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The Problems of Moderate Preterm Infants

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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 US¹, yet these infants have been the subjects of 89% of studies conducted by the NICHD Neonatal Research Network (NRN) between 1999 and 2010². Moderately preterm neonates (MPT 29–33 6/7 weeks gestational age) constituted 2.06% of all births in the United States in 2014¹. 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 morbidity³. 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

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Institutional Review Boards either by waiver of consent or by written consent of the patients' parents.

Neonatal information included birth weight (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 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 hours, 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 Papile⁵, 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 hours of age. Cranial sonograms and ROP exams were performed on MPT infants based on usual center practice.

Population characteristics

In the two years of the registry, 7,057 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 3,946 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 Fifty-three percent were managed with CPAP and without intubation. The problems experienced by MPTs are dramatically worse than those born at full term gestation. The duration of hospitalization of MPTs averaged 33.3 days with an interquartile range of 20 to 43 days while full term infants averaged a two day stay.

Six hundred twenty-four 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 to 20 times more frequently in MPT than in full term infants.^{12,13} Chen and colleagues showed a rate of sepsis or meningitis in term infants of

1.6/ 1000 which is substantially lower than our rate of 7.4/ 1000¹⁴. 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 most cases occurred in those with cyanotic heart disease. It is more difficult to compare the prevalence of intracranial hemorrhage between MPT and term infants because asymptomatic term infants rarely undergo neuroimaging. Looney et al evaluated MRI in a cohort of 88 term infants in a study of brain development. He found 7 (8%) infants with silent intracranial hemorrhage which is less than our 13.3% rate¹⁶.

As expected retinopathy of prematurity was a rare outcome.

Our data are among the first to describe a large unselected contemporary cohort of MPT in the United States. These infants experienced considerable in-hospital morbidity and prolonged hospitalizations. Our findings expand the data available to inform both obstetricians and neonatologists on MPT outcomes. They, in turn, can use the data to counsel families on the expected course of these infants. The morbidities of MPTs are the same as those experienced by EPTs but are less frequent among MPTs than EPTs.¹⁷ However, when contrasted to the outcomes reported in cohorts of term infants, the morbidities are much more common among MPTs.

Our MPT outcome data are comparable to those reported by Escobar and coworkers in 2006; however, fewer outcome measures were assessed in their study¹⁸. Manuck and co-investigators in the NICHD Maternal-Fetal Medicine Network performed a nested cohort analysis of all liveborn singleton infants between 2008–2011 with gestational ages ranging from 23 to 37 weeks¹⁹. They excluded any infants with known anomalies, which makes it difficult to compare their sample to our population. We are also unable to compare our cohort to theirs as they focused on a composite outcome of major or minor morbidity.

Much of the prior work in moderate preterm infants has focused on respiratory outcomes. Colin and colleagues conducted a systematic review to summarize the evidence demonstrating respiratory system vulnerability in infants aged 32 to 36 weeks' GA using all studies that reported epidemiologic data and respiratory morbidity from 2000 to 2009²⁰. Of the 24 studies identified, 16 were retrospective population-based cohort studies; 8 studies were observational. These studies consistently revealed that infants born at 32 to 36 weeks' GA, experience substantial respiratory morbidity compared with term infants. Levels of morbidity were, at times, comparable to those observed in very preterm infants. There is ample evidence that MPT carry respiratory morbidity into the future. Hibbs followed a cohort of 300 preterm infants born at 28 – 34.6 weeks gestational age and found that recurrent wheezing was identified in 45.7% of the cohort in the first year of life²¹. Saarenpää and colleagues studied 160 former very low birthweight infants in Finland in adulthood and found that even those without a diagnosis of bronchopulmonary dysplasia had measurable derangements in pulmonary function tests²².

While the hospital outcomes for most moderate preterm infants are favorable, the health and economic impact cannot be underestimated. A Scandinavian study has evaluated the economic impact among adult outcomes of those born preterm. They determined that

moderate preterm infants (defined as 33–36 weeks and marginal preterm infants (37–38 weeks) accounted for 74% of the economic burden of prematurity²³. The authors estimated that the cost savings of eliminating these moderate and marginal preterm births in Sweden in 2002 for a single year was €65 million. In another study in Norway, 1 in 24 infants born between 31 and 33 weeks gestation was receiving disability payments at adult age compared with 1 in 59 born at term ($p < 0.001$)²⁴. Comparable data have not been collected in the US but are desperately needed.

Unanswered Management Questions in MPT infants

There are numerous management questions that are unanswered for MPT infants. The majority of trials conducted have focused on the treatment of Respiratory Distress Syndrome. Because a large number of these MPT are managed on CPAP alone, trials have focused on minimally invasive methods for delivering surfactant without endotracheal intubation. These trials have demonstrated that administration of surfactant with the INSURE technique (intubate, surfactant, extubate) is both safe and effective. However, the practice is less likely to be successful if premedication with an analgesic is used.²⁵

Management trials focused on other systems do not exist. Issues ripe for exploration include such basic treatment questions as:

1. What is the optimal weight to discontinue care in a neutral thermal environment?
2. How can the ability to feed orally be enhanced?
3. Is it safe to discharge infants home on methylxanthines?
4. What is the optimal caloric density for post discharge enteral feedings?
5. What is the safe upper limit for bilirubin exposure in MPT infants?
6. Does skin to skin care improve the neurodevelopmental outcomes of MPT infants?

The NRN has launched a randomized trial comparing the efficacy of two different weights to move from an incubator to an open crib in medically stable MPT with the primary outcome of time to discharge. Recruitment is nearing completion. A second RCT has been designed to test the safety and utility of discharge home on caffeine for infants who have completed a 5 day period free from apnea to test if these infants are protected from apneic events in the 28 days post discharge.

Conclusion

Moderate preterm infants represent about 32% of all preterm births in the United States. In 2014 there were 82,154 moderate preterm infants born. They are an understudied but important group. There is a need for neonatal clinical trials focused on this group as trials may improve outcomes and health resource utilization.

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Table 1

Maternal and Infant Characteristics of MPT and fullterm 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

^aBoyle^bPrefumo

Table 2

Infant Care in the Delivery Room

	Moderate Preterm	Fullterm Infants [*]
Oxygen (%)	70	Na
CPAP (%)	53	na
Tracheal Intubation (%)	15	0.08
Chest compressions (%)	2	0.06
Epinephrine (%)	1	0.04
Thermal Wrap (%)	20	0

^{*} Data from: Wyckoff MH, Perlman JM, Laptook AR. Use of Volume expansion during delivery room resuscitation in near term and term infants. *Pediatrics* 2005; 115: 950–955.

Table 3

Key In-hospital Morbidities

	Moderate Preterm	Full Term
Bronchopulmonary dysplasia (%)	16	na
Early onset infection (%)	0.6	0.14 ^c
Late-onset sepsis (%)	2.8	0.01 ^e
Necrotising enterocolitis (%)	2.3	0.07 ^d
Cranial ultrasound done (%)	56	1.4 ^a
Any intracranial hemorrhage (%)	12	8 ^b
Severe intracranial hemorrhage (%)	2	1 ^b
Periventricular Leukomalacia (%)	8	na
ROP exam done (%)	33	0
Any ROP (%)	8	0
Severe ROP (%)	0.1	0
Treated for ROP (%)	0	0

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