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Length of Latency with Preterm Premature Rupture of Membranes before 32 Weeks' Gestation

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Abstract

Objective—To describe latency for patients with preterm premature membrane rupture (PPROM) between 24 0/7 and 31 6/7 weeks' gestation.

Study Design—Secondary analysis of data collected prospectively in a multicenter clinical trial of magnesium sulfate for cerebral palsy prevention. Women with PPROM and fewer than 6 contractions per hour at enrollment who were candidates for expectant management (n=1377) were included in this analysis. Length of latency was calculated in days by subtracting the time of delivery from the time of membrane rupture.

Results—At each week of gestation, median latency between 24-28 weeks was similar at approximately 9 days, but was significantly shorter with PPROM at 29, 30, and 31 weeks ($p<0.001$). In addition, the percentage of patients remaining undelivered at 7 days and 14 days was similar for PPROM between 24-28 weeks, but decreased significantly after that. For each gestational age, the proportion of patients remaining pregnant declined in a fashion similar to exponential pattern.

Conclusion—Median latency after PPROM is similar from 24-28 weeks' gestation, but shortens with PPROM at and after 29 weeks.

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INTRODUCTION

Preterm premature rupture of membranes (PPROM) complicates 3% of pregnancies and is a significant contributor to perinatal morbidity and mortality. This increase in morbidity and mortality is primarily related to the gestational age at which PPROM and subsequent preterm delivery occurs. Management before 34 weeks' gestation usually involves antibiotic administration and expectant management in an effort to prolong pregnancy. Length of latency until delivery appears to be inversely related to the gestational age at which PPROM occurs, but little data exist to describe this relationship against the background of prophylactic antibiotics.[1,2] Our research network conducted a trial evaluating the use of magnesium sulfate to prevent cerebral palsy in patients at high risk of early preterm delivery.[3] Because the majority of women entered into this large randomized trial had PPROM and were managed expectantly, it afforded the opportunity to estimate gestational age specific measures of latency in patients experiencing PPROM between 24-31 weeks' gestation and who routinely received antibiotics for pregnancy prolongation.

MATERIALS AND METHODS

We conducted a secondary analysis of a clinical trial of magnesium sulfate for the prevention of cerebral palsy performed at the 20 centers of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal Fetal Medicine Units Network.[3] Participants were women with singleton or twin gestations at 24 0/7-31 6/7 weeks' gestation and were at high risk for spontaneous preterm delivery because of rupture of the membranes, advanced preterm labor, or an indicated preterm delivery. They were randomly allocated to treatment with magnesium sulfate as a 6-g bolus followed by a constant infusion of 2 g per hour, or matching placebo. The primary study was approved by the Institutional Review Board at all participating centers, and all patients gave informed consent.

Within this cohort, 1377 patients who experienced PPROM from 24 to 31weeks and were contracting fewer than 6 times per hour at the time of randomization are the subject of this analysis. Criteria for assignment of gestational age were standardized,[4] as were criteria for the diagnosis of ruptured membranes. Neither the antibiotic treatment nor criteria for delivery were standardized, but antibiotics were routinely administered, and expectant management was routinely pursued until at least 32 weeks' gestation or until the patient entered spontaneous labor, developed intrauterine infection or bleeding, or the fetal status was deemed non-reassuring. Study medication was stopped after 12 hours if the patient was undelivered and regular uterine contractions were not present. Certified research personnel collected information on the mother's demographic features, medical history, social history at enrollment, and maternal and neonatal outcome data at delivery. Information on residual amniotic fluid volume and cervical length were not collected.

Latency was measured from time of reported rupture of membranes until time of delivery in hours. Median latency was calculated for patients with rupture at each week of gestational age between 24 to 31 weeks, rounded down to the nearest whole week (e.g. 28 0/7 to 28 6/7 weeks grouped as 28 weeks). For each week of gestational age at time of PPROM, the percent of women remaining undelivered at 7 days and 14 days after PPROM was also calculated. Data were analyzed using SAS (SAS Institute, Cary, NC). Wilcoxon rank sum test was used to compare the median difference and Cochran-Armitage trend test was used to evaluate the trend of proportion changes. Multivariable regression analysis (proportional hazards regression or logistic regression) was performed to determine clinical factors contributing to duration of latency. We used the proportional hazard regression to analyze the latency as the outcome. Then, we used the logistic regression to analyze a binary indicator (whether the latency is greater than 7×24 hours) as the outcome. We also used the logistic regression to analyze another similar binary indicator (whether the latency is greater than 14×24 hours) as the outcome. Twin gestation, nulliparity and treatment group were considered for adjustment in the regression analysis.

