Neonatal outcomes of moderately preterm infants compared to extremely preterm infants

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BACKGROUND: Extremely preterm infants (EPT, <29 weeks' gestation) represent only 0.9% of births in the United States; yet these infants are the focus of most published research. Moderately preterm neonates (MPT, 29–33[6/7] weeks) are an understudied group of high-risk infants.

METHODS: To determine the neonatal outcomes of MPT infants across the gestational age spectrum, and to compare these with EPT infants. A prospective observational cohort was formed in 18 level 3–4 neonatal intensive care units (NICUs) in the *Eunice Kennedy Shriver* NICHD Neonatal Research Network. Participants included all MPT infants admitted to NICUs and all EPT infants born at sites between January 2012 and November 2013. Antenatal characteristics and neonatal morbidities were abstracted from records using pre-specified definitions by trained neonatal research nurses.

RESULTS: MPT infants experienced morbidities similar to, although at lower rates than, those of EPT infants. The main cause of mortality was congenital malformation, accounting for 43% of deaths. Central Nervous System injury occurred, including intraventricular hemorrhage. Most MPT infants required respiratory support, but sequelae such as broncho-pulmonary dysplasia were rare. The primary contributors to hospitalization beyond 36 weeks' gestation were inability to achieve adequate oral intake and persistent apnea.

CONCLUSIONS: MPT infants experience morbidity and prolonged hospitalization. Such morbidity deserves focused research to improve therapeutic and prevention strategies.

Extremely preterm infants (EPT, <29 weeks' gestation) represent only 0.9% of births in the United States; yet these infants are the subject of the majority of published research on newborns (1,2). Moderately preterm neonates (MPT, 29–33[6/7] weeks), which constituted 2.8% of all births in the United States in 2013 and 22% of all preterm births, are an understudied group of high-risk infants (1). A medline search using the terms moderately preterm, preterm, and randomized trial found only one randomized trial in MPT neonates—a surfactant trial in 1993 (3). Thus, the care of MPT infants is extrapolated from studies of EPT or full-term infants rather than from randomized trials specific to MPT infants. MPT infants are at risk for substantial short-term morbidity. Most published studies have focused on late-preterm infants (34–36 weeks' gestational age) and some have included a subset of MPT infants. These limited studies have shown higher rates of abnormal respiratory outcomes, cognitive functioning, school performance, and behavior (4–8). Because of their large numbers (~93 000 in 2013), morbidities experienced by MPT neonates represent a substantial public health burden (7,8). Additional information about the morbidity in this group is needed from a contemporary cohort to inform the design of future interventional trials and improve the effectiveness of care. Thus, we performed a large prospective observational study of the outcomes in MPT infants and evaluated those outcomes by gestational age. In addition, we compared outcomes of MPT infants with those of EPT infants enrolled in a longstanding registry of the NICHD Neonatal Research Network (NRN).

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METHODS

The NRN is a network of neonatal intensive care units at 18 academic centers in the United States and a data coordinating center, which was formed to conduct research to improve the care of high-risk infants. All infants between $29^{0/7}$ and $33^{6/7}$ weeks' gestational age (GA) born between January 2012 and November 2013 and admitted within the first 72 h of life were included in the Moderately Preterm Registry. The comparison group comprised infants enrolled in the NRN Registry of inborn infants of gestational age $22^{0/7}$ to $27^{6/7}$ weeks (EPT) or having birth weight 401–1,000 g who were born during the same months. Infants who were born alive but who died in the delivery room were also included. Trained research nurses using pre-specified definitions abstracted maternal demographic, pregnancy, delivery, and infant data from birth to discharge, transfer, death, or 40 weeks' postmenstrual age (PMA), whichever occurred first. Detailed information on the EPT cohort by week of GA was published recently in JAMA (9). The Institutional Review Board at each center approved the registries.

Neonatal information included birth weight (BW), GA, gender, race/ethnicity, mode of delivery, delivery room interventions, final status, and cause of death. GA was determined as the best obstetric estimate by using ultrasonography and/or the date of the last menstrual period. Neonatal morbidities were recorded for infants surviving for >12 h, and included respiratory distress syndrome, patent ductus arteriosus (PDA), modified Bell's Stage ⩾IIA necrotizing enterocolitis (NEC) (10), any intracranial hemorrhage according to the criteria of Papile (11), severe intracranial hemorrhage (grade III or IV), periventricular leukomalacia, retinopathy of prematurity (ROP) (12), bronchopulmonary dysplasia (BPD) defined as supplemental oxygen at 36 weeks' PMA, and early- and late-onset sepsis defined by positive blood cultures before or after 72 h of age. Cranial sonograms and ROP exams were performed on the basis of usual center practice. Outcomes collected at 36 weeks' PMA included the reason for continued hospitalization (continued respiratory support; persistent apnea and/or bradycardia—defined by local center practice; inadequate oral feedings defined by continued gavage feedings; other). Data collection continued until discharge or 40 weeks' PMA, whichever occurred first. Only 16% of the cohort remained hospitalized at 40 weeks' PMA.

