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The problems of moderate preterm infants

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ABSTRACT

Moderate preterm infants are the largest group of preterm infants but are an understudied population. Care practices are adapted from studies of full term infants or extremely preterm infants. Studies are needed to tailor treatments for this vulnerable population. The NRN began investigation in this population with a registry of characteristics, and neonatal outcomes of these infants. This work compares outcomes of MPR with those of full term infants reported in the literature.

Background

The NICHD Neonatal Research Network (NRN) was formed to evaluate management of newborn infants, including both generally accepted care and novel interventions. Extremely preterm infants (<29 weeks gestational age) represent only 0.69% of those born in the United States,[1] yet these infants have been the subjects of 89% of studies conducted by the NICHD Neonatal Research Network (NRN)[2] between 1999 and 2010. Moderately, preterm neonates (MPT = 29–33 6/7 weeks gestational age) constituted 2.06% of all births in the United States in 2014.[1] The moderate preterm infant group has never been studied in a systematic way in the NRN, or in any other research network. Indeed, much of the care of these infants is either extrapolated from studies of extremely preterm newborns or from the care of full-term (FT) infants. Recent data suggest that these infants are in fact at risk for substantial short- and longer-term morbidity.[3] Because of their large numbers, (82,154 infants in 2014), long-hospital stays and morbidities, MPT represent a substantial proportion of the infants in our newborn intensive care units. To address this unmet need the NRN formed a registry of MPT with the goal of developing a comprehensive assessment of the pregnancy characteristics and neonatal outcomes of those born moderately preterm. It is hoped that such data will inform the design of clinical trials to improve the management and outcomes of moderately preterm infants.

Design and content of the registry

From 2012 to 2013 the NRN established a registry for all inborn and outborn moderately preterm infants born at 29 through 33 weeks' gestational age. The content of the registry was based on the longstanding registry of EPT infants maintained by the NRN. Standardized definitions were used. Data were abstracted from the medical records of the mothers and infants by trained research nurses, and electronically transmitted to the central data center at RTI International. All centers had approval for the study from their Institutional Review Boards either by waiver of consent or by written consent of the patients' parents.

Neonatal information included birthweight (BW), gestational age (GA), sex, race/ethnicity, mode of delivery, delivery room interventions, final outcome, and cause of death for infants who did not survive to hospital discharge. Gestational

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age 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 >12 h, and included respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), modified Bell's Stage ≥IIA necrotizing enterocolitis (NEC),[4] intracranial hemorrhage according to the criteria of Papile,[5] severe intracranial hemorrhage (Grade III or IV), periventricular leukomalacia, retinopathy of prematurity (ROP),[6] bronchopulmonary dysplasia (BPD) defined as supplemental oxygen at 36 weeks' postmenstrual age (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 MPT infants based on usual center practice.

Population characteristics

In the 2 years of the registry, 7057 infants were identified, of whom 636 (9.0%) were outborn. The range of enrollment across the 18 centers in the NRN was from 150 to 660 infants per center. During the same period, about 150,000 FT infants and 3946 EPTs were admitted to NRN sites. Table 1 summarizes the population characteristics and contrasts these with published reports of the characteristics of full-term infants.[7,8] Overall, 97.1% of MPT infants survived to 40 weeks gestational age.

Problems experienced by MPT

The care received in the delivery room by MPTs is shown in Table 2 and is compared to the resuscitation received by full-term infants.[9] In total, 53% were managed with CPAP and without intubation. The problems experienced by MPTs are dramatically worse than those born at full-term gestation.

Table 1 – Maternal and infant characteristics of MPT and full-term infants.

	Moderate preterm	Full-term infants
Maternal characteristics		
Age, mean (SD)	28.5 (6.5)	na
Race/ethnicity (%)		
Hispanic	15	28[a]
Black, non-hispanic	28	20
White, non-hispanic	47	28
Other	10	4
Any prenatal visit (%)	98	80[a]
Antenatal steroids (%)	88	na
Insulin-dependent diabetes (%)	8	6[b]
Hypertension (%)	35	na
Multiple birth (%)	30	28[a]
Infant characteristics		
Birthweight (g), mean (SD)	1711 (410)	3192 (524)[b]
Gestational age, weeks mean (SD)	31.5 (1.4)	Ref
Male (%)	52	51.2[a]
Birth defect/syndrome (%)	8	0.8[a]

[a] Boyle et al.[7]
[b] Prefumo et al.[8]

Table 2 – Infant care in the delivery room.

	Moderate preterm	Full-term infants[a]
Oxygen (%)	70	na
CPAP (%)	53	na
Tracheal intubation (%)	15	0.08
Chest compressions (%)	2	0.06
Epinephrine (%)	1	0.04
Thermal WRAP (%)	20	0

[a] Adapted with permission from Wyckoff et al.[9]

The duration of hospitalization of MPTs averaged 33.3 days with an interquartile range of 20–43 days while full-term infants averaged a 2-day stay.

Totally, 624 infants (8.9% of the cohort) had a major malformation or chromosomal syndrome. The incidence of malformation in full-term infants is estimated at 3%.[10] The large number of affected MPT infants was somewhat surprising. Among those who died, malformations were the largest contributor to death at 43%, followed by necrotizing enterocolitis (8%), lung disease (6%), and CNS injury (6%).

Rates of key in-hospital outcomes for MPT and FT infants are shown in Table 3.

Respiratory disease occurred in 16% of our MPT, but is estimated at 8% in the full-term population.[11] In a population of term infants Edwards et al. identified that 8% had respiratory disease at 39 weeks. Our rate of 70% in MPT far exceeds that rate. Both early-onset and late-onset sepsis occurred 6–20 times more frequently in MPT than in full-term infants.[12,13] Chen et al.[14] showed a rate of sepsis or meningitis in term infants of 1.6/1000, which is substantially lower than our rate of 7.4/1000. Necrotizing enterocolitis occurred 35 times more frequently in MPT than in full-term infants.[15] Maayan–Metzger studied the incidence of NEC in full-term infants and found a very low rate in full-term infants and that

Table 3 – Key in-hospital morbidities.

	Moderate preterm	Full-term
Bronchopulmonary dysplasia (%)	16	na
Early-onset infection (%)	0.6	0.14[b]
Late-onset sepsis (%)	2.8	0.01[d]
Necrotizing enterocolitis (%)	2.3	0.07[c]
Cranial ultrasound done (%)	56	1.4[a]
Any intracranial hemorrhage (%)	12	8[a]
Severe intracranial hemorrhage (%)	2	1[a]
Periventricular leukomalacia (%)	8	na
ROP exam done (%)	33	0
Any ROP (%)	8	0
Severe ROP (%)	0.1	0
Treated for ROP (%)	0	0

[a] Looney et al.[16]
[b] Shakib et al.[12]
[c] Bizzarro et al.[13]
[d] Maayan-Metzger et al.[15]