Published in final edited form as:

Am J Obstet Gynecol. 2014 September ; 211(3): 308.e1–308.e6. doi:10.1016/j.ajog.2014.05.030.

Neonatal and early childhood outcomes following early vs later preterm premature rupture of membranes

Tracy Ann Manuck, MD and Michael Walter Varner, MD

Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Utah Health Sciences Center, Salt Lake City, UT

Abstract

OBJECTIVE—Data regarding long-term outcomes of neonates reaching viability following early preterm premature rupture of membranes (PPROM; <25.0 weeks at rupture) are limited. We hypothesized that babies delivered after early PPRM would have increased rates of major childhood morbidity compared with those with later PPRM (≥25.0 weeks at rupture).

STUDY DESIGN—This was a secondary analysis of a multicenter randomized controlled trial of magnesium sulfate vs placebo for cerebral palsy prevention. Women with singletons and PPRM of 15-32 weeks were included. All women delivered at 24.0 weeks or longer. Those with PPRM less than 25.0 weeks (cases) were compared with women with PPRM at 25.0-31.9 weeks (controls). Composite severe neonatal morbidity (sepsis, severe intraventricular hemorrhage, periventricular leukomalacia, severe necrotizing enterocolitis, bronchopulmonary dysplasia, and/or death) and composite severe childhood morbidity at age 2 years (moderate or severe cerebral palsy and/or Bayley II Infant and Toddler Development scores greater than 2 SD below the mean) were compared.

RESULTS—A total of 1531 women (275 early PPRM cases) were included. Demographics were similar between the groups. Cases delivered earlier (26.6 vs 30.1 weeks, $P < .001$) and had a longer rupture-to-delivery interval (20.0 vs 10.4 days, $P < .001$). Case neonates had high rates of severe composite neonatal morbidity (75.6% vs 21.8%, $P < .001$). Children with early PPRM had higher composite severe childhood morbidity (51.6% vs 22.5%, $P < .001$). Early PPRM remained associated with composite severe childhood morbidity in multivariable models, even when controlling for delivery gestational age and other confounders.

CONCLUSION—Early PPRM is associated with high rates of neonatal morbidity. Early childhood outcomes at age 2 years remain poor compared with those delivered after later PPRM.

Keywords

childhood outcomes; neonatal outcomes; preterm pre-mature rupture of membranes

The views expressed herein are those of the authors and do not represent the views of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network or the National Institutes of Health.

The authors report no conflict of interest.

Presented, in part, in poster format at the 34th annual meeting of the Society for Maternal-Fetal Medicine, New Orleans, LA, Feb. 3-8, 2014.

The rate of preterm birth (delivery prior to 37 weeks' gestation) in the United States has recently begun to decline slightly but remains unacceptably high at 11.5% of all deliveries.¹ Preterm premature rupture of membranes (PPROM) is the leading identifiable cause of preterm birth and accounts for approximately one third of cases.² The etiology of PPRM is multifactorial and is likely related to factors including overt or subclinical infection/inflammation, abruption, uterine overdistension, smoking, and cervical insufficiency.³ However, many cases of PPRM occur without a clearly identifiable etiology.

In the United States, women with PPRM prior to 32-34 weeks' gestation are typically given an antibiotic regimen such as erythromycin and ampicillin; antibiotic administration in this setting has been shown to increase the latency period between membrane rupture and delivery and reduce neonatal morbidity and mortality.^{4,5} The majority of women are also administered antenatal corticosteroids to accelerate fetal lung maturity.⁶

Given the high risk of secondary complications such as placental abruption, cord prolapse, preterm labor, and intraamniotic infection, women with PPRM are typically managed as in-patients until delivery. In the absence of one of these complications, the majority of women are delivered at or by 32-34 weeks' gestation. The duration of latency between the timing of membrane rupture and delivery appears to be inversely related to the gestational age at PPRM; those women experiencing PPRM earlier in the gestation tend to have the longest latency periods.⁷

