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The nonimpact of gestational age on neurodevelopmental outcome for ventilated survivors born at 23–28 weeks of gestation

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Abstract

Aim—It has long been known that survival of preterm infants strongly depends upon birth weight and gestational age. This study addresses a different question – whether the gestational maturity improves neurodevelopmental outcomes for ventilated infants born at 23–28 weeks who survive to neonatal intensive care unit (NICU) discharge.

Methods—We performed a prospective cohort study of 199 ventilated infants born between 23 and 28 weeks of gestation. Neurodevelopmental impairment was determined using the Bayley Scales of Infant Development-II at 24 months.

Results—As expected, when considered as a ratio of all births, both survival and survival without neurodevelopmental impairment were strongly dependent on gestational age. However, the percentage of surviving infants who displayed neurodevelopmental impairment did not vary with gestational age for any level of neurodevelopmental impairment (MDI or PDI <50, <60, <70). Moreover, as a higher percentage of ventilated infants survived to NICU discharge at higher gestational ages, but the percentage of neurodevelopmental impairment in NICU survivors was unaffected by gestational age, the percentage of all ventilated births who survived with neurodevelopmental impairment rose – not fell – with increasing gestation age.

Conclusion—For physicians, parents and policy-makers whose primary concern is the presence of neurodevelopmental impairment in infants who survive the NICU, reliance on gestational age appears to be misplaced.

Keywords

Prematurity; Neurodevelopmental disability; Gestational age; Neonatal outcomes research; Neonatal ethics

INTRODUCTION

It has long been known, across many countries, that for premature infants, survival strongly depends upon birth weight and gestational age – smaller, more immature infants are more likely to die (1–8). We address here a different question – what is the impact of gestational maturity on neuro-developmental outcomes for the subset of infants who survive to NICU discharge?

Few studies have articulated this distinction explicitly – that is, distinguishing the impact of gestational age on survival, or even ‘intact survival’ (that is, survival without neurodevelopmental impairment) from the impact of gestational age on neurodevelopmental impairment for NICU survivors. This distinction is important. In our experience, parents requesting prognostic information from medical caregivers are rarely seeking information about the combined outcome of ‘either die in the NICU or survive with neurodevelopmental impairment’. Rather, parents are often specifically concerned about the likelihood of impairment if their baby survives.

We hypothesized that the neurodevelopmental outcome of ventilated NICU survivors born at 23–28 weeks of gestation would depend strongly on gestational maturity at birth. Specifically, we hypothesized that not only would the least mature infants be most likely to die, but the least mature survivors would also be most likely to be impaired. We further hypothesized that the likelihood of having a child who survived with impairment would diminish with increasing gestational maturity.

METHODS

Patient population

We studied 199 infants cared for in the University of Chicago NICU born between 23 and 28 weeks of gestation between 2003 and 2008. We limited our analyses to infants who at some time during their NICU course required mechanical ventilation (as opposed to those whose maximal ventilatory assistance was CPAP, nasal cannula or room air), because ethical alternatives to continued ventilation, that is, extubation and compassionate care, are feasible. Over 75% of infants born at 22–25 weeks were ventilated, at least briefly, and are consequently represented in our study population. In contrast, only 45% of infants born at 26–28 weeks required mechanical ventilation and were eligible to be included in this study. Each infant had been enrolled in one of the two ongoing clinical studies at our institution, and the likelihood of follow-up was consequently enhanced. We achieved a 2-year follow-up rate of 85% of eligible infants.

Neurologic evaluation

A total of 161 infants survived, and coordinated postdischarge monitoring was provided for all. At 24 months of corrected age, each infant was assessed using the second edition of the Bayley Scales of Infant Development. Each examination was performed by the same practitioner (S P-T). As is commonly reported, a mental developmental index (MDI) or psychomotor developmental index (PDI) less than two standard deviations from the mean (<70) was used to define neurodevelopmental impairment (1–7). However, in an attempt to

capture a more comprehensive description of the capabilities of NICU survivors, we further categorized infants as having MDI or PDI <60, or <50, and described the spectrum of MDI and PDI abnormalities considered separately as well as taken together.