The NRN has maintained a registry of the characteristics and outcomes of EPT infants for over 20 years (9). We utilized this long-standing registry to compare a cohort of MPT infants with a cohort of inborn EPT infants born during the same months. We further analyzed the outcomes in MPT infants across the GA continuum. Statistical significance in this observational study was tested using the χ^2-test for categorical variables and the Kruskall–Wallis test for continuous variables. Comparisons were made by GA and contrasted with the frequency seen in EPT infants born during the same period.

RESULTS

Population and Pregnancy Characteristics

Seven thousand and fifty-seven MPT infants met the study criteria. Of them, 6,419 (91%) were inborn and 638 (9%) were outborn. During the same period, 4,310 EPT infants were born at NRN sites. Maternal and infant characteristics are shown in Table 1. The average maternal age was 28.4 ± 6.5 (mean ± SD) years. Most women were White (57%) and non-Hispanic (83.3%). Nearly half had completed high school and additional higher education (49.9%). Almost all attended at least one prenatal visit (97%). The majority of women were publicly insured (55.2%), with a small percentage being uninsured (3.4%).

Multiple births were common in our MPT cohort ($n = 2,059$, 29.2%). Frequently observed pregnancy complications included hypertension ($n = 3,172$, 44.9%) and insulin-

dependent diabetes ($n = 527$, 7.5%). Prolonged preterm rupture of the membranes occurred in 1,267 (19.2%), and clinical chorioamnionitis was noted in 498 (7.1%). Overall, 85.3% of the cohort received antenatal steroids. Most mothers (68.5%) received antibiotics in the 72 h prior to delivery, and 53.7% received magnesium sulfate. Four thousand four hundred and sixty-five (63.3%) infants were delivered by cesarean section. The maternal characteristics of the MPT and EPT cohorts were similar (Table 1). Notable exceptions are a higher rate of Black race and lower rates of private insurance in the EPT cohort. EPT infants were more likely to receive resuscitation in the delivery room and higher rates of all interventions, including chest compressions.

MORBIDITY

Cardiorespiratory Outcomes

Respiratory illness was the most common morbidity noted (Table 2). With each 1-week increase in gestational age, surfactant administration declined by ~10%. Fifty percent of infants born at 29 weeks received surfactant compared with only 12.8% of those born at 33 weeks. In contrast, 77.8% of EPT infants were treated with surfactant. At 28 days of life, 59.7% of infants born at 29 weeks no longer required any respiratory support; at 33 weeks, 95.4% were without respiratory support. In comparison, only 15% of EPT infants were off all respiratory support by 28 days of life. Broncho-pulmonary dysplasia (based on oxygen use at 28 days of life) occurred in 16% of MPT infants and in 50% of EPT infants. Patent ductus arteriosus (PDA) was diagnosed in only 754 MPT infants (10.7%) compared with 43% of EPT infants. Most MPT infants diagnosed with PDA were not treated, but 150 (19.9% with PDA) were treated with indomethacin or ibuprofen and 34 (4.5% with PDA) with surgical ligation. In contrast, 60% of the EPT infants in whom PDA was diagnosed were treated.

Central Nervous System Outcomes

Overall, 58% of MPT infants were screened with cranial ultrasound, compared with 97% of EPT infants. The frequency with which an ultrasound was performed increased with decreasing gestational age. An intracranial hemorrhage (ICH) was diagnosed in 13.3% of the MPT cohort and the overall percentage did not vary across the gestational ages evaluated. However, with decreasing gestational age the severity of ICH increased; 17.7% of 29-week-old MPT infants who had undergone a head ultrasound had a grade 3 or 4 ICH, whereas only 1.8% of 33-week-old infants screened had a grade 3 or 4 ICH. In contrast to the MPT cohort, 26.9% of EPT infants had an ICH. Almost 30% of MPT infants received a late imaging study, with 26.5% of these showing an abnormal finding, including ventriculomegaly, periventricular leukomalacia, and porencephalic cyst. Among MPT infants, the frequency of these findings did not vary by gestational age.

