portion of live-born neonates who died shortly after delivery[§] Statistical analysis was not performed because findings were not assessed in a portion of live-born neonates who died shortly after delivery