Traditionally, when PPRM occurs prior to fetal viability (23-25 weeks' gestation), neonatal outcomes have been poor. However, contemporary studies have demonstrated that in an era of advanced neonatal care, outcomes for neonates delivered following very early PPRM may be better than previously expected.⁸ Despite advances in neonatal care and apparent improved neonatal outcomes, longer-term outcomes of children delivered following early PPRM are largely unknown. One small study⁹ examined early childhood outcomes among 13 neonates who were expectantly managed following spontaneous PPRM at less than 24 weeks; 3 (23%) died in the hospital, and only 2 (15%) survived without obvious long-term morbidity at age 4 years. In another small study, Pristaux et al¹⁰ reported that half of 12 infants surviving PPRM between 14.0 and 24.9 weeks had normal neurological and developmental outcomes at age 2 years.

Therefore, we sought to compare initial neonatal (as assessed at initial hospital discharge) and early childhood outcomes (as assessed at age 2 years) between children with early PPRM (prior to 25.0 weeks' gestation) compared with those with later PPRM (a gestation of 25 weeks 0 days to a gestation of 31 weeks 6 days). We hypothesized that children delivered after early PPRM would have higher rates of neonatal and childhood morbidity and mortality compared with those with later PPRM.

MATERIALS AND METHODS

This is a secondary analysis of a multi-center randomized controlled trial of magnesium sulfate vs placebo for cerebral palsy prevention conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units

Network (MFMU) Network. Briefly, women with singleton or twin gestations at high risk for imminent preterm birth were recruited and randomized to receive intravenous magnesium sulfate vs placebo. All women and their infants were followed up to hospital discharge and surviving children were reevaluated at or beyond age 2 years for cerebral palsy and neurodevelopmental outcomes. The methods and results from the primary study have been previously published.¹¹ Briefly, the main trial found that fetal exposure to magnesium sulfate did not reduce the combined risk of moderate or severe cerebral palsy or death, but the rate of cerebral palsy was reduced among survivors. All participants provided written informed consent at the time of enrollment in the original study. This secondary analysis was performed on a deidentified data set, was reviewed by our local institutional review board, was determined to be nonhuman subject research, and was deemed exempt from institutional review board approval.

For the purposes of this secondary analysis, we included women with singleton gestations who had a confirmed diagnosis of PPROM between 15 and 32 weeks' gestation and subsequently delivered less than 35 weeks' gestation. Women with free-flowing amniotic fluid from the cervix, a positive indigo carmine dye test, and a positive nitrazine and fluid pooling, positive nitrazine and fluid ferning, or positive fluid pooling and fluid ferning were considered to have PPROM.

Neonates diagnosed with major structural congenital anomalies and/or aneuploidy as well as those who delivered at a gestation of 35.0 weeks or longer were excluded from this analysis. With the exception of the study protocol infusion (magnesium sulfate vs placebo), women were managed per local practices with regard to obstetric management, antibiotic administration, and decision to proceed with delivery.

Trained research nurses obtained standardized data on neonatal outcomes during hospitalization and at discharge and at scheduled follow-up visits at 6, 12, and 24 months of age (corrected for prematurity) as a part of the original study. Specifically, each neonate was assessed for the presence of or history of intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, retinopathy of prematurity, and necrotizing enterocolitis. Additionally, charts were reviewed to determine whether the neonate had 1 or more documented (culture proven) episode(s) of sepsis during their hospitalization. Trained pediatricians or pediatric neurologists also evaluated those children who survived to age 2 years. Each child was assessed for the presence of cerebral palsy. Additionally, each child was evaluated with the Bayley II Scales of Infant Development Mental Development (MDI) and Psychomotor Development Indices (PDI).