Retinopathy of prematurity of any degree was diagnosed in 8% of the MPT cohort compared with 54% of the EPT cohort. Severe retinopathy (defined as stage 3 or worse) was

Table 1. Population characteristics of moderately preterm and extremely preterm infants

Characteristics	All MPT, N = 7,057 (%)	EPT, N = 4,310 (%)	P value
Maternal information			
Maternal age (years; mean ± SD)	28.4 ± 6.5	28.1 ± 6.3	0.038
Married (n, %)[a]	3,305 (46.9)	1,896 (44.0)	0.003
Highest level of education[b]			
High school or less	2,522 (50.1)	1,611 (50.4)	0.739
More than high school	2,512 (49.9)	1,584 (49.6)	
Insurance status			
Public or uninsured	4,128 (58.6)	2,607 (60.5)	0.019
Private	2,821 (40.0)	1,627 (37.8)	
Other/unknown	101 (1.4)	74 (1.7)	
Mother's ethnic category			
Hispanic	1,009 (14.3)	601 (14.0)	< 0.0001
Non-Hispanic or Latino	5,871 (83.3)	3,657 (84.9)	
Unknown	171 (2.4)	50 (1.2)	
Mother's race			
Black	2,232 (31.6)	1,703(39.5)	< 0.0001
White	4,025 (57.0)	2,163 (50.2)	
Other	463 (6.6)	279 (6.5)	
Unknown	337 (4.8)	165 (3.8)	
Pregnancy complications			
Multiple birth	2,059 (29.2)	1,193 (27.7)	0.087
Prenatal care	6,834 (97.0)	4,140 (96.1)	0.012
Insulin-dependent diabetes during or before pregnancy	527 (7.5)	225 (5.2)	< 0.0001
Hypertension before pregnancy	799 (11.6)	544 (12.8)	0.059
Hypertension during pregnancy	2,373 (33.7)	1,255 (29.1)	< 0.0001
Clinical chorioamnionitis[b]	498 (7.1)	522 (12.2)	< 0.0001
PROM (> 18 h)[b]	1,267 (19.2)	760 (19.2)	0.969
Antenatal steroids	5,963 (85.3)	3,701 (86.0)	0.281
Antibiotics given in this admission[b]	4,951 (71.6)	3,087 (72.0)	0.650
Magnesium given[b]	3,708 (53.7)	3,011 (70.4)	< 0.0001
Delivery mode			
Vaginal	2,582 (36.6)	1,449 (33.6)	< 0.0001
Cesarean section	4,465 (63.3)	2,855 (66.3)	
Unknown	8 (0.1)	5 (0.1)	
Neonatal information			
Birth weight, kg (mean ± SD)	1,695 ± 422	839.0 ± 251.6	< 0.0001
Male (n, %)	3,682 (52.2)	2,181 (50.7)	0.108
Resuscitation at delivery			
Oxygen and/or bag/mask	5,063 (71.8)	3,948 (91.7)	< 0.0001
Ventilation (CPAP or intubation)	4,292 (60.9)	3,809 (88.5)	< 0.0001
Chest compressions	180 (2.6)	338 (7.9)	< 0.0001

[a]Percentages calculated on the basis of non-missing information.
[b]More than 10% of data are missing for: maternal education (n = 2,023 for MPT and n = 1,115 for Generic Database (GDB)), clinical chorioamnionitis (n = 73 for MPT and n = 14 for GDB), PROM (n = 450 for MPT and n = 353 for GDB), antibiotics given in this admission (n = 140 for MPT and n = 21 for GDB), antibiotics given at 72 h prior to delivery (n = 155 for MPT and n = 23 for GDB), magnesium (n = 155 for MPT and n = 31 for GDB), thermal wrap used (n = 1,071 for MPT and n = 433 for GDB), temperature at admission (n = 768 for MPT and n = 637 for GDB).