Statistical analysis

Comparisons of proportions were made using chi-squared tests or Mantel–Haenszel tests for trend. Logistic regression was used to compare the differences in odds of outcomes by gestational age. Linear regressions were used to compare gestational age–adjusted length of stay for infants with varying degrees of neurodevelopmental impairment. Statistical significance was taken to require an alpha level of <0.05. This study was approved by the Institutional Review Board of the University of Chicago.

RESULTS

Figure 1 presents our central finding – displaying the like-lihood of survival (open diamonds), likelihood of survival without neurodevelopmental impairment (open circles) and the per cent of survivors without neurodevelopmental impairment (filled squares) for 199 ventilated NICU infants born at 23–28 weeks of gestation. As expected, both survival and survival without neurodevelopmental impairment were strongly dependent on gestational age (for survival, odds ratio 2.98 for each additional week of gestation, 95% CI 1.94–4.57, $p < 0.001$; for survival without neurodevelopmental impairment, odds ratio 1.36, 95% CI 1.09–1.68, $p = 0.006$). However, the percentage of surviving infants who had both MDI and PDI > 70 did not depend significantly on gestational age (odds ratio 1.07, 95% CI 0.84–1.36, $p = 0.571$). In other words, gestational age strongly influenced the likelihood that an infant would survive to NICU discharge. However, given that an infant survived, gestational age had no statistically significant impact on the infant’s neurologic outcome at 24 months.

Table 1 describes in more detail the outcomes of the 199 ventilated infants born between 23 and 28 weeks in our study. Of 199 ventilated infants, 38 (19%) died, 71 infants (36% of overall population and 44% of NICU survivors) survived with neurodevelopmental impairment, and 90 infants (44% of overall population and 56% of survivors) survived with both MDI and PDI >70. Nonsurvivors were younger (24.3 versus 25.8 weeks), lower birth weight (674 versus 837 g) and predominantly boys (66% versus 51%) compared with surviving infants (all $p < 0.01$). Infants who survived with neurodevelopmental impairment did not differ from infants who survived without neurodevelopmental impairment in either gestational age or birth weight. However, infants who survived with neurodevelopmental impairment were significantly more likely to be boys (65%) than infants who survived without neurodevelopmental impairment (40%) ($p < 0.01$).

Table 1 also reveals that, contrary to our hypothesis, the percentage of all ventilated births in a particular gestational age group who survived with neurodevelopmental impairment rose – not fell – with increasing gestation age, from 25% of all ventilated infants born at 23–24 weeks to 35% at 25–26 weeks and 46% of all ventilated infants born at 27–28 weeks ($p < 0.006$). This increase was explained by the observation that a higher percentage of ventilated

infants survived to NICU discharge at higher gestational ages, but the percentage of neurodevelopmental impairment in survivors was unaffected by gestational age.

Figure 2 displays in more detail the relationship of gestational age with MDI and PDI at 2 years for the 161 surviving infants in our study. Neither MDI/PDI <70, MDI/PDI <60 nor MDI/PDI <50 had any statistical dependence on gestational age between 23 weeks and 28 weeks (for survivors with MDI/PDI <70, odds ratio 0.93 for each additional week gestation, 95% CI 0.73–1.19, $p = 0.571$; for survivors with MDI/PDI <60, odds ratio 0.84, 95% CI 0.64–1.10, $p = 0.205$; for survivors with MDI/PDI <50, odds ratio 0.99, 95% CI 0.72–1.36, $p = 0.934$).

Finally, we categorized infants by the performance on MDI alone, PDI alone and a combination of MDI and PDI as a function of gestational age. Within each gestational age group, cognitive impairments were more common than motor impairments and more often placed children in a lower overall neurodevelopmental impairment group. This was true at all degrees of impairment. Again, we found no apparent dependence on gestational age for any level of MDI or PDI individually or in combination.

