Neurodevelopmental Outcomes of Infants Born at <29 Weeks of Gestation Admitted to Canadian Neonatal Intensive Care Units Based on Location of Birth

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Objective To compare mortality and neurodevelopmental outcomes of outborn and inborn preterm infants born at <29 weeks of gestation admitted to Canadian neonatal intensive care units (NICUs).

Study design Data were obtained from the Canadian Neonatal Network and Canadian Neonatal Follow-up Network databases for infants born at <29 weeks of gestation admitted to NICUs from April 2009 to September 2011. Rates of death, severe neurodevelopmental impairment (NDI), and overall NDI were compared between outborn and inborn infants at 18-21 months of age, corrected for prematurity.

Results Of 2951 eligible infants, 473 (16%) were outborn. Mean birth weight (940 ± 278 g vs 897 + 237 g), rates of treatment with antenatal steroids (53.9% vs 92.9%), birth weight small for gestational age (5.3% vs 9.4%), and maternal college education (43.7% vs 53.9%) differed between outborn and inborn infants, respectively (all *P* values <.01). The median Score for Neonatal Acute Physiology-II (*P* = .01) and Apgar score at 5 minutes (*P* < .01) were higher in inborn infants. Severe brain injury was more common among outborn infants (25.3% vs 14.7%, *P* < .01). Outborn infants had higher odds of death or severe NDI (aOR 1.7, 95% CI 1.3-2.2), death or overall NDI (aOR 1.6, 95% CI 1.2-2.2), death (aOR 2.1, 95% CI 1.5-3.0), and cerebral palsy (aOR 1.9, 95% CI 1.1-3.3).

Conclusions The composite outcomes of death or neurodevelopmental impairment were significantly higher in outborn compared with inborn infants admitted to Canadian NICUs. Adverse outcomes were mainly attributed to increased mortality and cerebral palsy in outborn neonates. *(J Pediatr 2017;■■:■■-■■).*

See editorial, p •••

Rates of neurodevelopmental impairment (NDI) increase as gestational age (GA) decreases.[1,2] A key factor that has been identified to improve outcomes of extremely low GA neonates is optimal support at birth.[1,2] Centralized perinatal care was introduced to optimize care of mothers and neonates during the perinatal period by providing access to tertiary care centers, but the evidence for this has been classified as "weak."[3] Canada has a centralized perinatal care system, and elective transfer is recommended for mothers with threatened preterm labor before 30-32 weeks of gestation. Despite all efforts, approximately 15%-20% of these infants are born outside of tertiary perinatal centers.[4,5] Infants born outside tertiary care centers (outborn) have higher rates of adverse neonatal outcomes than infants born within tertiary care centers (inborn).[4,6-10] However, the literature analyzing neurodevelopmental outcomes of outborn infants is limited. A cohort study from Australia reported no significant differences in neurodevelopmental outcome at 2-3 years of age between outborn and inborn extremely preterm infants born between 1998 and 2004,[11] albeit the rate of outborn preterm neonates in this report was low (<10%) when compared with other studies from Australia.[12,13] Bolbocean

Bayley	Bayley Scales of Infant and Toddler Development
Bayley-III	Bayley-Third Edition
GA	Gestational age
GMFCS	Gross Motor Function Classification System
NDI	Neurodevelopmental impairment
NICU	Neonatal intensive care unit
SGA	Small for gestational age
SNAP-II	Score for Neonatal Acute Physiology-Version II
TRIPS	Transport Risk Index of Physiologic Stability

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Although no specific funding was received for this study, organizational support for the Canadian Neonatal Network was provided by the Maternal-Infant Care Research Centre (MiCare) at Mount Sinai Hospital in Toronto. MiCare and the Canadian Neonatal Follow-Up Network are supported by a Canadian Institutes of Health Research (CIHR) Team Grant (FRN87518) and in-kind support from Mount Sinai Hospital. P.S. holds an Applied Research Chair in Reproductive and Child Health Services and Policy Research awarded by the CIHR (APR-126340). The authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2017.11.038

et al reported that nonambulatory cerebral palsy was not associated with outborn or inborn birth in a cohort of 360 infants from Quebec, Canada. This finding may have been related to early referral of high-risk pregnancies to regional centers, which may have artificially elevated the incidence of cerebral palsy in inborn infants, and the difference may not have been apparent.[14]

The objective of our study was to compare the mortality and neurodevelopmental outcomes of outborn preterm infants born at <29 weeks GA and transferred to tertiary neonatal intensive care units (NICUs) with those inborn at a tertiary care center in a large population-based cohort in Canada.