Table 2. Neonatal outcomes for moderately preterm infants by gestational age and compared with extremely preterm infants

	Gestational age					All MPT, N = 7,057 (%)	EPT, N = 4,310 (%)	P-value
	29, N = 815 (%)	30, N = 1,066 (%)	31, N = 1,255 (%)	32, N = 1,712 (%)	33, N = 2,209 (%)			
Cardiorespiratory	410 (50.3)	414 (38.8)	376 (30.0)	351 (20.5)	282 (12.8)	1,833 (26.0)	3,041 (77.8)	<0.0001 *<0.0001
Surfactant	778 (95.5)	1,032 (96.8)	1,230 (98.0)	1,673 (97.7)	2,156 (97.6)	6,869 (97.3)	3,523 (81.7)	0.0031 *<0.0001 <0.0001 *<0.0001
Respiratory support at 28 days among those alive	456 (59.7)	740 (73.5)	1,023 (85.5)	1,469 (92.5)	1,932 (95.4)	5,620 (85.4)	549 (15.7)	
None	35 (4.58)	34 (3.38)	24 (2.01)	25 (1.57)	16 (0.79)	134 (2.04)	1,329 (38.1)	
Ventilator	42 (5.50)	28 (2.78)	6 (0.50)	6 (0.38)	4 (0.20)	86 (1.31)	690 (19.8)	
CPAP	231 (30.2)	205 (20.4)	144 (12.0)	88 (5.54)	73 (3.60)	741 (11.3)	921 (26.4)	
Oxygen only	160 (19.7)	167 (15.7)	148 (11.8)	133 (7.78)	146 (6.62)	754 (10.7)	1,637 (41.9)	<0.0001 *<0.0001 0.0005 *<0.0001
PDA treatment in those with PDA diagnosis	100 (62.5)	114 (68.7)	113 (76.4)	113 (85.0)	126 (86.3)	566 (75.2)	636 (38.9)	
None	50 (31.3)	48 (28.9)	25 (16.9)	16 (12.0)	11 (7.53)	150 (19.9)	696 (42.5)	
Medical	10 (6.25)	4 (2.41)	8 (5.41)	3 (2.26)	9 (6.16)	34 (4.52)	92 (5.6)	
Surgery	0 (0)	0 (0)	2 (1.35)	1 (0.75)	0 (0)	3 (0.40)	213 (13.0)	
Both medical and surgical								
Central nervous system								
Head ultrasound first 28 days (n, %)[a]	769 (94.4)	919 (86.5)	952 (76.2)	821 (48.9)	607 (28.2)	4,068 (58.4)	3,798 (97.14)	<0.0001 *<0.0001
Any grade intracranial hemorrhage	113 (14.8)	130 (14.3)	114 (12.1)	98 (12.0)	82 (13.7)	537 (13.3)	995 (26.93)	0.3250 *<0.0001
Max grade intracranial hemorrhage								0.0047 *<0.0001
Grade 1	72 (63.7)	85 (65.4)	82 (71.9)	85 (86.7)	58 (70.7)	382 (71.1)	334 (33.6)	
Grade 2	21 (18.6)	30 (23.1)	16 (14.0)	5 (5.10)	13 (15.9)	85 (15.8)	195 (19.6)	
Grade 3	8 (7.08)	11 (8.46)	4 (3.51)	4 (4.08)	5 (6.10)	32 (5.96)	210 (21.1)	
Grade 4	12 (10.6)	4 (3.08)	12 (10.5)	4 (4.08)	6 (7.32)	38 (7.08)	256 (25.7)	
Late imaging done	565 (70.8)	616 (59.4)	501 (40.8)	233 (14.2)	109 (5.21)	2,024 (29.8)	3,137 (80.39)	<0.0001 *<0.0001
Late image Abnormal	127 (22.5)	151 (24.5)	133 (26.5)	78 (33.6)	48 (44.0)	537 (26.5)	828 (26.40)	<0.0001 *0.9103