RESULTS

Baseline maternal characteristics of the expectantly managed patients with PPROM are presented in Table 1. 97% of patients were treated with antibiotics, and <7% of patients delivered within 12 hours of randomization. Reasons for delivery included spontaneous labor (68%), infection (9%), non-reassuring fetal status (10%), and bleeding (2%). Information regarding the interval from time of PPROM to delivery is reported in Table 2, and illustrated in Figure 1. At each week of gestation, median latency between 24-28 weeks was similar at approximately 9 days, but was significantly shorter with PPROM at 29, 30, and 31 weeks ($p<0.001$, Wilcoxon rank sum test). In addition, the percentage of patients remaining undelivered at 7 days and 14 days was similar for PPROM between 24-28 weeks' gestation, but decreased significantly after that ($p<0.001$ for both, Cochran-Armitage trend test). For all gestational ages evaluated, the proportion of patients remaining pregnant declined in an exponential pattern (data not shown). Multivariable analysis demonstrated that twin gestation (hazard ratio 1.58, 95% CI 1.29-1.94), but neither nulliparity nor treatment with magnesium sulfate was associated with shorter latency. For twin gestations, median latency for those with PPROM between 24-28 weeks (n=71) was 7.0 days (interquartile range 2.0, 13.0) and for twin gestations with PPROM 29-31 weeks (n=33) median latency was 2.0 days (1.0, 6.0). Median latency for the magnesium sulfate group was 7.0 days, compared with 8.0 days for patients in the placebo arm ($p = 0.13$).

COMMENT

Preterm premature rupture of membranes is a common pregnancy complication, and is the precipitating cause of a significant portion of all preterm deliveries. Previous studies have noted that latency with PPROM can last for weeks, and that PPROM at earlier gestations appear to have longer latency to delivery.[1,2] However, little data exist to describe latency at specific gestational ages. We have taken the opportunity to utilize a large and well described cohort of patients with PPROM to describe latency of PPROM occurring between 24 and 31 weeks' gestation. We found that time from membrane rupture to delivery remains relatively

constant from 24 -28 weeks' gestation at 8-10 days, and then decreases to 5 days at 31 weeks. Further, the finding of exponential decay at each gestational age allows for prediction of likelihood of latency persisting to any point in the future. As an example, PPROM at 29 weeks' gestational age has a median latency of about 8 days, and roughly 25% of patients will remain undelivered at about 16 days, and 12.5% at about 24 days.

When considering duration of latency in this cohort, we examined the effect of treatment with magnesium sulfate. No significant difference was seen between the treatment and control groups with regard to length of latency. Whether this absence of difference is due to insufficient dosing or lack of benefit of magnesium sulfate for this purpose cannot be determined.[5] Another interesting finding was the considerably shorter median latency in twin gestations. The number of patients with twin gestations is too small to generate week specific ranges for latency, but counseling of patients in this situation should be different than for those patients with singleton pregnancy and PPROM.

Currently, the most common approach to management of PPROM at <34 weeks' gestation is expectant management with antibiotics to prolong latency. This practice is based on the understanding that gestational age at delivery is the most important factor impacting neonatal outcome. However, some concerns have been raised recently regarding this approach, primarily because of the increasing risks of developing intrauterine infection with delaying delivery in the face of ruptured membranes and the concerns for neurologic injury associated with the fetal inflammatory response.[6] We observed that less than half of patients with PPROM after 29 weeks' gestation remained undelivered for more than a week, exposing the majority to risks of infection with uncertain benefit of pregnancy prolongation after completion of antenatal corticosteroids. Two recent studies have addressed this issue with mixed results regarding increasing neonatal complications being associated with longer latency.[7,8] Manuck et al. found that in patients with PPROM, infection but not latency was associated with major perinatal morbidity, while Melamed et al. found higher rates of composite neonatal morbidity with latency greater than 7 days. Future studies regarding pregnancy prolongation could be helpful in determining the most beneficial management approach. Ultimately, it may be found that the risk benefit ratio for expectant management is not constant between 24-34 weeks' gestation, and different clinical approaches may be more appropriate.