Those with PPROM less than 25.0 weeks (cases) were compared with women with PPROM at 25.0-31.9 weeks' gestation (controls). Gestational age was determined using the best obstetric estimate, established per standard criteria utilizing menstrual period and ultrasonographic parameters as appropriate. Initially, enrollment in the main trial did not specify a lower gestational age restriction for PPROM. Partway through recruitment, the protocol was amended and only women with PPROM at or beyond 22.0 weeks' gestation were eligible for enrollment.

The primary outcomes of this analysis were as follows: (1) composite severe neonatal morbidity (defined as a diagnosis of sepsis, grade III or IV intraventricular hemorrhage, periventricular leukomalacia, grade II or III necrotizing enterocolitis, bronchopulmonary dysplasia, and/or death) and (2) composite severe childhood morbidity at age 2 years (moderate or severe cerebral palsy, Bayley MDI or PDI scores greater than 2 SD below the mean, and/or death). Outcomes were compared between those with early vs later PPRM.

Demographics, pregnancy characteristics, neonatal course and outcomes, and early childhood outcomes were also compared using a Student *t* test, χ^2 , and analysis of the variance as appropriate. Multivariable logistic regression was used to assess factors associated with severe neonatal morbidity and severe childhood morbidity; factors significant in the univariable analysis were included in the initial regression models. Covariates were then removed in a stepwise fashion until all covariates in the final model had a value of $P < .20$. Data were analyzed using STATA version 12.1 (StataCorp, College Station, TX).

RESULTS

Of 2241 women randomized in the original study, 1531 neonates/children met inclusion criteria for this secondary analysis (Figure). Of these, 275 (18%) were delivered following early PPRM at less than 25.0 weeks' gestation, at a mean gestational age of 23.7 ± 1.2 (range, 15.1–24.9) weeks' gestation. The remaining 1256 (82%) had later PPRM, at a mean gestational age of 28.7 ± 2.2 (range, 25.0–31.9) weeks' gestation.

Maternal demographic and pregnancy characteristics are shown in Table 1. Women with early PPRM were similar to those with later PPRM with regard to demographics. As expected, the gestational age at the time of randomization was earlier for those with early PPRM, 24.7 vs 28.9 weeks ($P < .001$). Delivery characteristics and initial neonatal outcomes are shown in Table 2. Women with early PPRM experienced significantly longer latency-to-delivery intervals yet delivered more than 3 weeks earlier than those with later PPRM.

The vast majority of all women (>98%) received antenatal corticosteroids, regardless of the timing of membrane rupture. A very small number of women received tocolysis ($n = 33$, 2.2% overall). The majority ($n = 1477$, 96.5% overall) received antibiotics between randomization and delivery; 1326 (86.6%) received ampicillin, amoxicillin, or penicillin, and 914 (59.7%) received erythromycin. Unfortunately, the data regarding antibiotic use prior to randomization or the reason/intent for antibiotic prescription are not available.

Neonates delivered following early PPRM were more likely to be delivered by cesarean and in general had higher rates of all adverse outcomes, including death (Table 2). Similar trends were seen when examining early childhood outcomes at age 2 years. In univariable analyses, those with early PPRM were more likely to be diagnosed with cerebral palsy and low Bayley II MDI and PDI scores (Table 3).

When controlling for confounders including gestational age at delivery, PPRM prior to 25 weeks' gestation remained associated with both composite severe neonatal morbidity (odds

ratio, 2.57; 95% confidence interval, 1.72–3.83; Table 4) and composite severe childhood morbidity (odds ratio, 1.57; 95% confidence interval, 1.12–2.20; Table 5). Other factors included in the initial model examining factors associated with adverse neonatal outcomes (Table 4) were the magnesium treatment group, race/ethnicity, and maternal drug use. The initial model examining variables associated with adverse childhood outcomes (Table 5) also included the magnesium treatment group and chorioamnionitis. These factors were excluded from the final models ($P > .20$).