Table 2. Continued

	Gestational age							
	29, N = 815 (%)	30, N = 1,066 (%)	31, N = 1,255 (%)	32, N = 1,712 (%)	33, N = 2,209 (%)	All MPT, N = 7,057 (%)	EPT, N = 4,310 (%)	P-value
Exam for ROP	691 (84.8)	770 (72.2)	521 (41.5)	299 (17.5)	116 (5.25)	2,397 (34.0)	3,364 (86.04)	<0.0001 *<0.0001
ROP stage 3 or greater	2 (0.29)	1 (0.13)	1 (0.19)	0 (0)	0 (0)	4 (0.17)	372 (11.06)	<0.0001 *<0.0001
Gastrointestinal and Nutrition Outcomes								
Days to regain weight (mean ± SD)	10.3 ± 5.3	10.0 ± 4.5	9.6 ± 4.3	9.9 ± 10.4	9.6 ± 13.0	9.8 ± 9.3	9.9 ± 7.9	<0.0001 *0.66
Fed human milk first 28 days	731(90.0)	952(89.6)	1,065(85.1)	1,381(80.9)	1,784(80.9)	5,913(84.0)	3,431(96.5%)	<0.0001 *<0.0001
First oral feed, day (mean ± SD)[b]	28.5 ± 12.1	22.5 ± 15.7	15.5 ± 10.3	9.7 ± 14.7	5.9 ± 15.7	13.5 ± 16.2	NA	<0.0001
Full oral feed, day (mean ± SD)[b]	45.6 ± 13.2	38.0 ± 12.5	29.4 ± 12.3	22.2 ± 16.7	15.1 ± 14.7	26.0 ± 17.7	NA	<0.0001
NEC, any	37 (4.6)	40 (3.8)	28 (2.2)	33 (1.9)	31(1.4)	169 (2.4)	343 (8.8%)	<0.0001 *<0.0001
Infection and hematology								
Early-onset infection (n, %)[a]	10 (1.23)	17 (1.60)	10 (0.80)	6 (0.35)	9 (0.41)	52 (0.74)	71 (1.8%)	0.0004 *<0.0001
Organism[b]								0.762 0.116
Group B Strep	1 (10.0)	2 (11.8)	3 (30.0)	0 (0)	2 (22.2)	8 (15.4)	10 (14.1%)	
E. coli	2 (20.0)	2 (11.8)	1 (10.0)	2 (33.3)	2 (22.2)	9 (17.3)	20 (23.6%)	
Other Gram positive	3 (30.0)	11 (64.7)	4 (40.0)	4 (66.7)	3 (33.3)	25 (48.1)	19 (26.8%)	
Other Gram negative	3 (30.0)	1 (5.88)	2 (20.0)	0 (0)	0 (0)	6 (11.5)	16 (22.5%)	
Other	1 (10.0)	1 (5.88)	0 (0)	0 (0)	2 (22.2)	4 (7.69)	6 (8.5%)	
Infant received antibiotics for ⩾ 5 days	170 (20.9)	189 (17.7)	200 (16.0)	194 (11.3)	223 (10.1)	976 (13.8)	1,465 (37.5)	<0.0001 *<0.0001
Late-onset infection	67 (8.26)	49 (4.62)	39 (3.13)	31 (1.82)	35 (1.59)	221 (3.15)	741 (19.0)	<0.0001 *<0.0001
Phototherapy given	749 (91.9)	959 (90.0)	1,070 (85.3)	1,359 (79.4)	1,515 (68.7)	5,652 (80.1)	NA	<0.0001
Phototherapy Days (mean, IQR)	5.0 (3.0,6.0)	4.9 (3.0,6.0)	4.4 (2.0,6.0)	4.0 (2.0,5.0)	3.8 (2.0,5.0)	4.3 (2.0,5.0)	NA	<0.0001
Highest total serum bilirubin (mean, IQR)	8.3 (6.8,9.7)	8.7 (7.3,10.0)	9.1 (7.7,10.4)	9.6 (8.1,11.2)	9.9 (8.3,11.6)	9.3 (7.7,10.9)	6.8 (5.6, 7.8)	<0.0001 *<0.0001

Full oral feeds (n = 1,025 overall, 29 weeks GA = 157, 30 weeks GA = 182, 31 weeks GA = 198, 32 weeks GA = 241, 33 weeks GA = 247). Date of first oral feed was not tracked in the EPT cohort.
[a]Percentages calculated on the basis of non-missing information. All categories have <10% missing data. First P-value compares the MPT gestational age distribution. Second P-value with an * compares all MPT vs. EPT.
[b]More than 10% of data are missing for: days to regain weight (n = 944 overall, 29 weeks GA = 76, 30 weeks GA = 90, 31weeks GA = 136, 32 weeks GA = 207, 33 week GA = 435).

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diagnosed in 11% of the EPT cohort, but in only four (0.17%) infants in the MPT cohort—all had stage 3 disease and none needed treatment.

Nutrition and Infectious Outcomes

MPT infants took, on average, 10 days to regain their birth weight. Although this figure varied significantly across the gestational age spectrum, the small differences are unlikely to be clinically meaningful. EPT infants regained their birth weight in a similar time frame of 9.9 days. The first oral feed was offered to MPT infants at about 33 weeks' PMA, regardless of GA at birth, although the time to reach that benchmark varied by GA. Less mature infants took longer to achieve full enteral feeds (17 days at 29 weeks' GA) than did more mature infants (9 days at 33 weeks' GA). The vast majority of both MPT and EPT infants were fed human milk (84% vs. 99%), with less mature MPT infants more likely to receive human milk than more mature MPT infants (90% at 29 weeks vs. 80.9% at 33 weeks, $P < 0.001$).