Methods

This was a retrospective study of an inception cohort of infants enrolled in the Canadian Neonatal Network and the Canadian Neonatal Follow-Up Network. All preterm infants with GA between $22^{0/7}$-$28^{6/7}$ weeks who were born in a participating tertiary care center (inborn) or transferred to a tertiary NICU after birth (outborn) from April 1, 2009, and September 30, 2011 were eligible for inclusion. To reduce cohort bias because of differences in admission policies for palliative care, we excluded infants with major congenital or chromosomal anomalies and those who were not offered mechanical ventilation or intensive care because of planned palliative care. The study protocol was approved by the Faculty Committee for the Use of Human Subjects in Research of the University of Manitoba and the steering committees of Canadian Neonatal Network and Canadian Neonatal Follow-Up Network.

Data collection and definitions were standardized using operations manuals across the centers a priori.[15,16] GA was calculated by using a hierarchy of in vitro fertilization date, last menstrual date, early antenatal ultrasound dating, obstetric estimate, and neonatal estimate in that sequence. Small for gestational age (SGA) was defined by birth weight below the 10th percentile for GA and sex.[17] Severe retinopathy of prematurity was defined as stage 3 or higher or retinopathy requiring treatment with laser or antivascular endothelial growth factor.[18] Severe brain injury included grade 3 or 4 intraventricular hemorrhage or persistent periventricular echogenicity or echolucency. Nosocomial infection was defined as the presence of a pathogenic organism in blood or cerebrospinal fluid in a symptomatic infant after 2 days of age. Necrotizing enterocolitis was defined using the Bell criteria.[19] Bronchopulmonary dysplasia was defined as the need for oxygen or respiratory support at 36 weeks postmenstrual age or at discharge. The Transport Risk Index of Physiologic Stability (TRIPS) score, a validated score of neonatal physiological status including temperature, systolic blood pressure, respiratory status, and response to a GA appropriate stimulus was used to compare the severity of illness immediately after arrival at the tertiary center and again 12 hours later.[20] Antenatal steroid use was defined as any corticosteroid administration before birth (complete and partial). The Score for Neonatal Acute Physiology-Version II (SNAP-II), a composite score of mean blood pressure, lowest temperature, serum pH, partial pressure arterial oxygen/fractional inspired oxygen (PaO_2/FiO_2) ratio, seizures, and urine output in the first 12 hours of admission[21] was collected at admission to the NICU and again 12 hours later.

Eligible neonates were assessed in the participating Canadian Neonatal Follow-Up Network centers using standard methods across the country.[15] At 18-21 months corrected age, children were assessed by experienced clinicians whenever possible. Assessments by community healthcare professionals were used for 6% of the children. Caregiver sociodemographic information and education were obtained at the follow-up visit. The assessment included a standardized history, physical and neurologic examinations, and administration of the Bayley Scales of Infant and Toddler Development (Bayley)-third edition (Bayley-III)[22] by trained assessors. Bayley-III cognitive, language and motor composite scores were obtained. In cases where the child could not be tested, the Bayley-III Adaptive Behavior questionnaire was administered. A diagnosis of cerebral palsy was made using standard definitions,[23] and if present, the degree of functional impairment was classified using the Gross Motor Function Classification System (GMFCS).[24] Hearing assessment results and the need for hearing aids or cochlear implants were obtained through history. Ophthalmology follow-up for retinopathy of prematurity and visual status was documented. If vision history was unknown, a small-scarred eye, sustained sensory nystagmus, or lack of response to a 1-cm object on a white background from 30 cm was defined as visual impairment.

The primary outcome of this study was a composite of death or severe NDI at 18-21 months corrected age. Severe NDI was defined as cerebral palsy with GMFCS ≥III, Bayley-III cognitive, language, motor, or general adaptive composite score of <70, need for hearing aids or a cochlear implant, bilateral visual impairment, or severe developmental delay that precluded using the Bayley-III for assessment. The secondary outcomes were the composite of death or overall NDI defined as any of cerebral palsy with GMFCS score ≥I, any Bayley-III composite score of <85, sensorineural/mixed hearing loss or unilateral or bilateral visual impairment,[25] and the individual outcome components at a corrected age of 18-21 months. The outcome of overall NDI included infants with severe NDI. We also analyzed common neonatal morbidities.

Statistical Analyses

Maternal details, infant characteristics, primary outcome, and secondary outcomes were compared for the outborn and inborn groups using the Pearson χ^2 test for categorical variables and Student *t* test or Wilcoxon rank test for parametric and nonparametric continuous variables as appropriate. Univariate and multivariable logistic analyses were applied for primary and secondary outcomes. For multivariable analysis, the model was adjusted for GA, SGA, use of antenatal steroids, cesarean delivery, multiple gestations, and SNAP-II score. aORs and 95% CIs were estimated. All analyses were conducted using SAS 9.3 (SAS Institute Inc, Cary, North Carolina) with significance level 0.05.

FLA 5.5.0 DTD ■ YMPD9611_proof ■ January 3, 2018