COMMENT

We found that neonates delivered following early PPRM were at a significantly higher risk for a multitude of adverse outcomes both during the neonatal period and in early childhood. These associations persisted when controlling for confounders, including gestational age at delivery, infectious morbidity, and other factors. Notably, the rates of death during the neonatal period were also significantly higher among those delivered following early PPRM, with nearly 17% of the early PPRM neonates dying, compared with 2.5% of those after later PPRM ($P < .001$). Rates of death during the initial childhood follow-up period were low and did not differ between groups.

Previous studies of neonatal outcomes among babies reaching fetal viability following early PPRM have reported a wide of both neonatal survival (20–68%) and neonatal morbidity (25–80%).^{8,12–14} The wide range of outcomes is likely related to an inherent selection bias (given the high rate of elective termination prior to viability), small sample sizes (as few as 25 cases), and the upper gestational age at which PPRM is considered to be early or periviable (which was as high as 28 weeks in some older studies).

Outcome rates in this current study are consistent with these prior reports. Limited data are available regarding outcomes later in life for children who are delivered after early PPRM and survive the initial neonatal period. These data provide valuable insights into the challenges that are faced by children delivered following early PPRM.

The optimal management following early PPRM remains uncertain. In this secondary analysis, women were cared for across the United States at tertiary care centers participating in the MFMU Network; results and outcomes are thus more generalizable to tertiary care centers nationwide. The vast majority received antenatal corticosteroids and antibiotics prior to delivery. Only a very small proportion received tocolysis. This management reflects American College of Obstetricians and Gynecologists' recommendations.³

Several study limitations must be kept in mind when considering the generalizability of these data. These data cannot provide a population-based estimation of outcomes following PPRM because of the enrollment criteria in the original study and the referral nature of the tertiary care centers participating in the MFMU Network. Also, given that enrollment criteria were changed during the study, those with PPRM less than 22 weeks' gestation were ineligible for the main trial for the majority of the recruitment period. For that reason, the majority of women included in the early PPRM group experienced PPRM between 22 and 25 weeks' gestation. It would be reasonable to conclude that outcomes might be

worse if a larger proportion of the population experienced PPROM prior to 22 weeks' gestation, but this cannot be concluded with certainty from these data. Ideally, we would control for delivery gestational age by matching those with early vs later PPROM by delivery gestational age. However, even in this large cohort, we had insufficient numbers to conduct the analysis in this fashion.

Additionally, we were unable to include twin gestations in this secondary analysis because we did not have data regarding which twin's gestational sac was the ruptured sac. Whether these neonatal and early childhood outcome data may be appropriately extrapolated to twin gestations is uncertain.

Lastly, as with any secondary analysis, we were limited by the data collected during the original study. Thus, we do not have data available regarding neonatal outcomes specific to early and prolonged PPROM such as pulmonary hypoplasia and joint contractures. Fortunately, it is likely that babies with pulmonary hypo-plasia would also have bronchopulmonary dysplasia or would not survive; likewise, those with clinically significant joint contractures would have a high change of psychomotor delay at age 2 years; these other diagnoses may be appropriate surrogate outcomes.

Our study had several strengths. This secondary analysis was derived from a large, prospectively collected cohort, providing a relatively large number of women with early PPROM. Data were collected by trained research nurses using standardized definitions and protocols. We were able to compare them with similarly well-characterized women from the same initial study who had PPROM at a later point in pregnancy, reducing potential confounding that could occur if compared with neonatal and childhood outcomes after preterm birth for other indications. Previous studies have suggested that neonatal outcomes are worse following delivery after PPROM vs spontaneous preterm labor.¹⁵

These data provide realistic estimates regarding outcomes after early PPROM from a large cohort of women who sub-sequently achieved sufficient latency to reach fetal viability. Limited data regarding longer-term outcomes of children delivered following early PPROM are currently available. Thus, these data add significantly to the current literature and will be useful in counseling patients regarding pregnancy management and in decisions regarding neonatal resuscitation when PPROM occurs at the limits of viability.