As expected, necrotizing enterocolitis was diagnosed less frequently in MPT infants than in EPT infants (2.4% vs. 8%), and was more likely to be treated with medical treatment only (1.7% vs. 4%).

MPT infants experienced early-onset sepsis at similar rates to EPT (0.7% vs. 1.8%) with a predominance of Gram-positive organisms, including Group B *Streptococcus* (33/52 (63%) infections). No infants in either cohort were infected with *Listeria*. Late-onset infection occurred less frequently in MPT than in EPT infants (3.2% vs. 19%).

Mortality and Hospital Course

Overall, 2.9% of the MPT cohort died compared with 24% of the EPT cohort. Deaths occurred early, with most MPT infants dying at 7–12 days of age. The primary cause of death was related to congenital malformation (43%) in the MPT cohort and to respiratory distress syndrome in the EPT cohort (Table 2). Although EPT infants remained in the hospital for an average 99 ± 46 days and usually were hospitalized past their due date, MPT infants were discharged at an earlier postmenstrual age, with 38.1% discharged by 36 weeks' PMA. The reasons for MPT infants remaining in the hospital at 36 weeks included inadequate oral intake (69.8%), apnea or bradycardia (37.5%), and continued respiratory issues (16.7%). By 40 weeks' PMA, 83.9% of MPT infants were discharged home with an average weight of 2.4 kg, compared with 58% of EPT infants.

DISCUSSION

Our cohort study contributes valuable information that will inform both clinicians and parents about the expected outcomes of these infants. The vast majority of neonatal clinical trials have focused on EPT infants. Yet, MPT infants experience many of the same risks for adverse outcomes, albeit at lower rates than EPT infants. Given their much larger numbers in the population, MPT infants spend a substantial number of days in intensive care units and contribute significantly to the societal costs of neonatal intensive care and to the emotional toll on their families. The burden of disease borne by MPT infants is substantial. For example, based on estimates from our study and from the national birth data, 12,447 MPT and 10,907 EPT infants suffered an ICH (1). This suggests that from an absolute number perspective, the MPT cohort may contribute to the burden of disease more than does the EPT cohort.

Research that focuses on the large group of MPT infants may generate novel ideas to support optimal growth and development and reduce the duration of hospitalization. Conditions associated with developmental immaturity, including apnea and bradycardia and inadequate oral feeding, were the predominant causes of continued hospitalization at 36 weeks. Across the MPT infants' GA continuum, oral feedings were first introduced, on average, at 33 weeks' PMA. Approaches for assessing an infant's readiness for oral feeding vary (13). It is possible that a more standardized approach and earlier introduction of oral feeding may facilitate the development of this skill. Oral feeding of the MPT infant is an area ripe for additional investigation. There are also differences in the approach to treatment of apnea of prematurity, including when to discontinue treatment with methylxanthines. After discontinuation of methylxanthines, most neonatologists in the United States continue hospitalization for an apnea-free period of observation of variable duration (14,15). It is not known whether being discharged on methylxanthine treatment is a safe and effective method to reduce the length of stay.

An often-stated "rule of thumb" is that families may expect a preterm infant to be discharged home by their estimated due date. However, among MPT infants, 38% were discharged home by 36 weeks' PMA, 4 weeks prior to their estimated due date, and 43% were discharged home by 40 weeks. Infants with congenital malformation were overrepresented in the population remaining in hospital at 40 weeks' PMA.

Our study can be compared with an analysis of preterm morbidity led by Manuck and conducted in the NICHD Maternal Fetal Network as a study nested within a large observational study to develop quality measures for intrapartum obstetric care (Assessment of Perinatal Excellence; APEX) (16,17). Mothers who were at at least 23 weeks of gestation and up to $35^{6/7}$ weeks of gestation with a live fetus on admission had their data abstracted from records during a 24-h period of randomly selected days from 25 hospitals nationwide between 2008 and 2011; the main study included 115,502 women. In the nested study, infants with anomalies and multiple gestations were excluded, as were infants who died in the delivery room and those >36 weeks. Once all exclusions were applied, the original sample of 118,422 infants was reduced to 8,334 infants, of whom 1,877 were MPT. Thus, a subset of the APEX population included MPT infants of similar gestational age (29–33 weeks) as our cohort. The outcomes evaluated were reported as major morbidity, as defined by pulmonary hypertension, intraventricular hemorrhage of grade 3 or 4, hypoxic–ischemic encephalopathy,

necrotizing enterocolitis stage 2 or 3, or bronchopulmonary dysplasia. The rates of major morbidity increased with decreasing GA, which parallels our data. The rate of major morbidity was 22.5% at 29 weeks and decreased to 4.2% at 33 weeks. Our study includes a larger sample size and a more robust slate of outcome variables.

