

The Outcomes of Very Preterm Infants: Is It Time to Ask Different Questions?

Marie C. McCormick, MD, ScD,^{a,b,c} Jonathan S. Litt, MD, MPH, ScD^{a,c}

The birth of a very preterm (VPT, <32 weeks) infant is a medical emergency associated with life-threatening complications and high costs of care. Decision-making by providers and parents requires information on possible outcomes. Here we describe the evolution of outcomes assessments for VPT infants, their limitations, and alternative strategies.

EVOLUTION OF A CONVENTION: THE SPECTRUM OF REPRODUCTIVE CASUALTY

Much of the literature on the follow-up of very low birth weight (<1500 g) or VPT infants focuses on neurodevelopmental disability (NDD; ie, intelligence/developmental quotients generally <70); cerebral palsy [CP], and blindness/deafness). Characterizing the risk of these conditions followed adding birth weight to the US birth certificate in 1949. An early investigator, Lillienfeld,¹ demonstrated higher rates of prematurity among children with CP, mental deficiency, and epilepsy than in children without these conditions. These findings were reinforced in the large, prospective Collaborative Perinatal Study.² The large size and rigorous methods informed the assessment ages and content of subsequent follow-up studies, allowing later investigators to “benchmark” their results.

Lillienfeld¹ postulated that certain events in utero lead to an array of outcomes including spontaneous abortion, stillbirth, premature delivery, and infant morbidity. His intent was to underscore the diversity of potential outcomes—a spectrum of reproductive casualty. Later investigators hypothesized that this spectrum suggested a potential trade-off between survival and disability, that is, a relatively fixed quantum of adverse outcomes in which increased survival came at the expense of increased morbidity. The increased survival of premature infants that underlay the decline in neonatal mortality beginning in the late 1960s stimulated a steady stream of studies on the neurodevelopmental outcomes of low birth weight, especially very low birth weight, infants.³ So entrenched was this concept that composite measures of death and/or NDD became commonly used in randomized trials of neonatal interventions.⁴ However, examination of the components of NDD noted earlier suggests that they may have quite

^aDepartment of Social and Behavioral Science, The Harvard T. H. Chan School of Public Health, Boston, Massachusetts; ^bDepartment of Neonatology, Beth Israel Deaconess Medical Center, Boston, Massachusetts; and ^cDepartment of Pediatrics, Harvard Medical School, Boston, Massachusetts

Drs McCormick and Litt actively participated in drafting this paper, and both authors approved the final manuscript as submitted.

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Address correspondence to Marie C. McCormick, MD, ScD, Sumner and Esther Feldberg Professor of Maternal and Child Health, Department of Social and Behavioral Sciences, The T.H. Chan Harvard School of Public Health, 677 Huntington Ave, Boston, MA 02115. E-mail: mmccormi@hsph.harvard.edu

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different etiologies, and they may not reflect the contribution of respiratory conditions to mortality.⁴

CHALLENGING THE NOTION OF A CONTINUUM OF REPRODUCTIVE CASUALTY

Clearly, the risk of NDD increases with birth at lower gestational ages. However, if a relatively constant proportion of survivors at a certain gestational age experience this morbidity, then (1) reductions in the morbidity can only be achieved by decreasing incidence of premature births⁴ and (2) efforts to save very premature infants serve to increase the absolute numbers of disabled infants. Is this the case?

Comparisons among institutions with comparable preterm populations reveal substantial differences in neurodevelopmental outcomes. Vohr et al⁵ reported almost threefold differences in CP and low IQ from those with the lowest to the highest rates across 12 centers. Likewise, Platt et al⁶ have reported substantial variation among the 16 centers in the Surveillance of Cerebral Palsy in Europe. Several reports indicate that the rates of CP increased until about 1990 and then plateaued or declined. Evidence for changes in IQ is more limited but does not indicate a sharp increase with increased survival. These observations suggest that the risk of CP in comparable survivors is variable and depends on medical care either at the institution level or with improvements in neonatal care over time, but additional evidence (cited below) indicates even greater malleability in outcomes.