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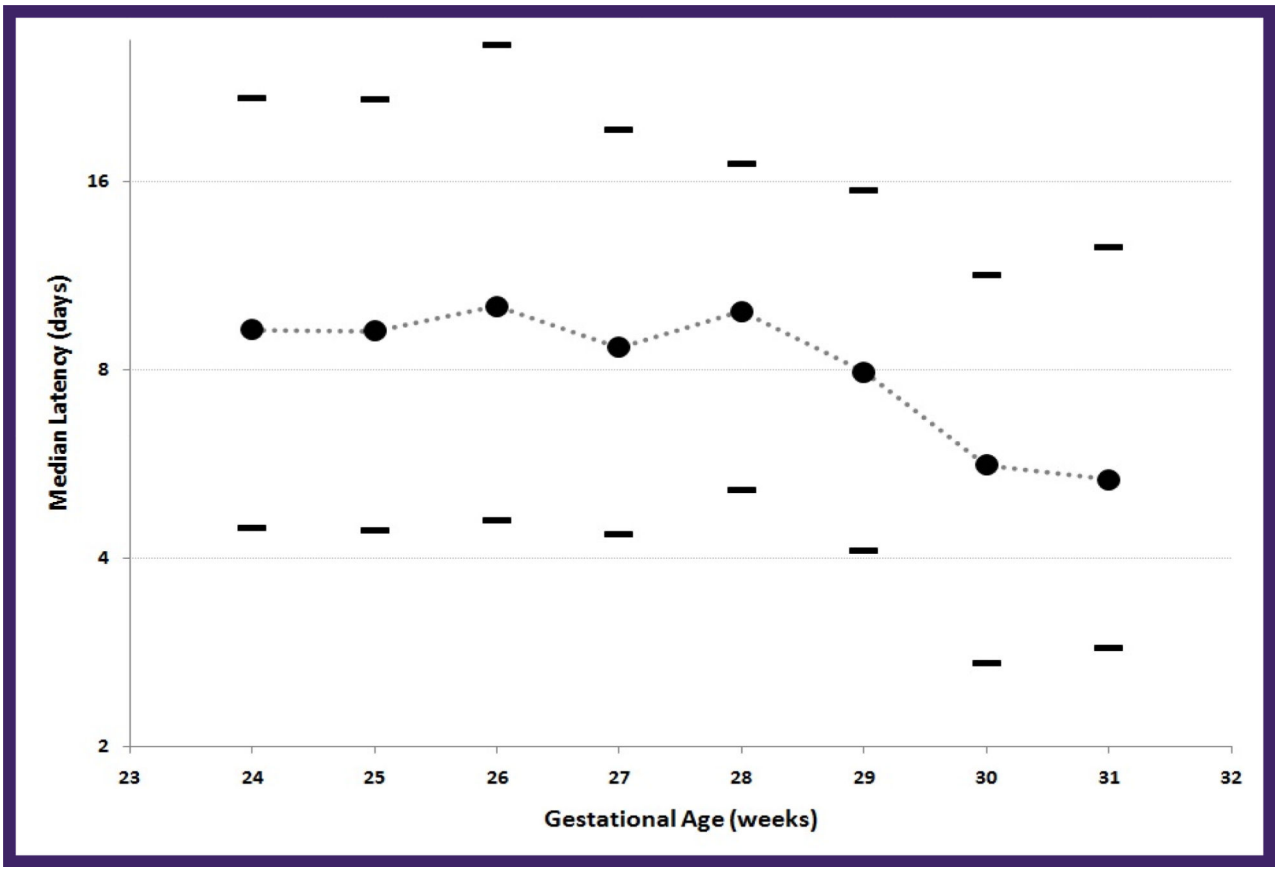

Figure 1.

Latency with PPROM

Median latency in days (with interquartile range) by gestational age at PPROM.

Table 1

Maternal baseline characteristics

Mean weeks gestation at randomization (SD)	**28.3 (2.30)**
Mean maternal age—years (SD)	26.5 (6.30)
Maternal prepregnancy Body Mass Index* (SD)	26.6 (6.81)
Maternal race or ethnic group—no. (%)	
Black	610 (44.3)
White	522 (37.9)
Hispanic	209 (15.2)
Other	36 (2.6)
Nulliparous—no. (%)	459 (33.3)
Twins—no. (%)	104 (7.6)
Smoking during pregnancy—no. (%)	398 (28.9)

*In kg/m^2

Table 2

Interval in days (d) from time of PPROM to delivery

Gestational Age	24 N=171	25 N=166	26 N=138	27 N=169	28 N=172	29 N=185	30 N=181	31 N=195
Median latency (d) [Q1, Q3]	9.0 [4.0, 21.0]	9.0 [4.0, 21.0]	9.5 [4.0, 26.0]	8.0 [4.0, 19.0]	9.5 [5.0, 17.0]	7.0 [4.0, 15.0]	5.0 [2.0, 11.0]	5.0 [2.0, 12.0]
Hazard ratio * [95% CI]	1 (ref)	1.0 [0.8,1.3]	1.0 [0.8,1.3]	1.1 [0.9,1.4]	1.2 [0.9,1.4]	1.5 [1.2,1.8]	1.7 [1.4,2.1]	1.9 [1.5,2.3]
Undelivered 7d	64%	61%	64%	60%	62%	53%	44%	42%
OR [95% CI]	1 (ref)	0.9 [0.6,1.3]	1.0 [0.6,1.6]	0.9 [0.6,1.3]	0.9 [0.6,1.4]	0.6 [0.4,0.9]	0.4 [0.3,0.7]	0.4 [0.3,0.6]
Undelivered 14d	34%	36%	41%	35%	34%	30%	21%	22%
OR [95% CI]	1 (ref)	1.1 [0.7,1.7]	1.3 [0.8,2.1]	1.0 [0.7,1.6]	1.0 [0.6,1.5]	0.8 [0.5,1.3]	0.5 [0.3,0.8]	0.5 [0.3,0.8]

* risk of latency being less than for those with PPROM at 24 weeks