Another recent cohort study, The Late and Moderately Preterm Birth Study (LAMBS), was conducted by Boyle *et al.* (18) in the United Kingdom. This prospective, population-based study included outcomes for infants born at 32–36 weeks' gestation from a geographic area in Northern England in 2009–2010. The study included 1,376 infants, of whom 1,125 (99.5%) were discharged home. This cohort overlaps with our study at 32 and 33 weeks' gestation ($n=132$), but excluded infants with congenital anomalies. Their findings were similar to ours in that MPT infants had a gradient of increasing risk with decreasing gestation, including an increasing length of stay.

Our study has several strengths. The infants were delivered at 18 level 3–4 centers across the United States and include both inborn and outborn infants, which contributes to the generalizability of the information. Another strength is that all data were collected by experienced research staff using standardized definitions, which were identical between the MPT and EPT cohorts. The large cohort allows us to present results by each week of GA, providing more precise information for counseling. One limitation is that information on the reason for preterm delivery was not uniformly collected for either inborn or outborn infants. Another possible concern is that the NRN population may not reflect similar populations of MPT that are not transferred to level 3 centers. Ninety percent of the cohort in this population was born at the NRN center and only 10% was transferred after birth. We have previously compared the outcome of infants in NRN centers and in the Vermont Oxford Network of both academic and private practice level 2 and level 3 units, and found the infant population to be comparable (19). Thus, we believe that the findings in this study are generalizable to other US neonatal intensive care units.

CONCLUSION
About 100,000 MPT infants are born in the United States each year but remain an understudied group. Because of the high numbers of MPT births in the United States, morbidities in this group are an important public health concern. This study will inform the counseling of parents faced with the birth of a MPT infant. MPT infants experience significant morbidity, as evidenced by the high rates of respiratory support and prolonged hospitalization. Such morbidity deserves focused research with an aim to develop novel therapeutic and prevention approaches.

AUTHOR CONTRIBUTIONS
The contributions made by each author for this manuscript are given in detail below.
The MPR Subcommittee investigators have monthly conference calls, during which protocol design and implementation issues are discussed, manuscripts are reviewed, and input obtained. The following authors have made significant contributions as determined by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals:
Michele C. Walsh, MD, MS, is the Lead Principal Investigator (PI) at Case Western Reserve University (CWRU) and the Chair of the Moderately Preterm Registry Protocol Subcommittee. She developed the study and managed protocol implementation. As the PI at CWRU, she oversaw enrollment at the site—which enrolled 302 infants in this study. Walsh drafted the manuscript and received input from the authors below as part of manuscript revision. Walsh had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Edward F. Bell, MD, is the PI at the University of Iowa and a member of the Moderately Preterm Registry Protocol Subcommittee. He helped develop the study and manage protocol implementation. As the PI at the University of Iowa, he oversaw enrollment at the site—which enrolled 495 infants in this study. He contributed critical revisions of the manuscript and approved the final manuscript for submission.
Sarah Kandefer, BS, served as the primary statistician for the study, and completed the statistical analyses for the paper. She developed the tables for the paper and provided critical revision to the manuscript and approved the final version of the manuscript.
Waldemar A. Carlo, MD, is the PI at the University of Alabama at Birmingham (UAB) and a member of the Moderately Preterm Registry Protocol Subcommittee. He helped develop the study and manage protocol implementation. As the PI at UAB, he oversaw enrollment at the site—which enrolled 537 infants in this study. He contributed critical revisions of the manuscript and approved the final manuscript for submission.
Carl T. D'Angio, MD, is the PI at the University of Rochester and a member of the Moderately Preterm Registry Protocol Subcommittee. He helped develop the study and manage protocol implementation. As the PI at the University of Rochester, he oversaw enrollment at the site—which enrolled 617 infants in this study. He contributed critical revisions of the manuscript and approved the final manuscript for submission.
Abbot R. Laptook, MD, is the PI at Brown University and a member of the Moderately Preterm Registry Protocol Subcommittee. He helped develop the study and manage protocol implementation. As the PI at Brown University, he oversaw enrollment at the site—which enrolled 424 infants in this study. He contributed critical revisions of the manuscript and approved the final manuscript for submission.
Pablo J. Sanchez, MD, is the PI at Nationwide Children's Hospital and a member of the Moderately Preterm Registry Protocol Subcommittee. He helped develop the study and manage protocol implementation. As the PI at Nationwide Children's Hospital, he oversaw enrollment at the site—which enrolled 512 infants in this study. He contributed critical revisions of the manuscript and approved the final manuscript for submission.
Barbara J. Stoll, MD, is the PI at Emory University and the Vice Chair of the Moderately Preterm Registry Protocol Subcommittee. She helped develop the study and manage protocol implementation. As the PI at Emory University, she oversaw enrollment at the site—which enrolled 335 infants in this study. She contributed critical revisions of the manuscript and approved the final manuscript for submission.
Seetha Shankaran, MD, is the PI at Wayne State University and a member of the Moderately Preterm Registry Protocol Subcommittee. She helped develop the study and manage protocol implementation. As the PI at Wayne State University, she oversaw enrollment at the site—which