In conclusion, neonates who survive to viability following PPROM during pre- or periviability are at high risk for neonatal death, neonatal morbidity, and significant morbidity in early childhood, even when compared with their later-PPROM counterparts.

ACKNOWLEDGEMENTS

We acknowledge the assistance of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the Maternal Fetal Medicine Unit's Network, and the Beneficial Effects of Antenatal Magnesium protocol subcommittee for the conduct of the original study and for making the database available for this research.

This work was supported by National Institutes of Health grant 1K23HD067224.

REFERENCES

1. Hamilton BE, Martin JA, Ventura SJ. Births: preliminary data for 2012. *Natl Vital Stat Rep.* 2013; 62:1–20.
2. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet.* 2008; 371:75–84. [PubMed: 18177778]
3. American College of Obstetricians and Gynecologists. Premature Rupture of Membranes. *Obstet Gynecol.* 2013; 122:918–30. ACOG Practice bulletin no. 139. [PubMed: 24084566]
4. Hutzal CE, Boyle EM, Kenyon SL, et al. Use of antibiotics for the treatment of preterm parturition and prevention of neonatal morbidity: a metaanalysis. *Am J Obstet Gynecol.* 2008; 199:620.e1–8. [PubMed: 18973872]
5. Egarter C, Leitich H, Karas H, et al. Antibiotic treatment in preterm premature rupture of membranes and neonatal morbidity: a meta-analysis. *Am J Obstet Gynecol.* 1996; 174:589–97. [PubMed: 8623790]
6. Mercer BM, Miodovnik M, Thurnau GR, et al. Antibiotic therapy for reduction of infant morbidity after preterm premature rupture of the membranes. A randomized controlled trial. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *JAMA.* 1997; 278:989–95. [PubMed: 9307346]
7. Melamed N, Hadar E, Ben-Haroush A, Kaplan B, Yogev Y. Factors affecting the duration of the latency period in preterm premature rupture of membranes. *J Matern Fetal Neonatal Med.* 2009; 22:1051–6. [PubMed: 19900043]
8. 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; 114:29–37. [PubMed: 19546755]
9. Chauleur C, Rochigneux S, Seffert P, Chene G, Billiemaz K, Collet F. Neonatal outcomes and four-year follow-up after spontaneous or iatrogenic preterm prelabor rupture of membranes before 24 weeks. *Acta Obstet Gynecol Scand.* 2009; 88:801–6. [PubMed: 19449217]
10. Pristauz G, Bauer M, Maurer-Fellbaum U, et al. Neonatal outcome and two-year follow-up after expectant management of second trimester rupture of membranes. *Int J Gynaecol Obstet.* 2008; 101:264–8. [PubMed: 18289539]
11. Rouse DJ, Hirtz DG, Thom E, et al. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. *N Engl J Med.* 2008; 359:895–905. [PubMed: 18753646]
12. Azria E, Anselem O, Schmitz T, Tsatsaris V, Senat MV, Goffinet F. Comparison of perinatal outcome after pre-viable preterm prelabour rupture of membranes in two centres with different rates of termination of pregnancy. *BJOG.* 2012; 119:449–57. [PubMed: 22260429]
13. Soylu H, Jefferies A, Diambomba Y, Windrim R, Shah PS. Rupture of membranes before the age of viability and birth after the age of viability: comparison of outcomes in a matched cohort study. *J Perinatol.* 2010; 30:645–9. [PubMed: 20220762]
14. Waters TP, Mercer BM. The management of preterm premature rupture of the membranes near the limit of fetal viability. *Am J Obstet Gynecol.* 2009; 201:230–40. [PubMed: 19733274]
15. Melamed N, Ben-Haroush A, Pardo J, et al. Expectant management of preterm premature rupture of membranes: is it all about gestational age? *Am J Obstet Gynecol.* 2011; 204:48.e1–8. [PubMed: 21074135]

FIGURE.