THE BROADER SCOPE OF OUTCOMES AND THEIR IMPLICATIONS

Although adverse neurodevelopmental outcomes have received considerable attention, recent reviews have shown that VPT children are at risk for ongoing

problems in growth, respiratory health, and behavior.⁷ Emerging evidence suggests that VPT infants are may also be at increased risk for complications of aging such as hypertension, obesity, metabolic syndrome, chronic kidney disease, and severe osteoarthritis of the hip. This broader range of potential complications of preterm birth suggests outcome assessments should involve dynamic, integrated, and interactive approaches addressing at least 3 additional factors.

The Impact of Comorbidity

The literature to date has failed to consider the effect of multiple conditions on the outcomes of VPT infants. Studies of term children with chronic health conditions indicate potential interactions, such as between obesity and asthma or obesity and behavior problems, as well as different trajectories of these associations. In addition, we currently have limited understanding about whether multiple risks have additive, synergistic, or competing effects on outcomes.

The Impact on Functional Abilities

Diagnoses and IQ scores do not necessarily reflect the day-to-day functioning of the child. The cumulative effect of multiple conditions, even if each is not severe, may lead to significant disability. Even relatively severe conditions may have different effects on function in different contexts, as indicated by the poignant stories of Saigal's cohort, many of whom would be considered disabled. Characterization of childhood illness not tied to specific diagnoses include strategies for general populations, the rubric for children with special health care needs used in the United States, and the disability strategy of the World Health Organization. Although rare, application of these approaches may be particularly important in

situations where interventions improve task performance regardless of the underlying pathology.

The Impact of the Postdischarge Environment

The profound effect of the environment on infant health and development cannot be overestimated. There are extensive reviews of the effect of children's environments, especially disadvantaged environments on cognitive functioning and health problems.^{8,9} This may be of special significance for preterm infants who are disproportionately more likely to come from disadvantaged families. Broader concepts of the environment include an ever-expanding array of neighborhood exposures, health and education services, and the social policy milieu.^{8,9} As yet, these factors are understudied or omitted in outcomes studies. The influence of postnatal, postdischarge events on development is reinforced by the literature on interventions to improve outcomes.¹⁰ Although interventions may result in improvements in cognitive and behavioral scores, many benefits wane after discontinuation. As many interventions are restricted to the preschool period, it is unclear what is needed to sustain the advantages of these interventions over time.

TOWARD A COMPREHENSIVE CONCEPTUAL MODEL

A necessary step in addressing the gaps in the current literature is the use of a more comprehensive, dynamic model of child health incorporating multiple domains of health, the interplay of different health states, and the effect of environment at multiple levels. Such a model would emphasize the trajectory of these events across the life course, underscoring the effects of susceptibility and resilience.⁷

However, there are significant challenges in implementing such a model. Among them is the development of measures of relevant health information. Measurement will continue to depend heavily on caretaker report. The utility of existing instruments to capture functional capacity must be assessed and new measures proposed. Moreover, caregiver reports must be calibrated against clinical observations to understand the potential deficits that require intervention and linkage to medical information. Finally, the measures need to be sensitive to interventions.

Using such models in practice requires analytic techniques that can capture the interaction among various risks and outcomes and the dynamism of developmental trajectories over time. Simple comparisons between term and preterm infants at single time points will neither adequately explain mechanisms of dysfunction nor provide the information needed to inform multimodal interventions to improve outcomes. One such model has been described by the National Research Council/Institute of Medicine,⁹ although actual measures and analytic strategies remain to be developed.

SUMMARY

The era of purely descriptive outcome studies with a narrow range of outcomes for VPT infants should largely be over. Although

some exploration may still need to be done, especially for adult chronic illness, there is a need to shift to multifaceted conceptual frameworks accounting for physiologic and environmental influences on health and development. Broadly construed, such models should incorporate longitudinal observations of function and changes in function due to maturation, family dynamics, and social environmental contexts. Of particular importance is the identification of appropriate interventions to buttress the child's ability within his or her familial environment. Finally, in view of the interinstitutional variation in outcomes, applications of these approaches should be integral to quality improvement efforts designed to reduce neonatal complications.

ABBREVIATIONS

CP: cerebral palsy
 NDD: neurodevelopmental disability
 VPT: very preterm

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