enrolled 363 infants in this study. She contributed critical revisions of the manuscript and approved the final manuscript for submission.

Krisa P. Van Meurs, MD, is the PI at Stanford University and a member of the Moderately Preterm Registry Protocol Subcommittee. She helped develop the study and manage protocol implementation. As the PI at Stanford University, she oversaw enrollment at the site—which enrolled 205 infants in this study. She contributed critical revisions of the manuscript and approved the final manuscript for submission.

Betty R. Vohr, MD, is the Follow-up PI at Brown University and a member of the Moderately Preterm Registry Protocol Subcommittee. She helped develop and implement the study and contributed critical revisions of the manuscript and approved the final manuscript for submission.

Rosemary D. Higgins, MD, served as the Program Scientist for the NICHD NRN and is a member of the Moderately Preterm Registry Protocol Subcommittee. Dr Higgins helped develop the protocol, oversaw recruitment, and assisted with data edits from the sites. She also provided critical revision to the manuscript and approved the final version of the manuscript.

Abhik Das, PhD, is the PI for the NRN Data Coordinating Center and a member of the Moderately Preterm Registry Protocol Subcommittee. Das oversaw all aspects of the statistical analysis, provided critical revisions to the manuscript, and approved the final version of the manuscript.

Ellen C. Hale, BS, RN, CCRC, is the Coordinator at Emory University and a member of the Moderately Preterm Registry Protocol Subcommittee. She helped develop the study and manage protocol implementation. As the Coordinator at Emory University, she enrolled 335 infants in this study. She contributed critical revisions of the manuscript and approved the final manuscript for submission.

Nancy S. Newman, RN, is the Coordinator at CWRU and a member of the Moderately Preterm Registry Protocol Subcommittee. She helped develop the study and manage protocol implementation. As the Coordinator at CWRU, she enrolled 302 infants in this study. She contributed critical revisions of the manuscript and approved the final manuscript for submission.

Kurt Schibler, MD, is the PI at Cincinnati Children's Medical Center (CCMC). As the PI he oversaw enrollment at the site—which enrolled 683 infants in this study. He contributed critical revisions of the manuscript and approved the final manuscript for submission.

Barbara Schmidt, MD, is the PI at the University of Pennsylvania. As the PI she oversaw enrollment at the site—which enrolled 511 infants in this study. She contributed critical revisions of the manuscript and approved the final manuscript for submission.

C. Michael Cotten, MD, MHS, is the PI at Duke University. As the PI he oversaw enrollment at the site—which enrolled 457 infants in this study. He contributed critical revisions of the manuscript and approved the final manuscript for submission.

Kathleen A. Kennedy, MD, MPH, is the PI at the University of Texas Health Science Center at Houston. As the PI she oversaw enrollment at the site—which enrolled 456 infants in this study. She contributed critical revisions of the manuscript and approved the final manuscript for submission.

Brenda B. Poindexter, MD, MS, is the PI at Indiana University. As the PI, she oversaw enrollment at the site—which enrolled 333 infants in this study. She contributed critical revisions of the manuscript and approved the final manuscript for submission.

Kristi L. Watterberg, MD, is the PI at the University of New Mexico. As the PI, she oversaw enrollment at the site—which enrolled 242 infants in this study. She contributed critical revisions of the manuscript and approved the final manuscript for submission.

William E. Truog, MD, is the PI at Children's Mercy Hospital, Kansas City. As the PI, he oversaw enrollment at the site—which enrolled 172 infants in this study. He contributed critical revisions of the manuscript and approved the final manuscript for submission.

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