Original Research

A Proactive Approach to Neonates Born at 23 Weeks of Gestation

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OBJECTIVE: To evaluate in-hospital survival, survival without major morbidity, and neurodevelopmental impairment for neonates born at 23 weeks of gestation provided proactive, coordinated, and comprehensive perinatal and neonatal management.

METHODS: This was a retrospective cohort study conducted at a single, tertiary care center between 2004 and 2013. Enrollment was limited to mother–neonate dyads at 23 weeks of gestation who were provided a proactive approach defined as documented evidence of antenatal corticosteroid administration, willingness to provide cesarean delivery for fetal distress, and neonatal resuscitation and intensive care. Among survivors, major morbidities (predischarge) and neurodevelopmental assessments at corrected ages of 18–22 months were examined.

RESULTS: Among 152 live births identified, 101 neonates received proactive care, of whom 60 (59%) survived to hospital discharge. Preterm premature rupture of membranes (adjusted odds ratio [OR] 0.29, 95% confidence interval [CI] 0.09–0.94), fetal growth restriction (OR 0.16, 95% CI 0.03–0.89), delivery room cardiopulmonary resuscitation (OR 0.07, 95% CI 0.02–0.32), and prolonged intubation sequence (OR 0.15, 95% CI 0.05–0.45) were associated with lower neonatal survival. Among neonatal intensive care unit survivors, 62% had at least one major morbidity. Among 50 survivors with assessment at 18–22 months, six (12%) were unimpaired, 20 (40%) had mild impairment, and 24 (48%) had moderate or severe neurodevelopmental impairment.

CONCLUSION: Proactive, interdisciplinary care enabled more than half of the neonates born at 23 weeks of gestation to survive, and approximately half of children evaluated at 18 months exhibited no or mild impairment. This information should be considered when providing prognostic advice to families with threatened preterm birth at 23 weeks of gestation.

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LEVEL OF EVIDENCE: II

Markers of a proactive approach to perinatal and neonatal management include interventions by obstetricians (antenatal corticosteroids and cesarean deliveries for fetal distress) and neonatologists (delivery room resuscitation and intensive care).[1] A recent study from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) shows that more than 95% of neonates born at 24 weeks of gestation receive proactive lifesaving treatment, whereas those born at or before 22 weeks of gestation are typically considered too immature for treatment to be effective and receive comfort care.[2] However, the decision to initiate or withhold treatment at 23 weeks of gestation remains controversial, with marked differences across hospitals in the obstetric and neonatal approach at this gestation.[3,4] Among neonates born at 23 weeks of gestation, use of antenatal corticosteroids ranged from 10% to 100%, cesarean delivery for fetal distress from 3% to 100%, and active resuscitation from 10% to 100%.[5] Furthermore, disagreement among obstetricians and neonatologists in the perceived likelihood of a positive outcome has led to inconsistent care, wherein some neonates born

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at 23 weeks of gestation are provided antenatal corticosteroids and not resuscitated or vice versa.[6]

Not surprisingly, differences in perinatal and neonatal care across hospitals have led to survival estimates ranging from 1% to 52% among neonates born at 23 weeks of gestation.[7,8] Limitations of prior reports on the survival and outcomes among neonates born at 23 weeks of gestation are the inclusion of neonates either not provided proactive care or provided only certain aspects of care rather than a consistent perinatal and neonatal treatment approach.[1] The primary objective of the present study was to evaluate in-hospital survival, survival without major morbidity, and neurodevelopmental impairment for neonates born at 23 weeks of gestation provided proactive, coordinated, and comprehensive perinatal and neonatal management. The secondary objective was to identify obstetric and neonatal factors associated with in-hospital survival.

MATERIALS AND METHODS

This was a retrospective cohort study conducted at a single, tertiary care center between January 1, 2004, and December 31, 2013, conducted after Nationwide Children's Hospital institutional review board approval (IRB #14-00395). Women with singleton pregnancies at 23 0/7–23 6/7 weeks of gestation were candidates for inclusion in the study. The determination of gestational age was based on best obstetric estimate. Extramural deliveries, antepartum stillbirths, and elective pregnancy terminations were excluded. Neonates with recognized syndromes or major anomalies identified after delivery were excluded, because factors besides prematurity may have influenced the prognosis, management, and outcomes for these neonates.