DISCUSSION

There are four possible outcomes for infants born at extremely low gestational age. First, their parents and doctors can agree not to resuscitate them. These infants die quickly, and we will not discuss them further. Second, the infants can be resuscitated and, at some later time, die in the NICU. Third, the infants can survive to be discharged from the NICU and eventually display neurodevelopmental impairment. Fourth, infants can survive the NICU with normal neurologic capability.

Most descriptions of neonatal ethics and epidemiology begin by calculating mortality – the ratio of all survivors to all births. For these calculations, any survival is a ‘good’ outcome and death in the NICU is the adverse outcome. A second description of neonatal outcomes calculates ‘intact survival’ – the ratio of survivors without neurodevelopmental impairment to all births. When calculating ‘intact survival’, either survival with neurodevelopmental impairment or death in the NICU is an adverse outcome. It is well known that both overall survival and ‘intact survival’ depend strongly on gestational age (1–7).

However, for some parents, death of their child in the NICU is not, on balance, a negative outcome. Some parents find moral worth and emotional solace in ‘giving their child a chance’ and ‘not giving up without a fight’. For these parents, the only negative outcome after birth is survival with neurodevelopmental impairment. For these parents, the only relevant statistic is the percentage of NICU survivors who display neurodevelopmental impairment.

We provide here a thick description of outcomes for 199 ventilated infants cared for in a single NICU born between 23 and 28 weeks of gestation. We restricted our analysis to infants who required mechanical ventilation at some point during their NICU stay because, for these infants, an ethically acceptable alternative to continued NICU intervention (extubation and compassionate care) is available. Recognizing the biologic and historical

plausibility of the correlation between mortality and morbidity, we hypothesized that neurodevelopmental outcome of ventilated NICU survivors born at 28 weeks of gestation or younger would be strongly dependent on gestational maturity at birth. Specifically, we hypothesized that not only would the least mature infants be most likely to die, but that the least mature survivors would also be most likely to be impaired. We were wrong.

We note two important findings. First, for our population of ventilated infants born between 23 and 28 weeks of gestation, as expected, when calculated as a function of all births, both survival and survival without neurodevelopmental impairment (defined as either MDI or PDI <70 at 2 years of age) were strongly dependent on gestational age. However, unexpectedly, we found that the percentage of surviving infants who performed at any prescribed level of MDI or PDI (e.g. MDI or PDI <70, <60 or <50) did not vary significantly as a function of gestational age.

Second, for ventilated infants born between 23 and 28 weeks of gestation, the likelihood that an individual infant would survive and exhibit neurodevelopmental impairment rose, not fell, at higher gestational age – precisely because survival increases so strongly with gestational age, while the percentage of impaired survivors does not. We discuss the implications of these observations in turn.

Previous descriptions of neurodevelopmental outcomes have, in our view, often been inadequate along three distinct dimensions. First, most outcome studies have largely been limited to dichotomous descriptions of ‘normal’ or ‘abnormal’, where abnormal outcomes were defined as MDI or PDI <70 (1–8). Second, most studies have described outcomes for entire infant groups categorized by large birth weight or gestational age groups – for example, all extremely low-birth-weight infants or all infants born $\geq$ 28 weeks of gestation (1–8). Third, most studies have ignored the possibility that some parents might find moral value in a trial of therapy in the NICU, even if that trial ended in the death of their infant (9–13). We attempted to address each of these perceived inadequacies.

The lack of clinically important differences in neuro-developmental impairment comparing surviving ventilated infants born at 23–24 weeks of gestation with surviving ventilated infants born at 25–26 weeks of gestation is particularly pertinent to both discussions of medical ethics and public policy. In the United States as in many other countries, resuscitation of infants born at or above 25 weeks of gestation is considered morally obligatory, whereas resuscitation of infants born at 24 weeks or below is considered optional (9–13). Our data suggest that these policies make sense only if ‘trying and failing’ in the NICU is deemed to have no moral worth.