Eligibility and inclusion in current study

Manuck. Outcomes following early PPROM. Am J Obstet Gynecol 2014.

TABLE 1

Demographic and pregnancy characteristics of women with early vs later PPRM

Characteristic	Early PPRM (n = 275)	Later PPRM (n = 1256)	P value
Maternal age, y, mean $\pm$ SD	27.0 $\pm$ 5.9	26.4 $\pm$ 6.2	.127
Maternal prepregnancy body mass index, kg/m ² , mean $\pm$ SD	26.6 $\pm$ 7.3	26.1 $\pm$ 6.5	.258
Married	134 (48.9)	601 (47.9)	.769
Maternal race or ethnic group ^a			
Black	131 (47.6)	562 (44.8)	
White	104 (37.8)	467 (37.2)	.332
Hispanic	34 (12.4)	198 (15.8)	
Other	6 (2.2)	29 (2.3)	
Maternal education, highest level completed, mean $\pm$ SD	12.2 $\pm$ 2.3	11.8 $\pm$ 2.5	.016
Prior preterm delivery	70 (25.5)	351 (28.0)	.402
Smoked cigarettes during pregnancy	78 (28.4)	367 (29.2)	.894
Drank alcohol during pregnancy	30 (10.9)	117 (9.3)	.416
Used illicit drugs during pregnancy	21 (7.6)	147 (11.7)	.051
Gestational age at randomization, wks, mean $\pm$ SD	24.7 $\pm$ 0.9	28.9 $\pm$ 2.0	< .001
Randomized to magnesium sulfate	133 (48.4)	616 (49.0)	.838
Received antenatal corticosteroids	272 (98.9)	1226 (97.6)	.180

Unless otherwise specified, data are listed as n (percentage).

PPROM, preterm premature rupture of membranes.

Manuck. Outcomes following early PPRM. Am J Obstet Gynecol 2014.

^aMaternal race was analyzed by analysis of the variance. Continuous variables were compared with the use of the Student *t* test and categorical variables with the χ^2 test.

TABLE 2

Delivery characteristics and neonatal outcomes of those with early vs later PPRM

Characteristic	Early PPRM (n = 275)	Later PPRM (n = 1256)	P value
Rupture-to-delivery interval, d, mean $\pm$ SD	20.0 $\pm$ 20.2	10.4 $\pm$ 10.7	< .001
Gestational age at delivery, wks, mean $\pm$ SD	26.6 $\pm$ 2.5	30.1 $\pm$ 2.2	< .001
Received antenatal corticosteroids	272 (98.9)	1226 (97.6)	.180
Placental abruption	29 (10.6)	99 (7.9)	.148
Chorioamnionitis	45 (16.4)	151 (12.0)	.051
Cesarean delivery	127 (46.2)	456 (36.3)	.002
Postpartum endometritis	24 (8.7)	74 (5.9)	.082
Maternal length of hospitalization, d, mean $\pm$ SD	19.1 $\pm$ 17.1	12.5 $\pm$ 11.2	< .001
Male fetus	153 (55.6)	667 (53.1)	.446
Birthweight, g, mean $\pm$ SD	930 $\pm$ 415	1481 $\pm$ 444	< .001
Culture-proven sepsis	111 (40.4)	143 (11.4)	< .001
Necrotizing enterocolitis			
Any severity	40 (14.6)	91 (7.3)	< .001
Severe (stage 2 or 3)	22 (8.0)	43 (3.4)	.001
Retinopathy of prematurity	138 (50.2)	190 (15.1)	< .001
Bronchopulmonary dysplasia	136 (49.5)	127 (10.1)	< .001
Neonatal seizures	15 (5.5)	15 (1.2)	< .001
Intraventricular hemorrhage			
Any severity	76 (29.5)	237 (19.4)	< .001
Severe (grade III or IV)	15 (5.8)	13 (1.1)	< .001
Periventricular leukomalacia	10 (3.9)	16 (1.3)	.004
Death prior to initial hospital discharge	46 (16.7)	31 (2.5)	< .001
Composite severe neonatal morbidity ^a	208 (75.6)	274 (21.8)	< .001

Unless otherwise specified, data are listed as n (percentage).

