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The Value of Preterm Infant Environmental Health Cohorts:

The Canary in the Coal Mine

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It has long been recognized that early-life environmental exposures can alter developmental trajectories in critical and often unexpected ways that may produce clinically important outcomes years to decades later. Starting with Barker's work in the 1960s,[1] research on the developmental origins of disease has relied on exposure assessment of pregnant women and longitudinal follow-up of their offspring. Third-trimester fetal life, a critical period for neurobehavioral and pulmonary development as well as for metabolic programming, is now known to be particularly sensitive to environmental perturbations. Numerous prospective birth cohorts, often drawn from communities with high pollutant burden, have used maternal biomarkers as estimates of fetal exposure to explore the influence of chemical and social exposures during late pregnancy on long-term child health outcomes. Traditional birth cohorts explicitly exclude or minimally represent preterm children to reduce potential confounding by morbidities of prematurity.

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Morbidities associated with prematurity include developmental delay, cognitive dysfunction, attention-deficit/hyperactivity disorder, autism, psychiatric disorders, chronic lung disease, and maladaptive growth.[2] However, prematurity is not uniformly predictive or well-understood in the causal pathway of long-term childhood morbidity. The risk of deficit in a child born preterm is only partially explained by gestational age at birth or severity of illness during the newborn period.[3]

Preterm infants spend all or part of the third-trimester developmental window ex utero in the neonatal intensive care unit (NICU). During this critical period of structural and functional development, preterm infants experience an intense medical environment. The plastic milieu of the NICU brings these small infants into constant contact with chemical (eg, phthalates and metals) and nonchemical (eg, stress, pain, and maternal depression) toxicants that have been associated with abnormal neurobehavioral and somatic development in term-born cohorts.[4,5] Third-trimester in utero exposure to the phthalate family of plasticizers, ubiquitous in the NICU, has been linked to poorer childhood performance in cognition, motor function, attention, hyperactivity, and social behavior.[6] Early-life phthalate exposure is also associated with altered onset of puberty and asthma in term cohorts. Parenteral nutrition solutions, routinely used to nourish preterm infants, are supplemented with a trace element cocktail that contains metals with toxic potential. Physical stress and social isolation —common features of the preterm infant NICU experience—are also associated with abnormal multisystem development in term-born cohorts.

To date, the premise that preterm newborns are particularly susceptible to the effects of environmental toxicants has not been sufficiently explored. Their small body size and large surface area to body mass ratio, immature hepatic and renal clearance mechanisms, immature capacity to counteract oxidant and other environmental stressors, and critical stage and rapid rate of development indicate the likelihood of vulnerability to environmental toxicants. If in utero exposures to specific toxicants during the third trimester are implicated in long-term adverse outcomes in term cohorts, there is reason to believe that these same exposures at the same developmental point could contribute to morbidity among preterm infants who lack the protective placental and maturity-related detoxification physiology of term infants.[7]

In addition to providing actionable information to improve neonatal intensive care, environmental health studies of NICU populations could potentially benefit term-born children. Existing studies of the impact of chemical and nonchemical exposures during the critical window of third-trimester neurodevelopment rely on surrogate biomarkers—maternal urine, hair, and saliva—or self-report surveys that may not accurately reflect the magnitude of fetal exposure. In the NICU setting, biomarkers can be measured directly from the infant during the critical third-trimester developmental window, eliminating confounding by variable maternal metabolism and placental filtration. Additionally, the NICU is a highly regulated and recorded environment, facilitating improved accuracy of exposure assessment.

Multiple focus areas of children’s environmental health research, including neurodevelopmental deficits, pulmonary morbidity, and maladaptive growth, are common in children born preterm, improving the power of NICU-based study designs to assess

outcomes. Like the canary in the coal mine—or asthmatics in air pollution studies—children born preterm may serve as a sentinel population owing to increased susceptibility to the sometimes modest effects of common toxicants, improving study power and decreasing necessary sample size owing to this larger effect size. Although the maternal-placental unit may offer improved metabolic clearance for various environmental toxicants, it is likely that the fetus in utero and the newborn ex utero experience similar mechanisms of action of environmental toxicity. The preterm infant is in many ways more accessible to study than the third-trimester fetus. Additionally, pre-term infants are closely monitored in medical and developmental follow-up through childhood. This offers particularly high-quality longitudinal data from the medical record. Families of preterm infants recognize the importance of medical advances to the survival of their children and subsequently show high rates of research participation with excellent retention in long-term follow-up studies.[8]

To date, the nascent field of NICU-based environmental health research has focused on single exposures in small pilot cohorts, rather than comprehensive studies of multiple concurrent exposures that use statistical approaches capable of evaluating mixture effects on long-term outcomes. The application of multicenter collaborations and rigorous environmental epidemiologic study design to the NICU population is necessary for development of the field. As was done in a randomized clinical trial of NICU-based aluminum exposure from parenteral nutrition,[9] comparison of infants who require the same intensity of care for prematurity-related illness but experience different exposure profiles because specific medical equipment and care practices differ across sites may elucidate mitigatable exposure sources. Traditional NICU outcomes research has focused on medical complications and genetic vulnerability without accounting for the role of the hospital environment. These studies have not yielded fully predictive outcome models,[3,10] indicating an opportunity to improve morbidity prediction and reduction by identifying modifiable environmental exposures that contribute to adverse outcomes.

In 2015, the US Congress and the National Institutes of Health charged the Environmental Influences on Child Health Outcomes (ECHO) program leadership with constructing a “multicohort,” bringing together existing disparate prospective cohorts with the common goal of elucidating the effects of environmental exposures on child health and development. We applaud the architects of ECHO for funding 4 proposals comprising 7 preterm birth cohorts among the 84 cohorts included in ECHO. By including preterm cohorts in this mandate, the ECHO program is poised to open a path to rapid generation of evidence-based improvements to NICU care, while capitalizing on the unique features of the preterm population to advance our understanding of the impact of early-life environmental exposures. Preterm infants are a novel population for environmental health research. Epidemiological advantages of this population include high exposure to certain toxicants, easily obtainable bio-specimens for direct exposure measurements, high prevalence of adverse health outcomes, and a highly engaged parental community motivated to participate in research.

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