Second, our data support previous reports that infants born at 23–24 weeks of gestation contribute relatively little financial burden compared to more mature infants in the NICU (14,15). In our study of ventilated infants born between 23–28 weeks of gestation, only 12% of survivors, 17% of infants who survived with neuro-developmental impairment and 18% of NICU bed-days were attributed to infants born at 23–24 weeks. Consequently, policies restricting resuscitation of these infants find little justification from the perspective of saving societal resources.

We note that our overall rate of neurodevelopmental impairment was disappointingly high – 44% of surviving patients. Two factors are likely to contribute to this finding. First, our study population was restricted to infants who required mechanical ventilation at some point during their NICU stay. In our experience as well as that reported by others (1–8), virtually all infants born at 23–24 weeks require intubation – however, an increasingly large fraction of infants born between 25 and 28 weeks of gestation can be managed with CPAP or nasal cannula, and they would not be included in our analyses. It is likely that these non-ventilated infants would survive with less neurodevelopmental consequences.

The second risk factor that might account for our high rate of neurodevelopmental impairment is the sociodemographic status of our patient population. Our inner-city population is predominantly poor and educationally disadvantaged. These risk factors are well known to contribute to impaired neurodevelopmental outcomes for children (16).

Limitations of our study are straightforward. We describe outcomes in only one NICU, in a predominantly poor, underserved maternal population. Consequently, the generalizability of our findings remains unproven. Moreover, we have only 2-year follow-up available, and several studies have suggested that 2-year outcomes correlate only imperfectly with 5-year or school-age performance (16–19). Nonetheless, our principle observation – that neurodevelopmental impairment in survivors depends much less strongly on gestational age than does overall survival – finds some support in previously published studies (5,7,19–22).

In sum, for a population of 199 ventilated infants born between 23 and 28 weeks, we found that although both overall survival and survival without neurodevelopmental impairment depend strongly on gestational age, the percentage of NICU survivors who displayed cognitive or motor deficits of varying degree did not vary with the gestational age. If mortality in the NICU is the outcome that parents most fear, then physician counselling and public policy pronouncements that rely strongly on gestational age are epidemiologically and ethically appropriate. However, if survival of an infant with severe neurologic impairment is the outcome most feared, then reliance on gestational age appears to be misplaced.

Abbreviations

NICU	neonatal intensive care unit
CPAP	continuous positive airway pressure
MDI	mental developmental index
PDI	psychomotor developmental index

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Key notes

- It has long been known that survival of preterm infants strongly depends upon gestational age. Does gestational maturity also improve neurodevelopmental outcomes for infants who survive to neonatal intensive care unit (NICU) discharge? Surprisingly, it does not. For parents, physicians and policy-makers whose primary concern is neurodevelopmental impairment in NICU survivors, reliance on gestational age for decisions about either initial resuscitation or continued NICU intervention appears to be misplaced.

Survival, intact survival, and neurologic outcome among surviving infants

Figure 1.

Likelihood of survival (dashed line – open diamonds; $n = 199$), survival without neurodevelopmental impairment (dashed line – open circles; $n = 199$) and likelihood of being without morbidity among surviving infants (solid line – filled squares; $n = 166$) as a function of gestational age.

Figure 2.

Likelihood of Bayley MDI or PDI <70 (diamonds), <60 (squares) and <50 (triangles) for 166 surviving infants 23–28 weeks who required mechanical ventilation in the NICU. MDI = mental developmental index; PDI = psychomotor developmental index.

Table 1

Rate of survival and neurodevelopmental impairment among 199 ventilated infants, 23–28 weeks of gestation.
p values indicate Mantel–Haenszel test for trend as gestational age increases

	<u>All ventilated infants</u>	<u>Infants distributed by gestational age</u>			p
	23–28 weeks	23–24 weeks	25–26 weeks	27–28 weeks	
Number of infants					
N	199	52	93	54	
Survived to NICU discharge					
N	161	26	83	52	
% of total births	0.81	0.5	0.89	0.96	<0.001
Survived with NDI					
N	71	13	33	25	
% of total births	0.36	0.25	0.35	0.46	0.006
% of survivors	0.44	0.5	0.4	0.48	0.905

NDI, neuro-developmental impairment.