PPROM, preterm premature rupture of membranes.

Manuck. Outcomes following early PPRM. Am J Obstet Gynecol 2014.

^aDiagnosis of sepsis, bronchopulmonary dysplasia, severe grade III or IV intraventricular hemorrhage, periventricular leukomalacia, severe stage 2 or 3 necrotizing enterocolitis, and/or death.

TABLE 3

Early childhood outcomes at age 2 years of children delivered following early vs later PPROM

Characteristic	Early PPROM (n = 275)	Later PPROM (n = 1256)	P value
Cerebral palsy			
Any	27 (9.8)	36 (2.9)	< .001
Moderate/severe	12 (4.4)	16 (1.3)	.001
Bayley II MDI <70	61 (29.5)	156 (14.2)	< .001
Bayley II MDI score, mean $\pm$ SD	79.6 $\pm$ 19.0	87.5 $\pm$ 17.0	< .001
Bayley II PDI <70	66 (31.0)	134 (12.2)	< .001
Bayley II PDI score, mean $\pm$ SD	82.5 $\pm$ 19.6	92.4 $\pm$ 17.2	< .001
Death after initial hospital discharge during follow-up period	5 (1.8)	21 (1.7)	.87
Severe composite early childhood morbidity ^a	142 (51.6)	282 (22.5)	< .001

Unless otherwise specified, data are listed as n (percentage).

MDI, Scale of Infant Development Mental Development; *PDI*, Scale of Psychomotor Development Indices; *PPROM*, preterm premature rupture of membranes.

Manuck. Outcomes following early PPROM. Am J Obstet Gynecol 2014.

^aDiagnosis of moderate or severe cerebral palsy, Bayley MDI and/or PDI scores greater than 2 SD below the mean, and/or death.

TABLE 4Regression results: factors associated with composite severe neonatal morbidity^a

Variable	OR	95% CI	P value
PPROM prior to 25 wks' gestation	2.57	1.72–3.83	< .001
Male infant	1.58	1.18–2.11	.002
Delivery gestational age (per 1-wk interval)	0.53	0.49–0.57	< .001
Cesarean delivery	1.40	1.05–1.87	.022
Chorioamnionitis	1.35	0.91–2.01	.138

CI, confidence interval; OR, odds ratio; PPRM, preterm premature rupture of membranes.

Manuck. Outcomes following early PPRM. Am J Obstet Gynecol 2014.

^aOther factors included in the initial model but not remaining in the final model ($P > .20$) included race/ethnicity, maternal drug use, and treatment group (magnesium sulfate vs placebo).

TABLE 5Regression results: factors associated with composite severe childhood morbidity at age 2 years^a

Variable	OR	95% CI	P value
PPROM prior to 25 wks' gestation	1.57	1.12–2.20	.009
Severe composite neonatal morbidity	2.13	1.56–2.90	< .001
White	0.82	0.63–1.06	.123
Male infant	1.56	1.22–2.00	< .001
Delivery gestational age (per 1-wk interval)	0.86	0.81–0.92	< .001
Cesarean delivery	1.31	1.02–1.68	.031
Maternal drug use during pregnancy	1.65	1.14–2.37	.008

CI, confidence interval; OR, odds ratio; PPRM, preterm premature rupture of membranes.

Manuck. Outcomes following early PPRM. Am J Obstet Gynecol 2014.

^aOther factors included in the initial model but not remaining in the final model ($P > .20$) included chorioamnionitis and treatment group (magnesium sulfate vs placebo).