Enrollment was limited to mother–neonate dyads provided a proactive perinatal and neonatal approach, defined as documented evidence of antenatal corticosteroids administration, willingness to provide cesarean delivery for fetal distress, and neonatal resuscitation and intensive care.[1] Because we intended to describe neonatal outcomes after the provision of comprehensive and coordinated perinatal and neonatal care, cases in which health care providers were unwilling to intervene or where mother–neonate dyads were provided inconsistent care (eg, antenatal corticosteroids but no delivery room resuscitation or vice versa) were excluded (described subsequently). Family counseling was provided before delivery, including discussion on anticipated intervention and outcomes. Resuscitations in the delivery room by the neonatal team were consistent with published guidelines.[9] At our institution, endotracheal intubation of neonates at less than 28 weeks of gestation is performed by a neonatology fellow, neonatal nurse practitioner, or neonatology attending. Neonates surviving the delivery room were provided care in accordance with previously published guidelines for extremely premature neonates at our center.[10]

Neonatal and maternal characteristics were recorded in a standard format. We recorded maternal age, maternal race or ethnic group assigned by maternal report (black [not Hispanic], white [not Hispanic], Hispanic, or other), prenatal care, and enrollment in private insurance. Based on previous studies,[11] cesarean deliveries were classified as vertical uterine incisions (classical or low uterine) or transverse. The definition of fetal distress was based on fetal heart rate, periodic and nonperiodic patterns of change, beat-to-beat variability, and scalp pH or electrode, but the timing and need for clinical intervention were at the discretion of the treating physician. Antibiotics were used for preterm premature rupture of membranes (PROM) and group B streptococci carrier status, but not to prolong gestation in women with preterm labor.[12] Antenatal corticosteroids were provided as betamethasone with a second dose given (if possible) 24 hours after the first dose. Chorioamnionitis and severe preeclampsia were defined according to previous work.[13,14]

Fetal growth restriction was defined as an estimated fetal weight less than the 10th percentile for gestational age.[15] We defined a prolonged intubation sequence as need for greater than three intubation attempts.[16] Cardiopulmonary resuscitation (CPR) in the delivery room was defined as receipt of chest compressions or epinephrine.[17] The presence of a neonatology attending in the delivery room was also recorded. Umbilical artery pH was recorded, when available. To examine fractional portions within 23 weeks of gestation, neonates were categorized as "early" (23 0/7–23 3/7 weeks of gestation) and "late" (23 4/7–23 6/7 weeks of gestation). To compare potential changes with time in survival over the 10-year period, the cohort was divided into 5-year epochs: "first era" (2004–2008) and "second era" (2009–2013).

Among survivors, major morbidities (predischarge) and neurodevelopmental assessments at corrected ages of 18–22 months were examined. Severity of bronchopulmonary dysplasia (BPD) was defined using the NICHD Workshop consensus diagnostic criteria.[18] Consistent with previous studies,[19] major in-hospital morbidity was defined as the presence of severe BPD, retinopathy of prematurity stage 3 or

greater, intraventricular hemorrhage grade 3 or 4, or periventricular leukomalacia. Neurodevelopmental evaluations were performed in the neonatal developmental clinic. Children were classified as unimpaired if they had Bayley Scales of Infant Development (II or III) scores within 1 standard deviation (SD) of the mean and normal neurologic examination findings, vision, hearing, and walking.[20] Mild impairment comprised a score on the relevant composite scale from −2 SD to less than −1 SD of the mean, mild cerebral palsy, or minor sensory impairment (need for glasses, transient conductive hearing loss, or less than 20/200 in one eye). Moderate or severe neurodevelopmental impairment included scores greater than −2 SD from the mean, moderate or severe cerebral palsy with gross motor function classification system level 2 or greater, vision impairment (less than 20/200) in both eyes, or severe hearing impairment (permanent hearing loss that does not permit the child to understand the directions of the examiner and communicate despite amplification).

Data are presented as number and percent, mean±SD, or median (range). Neonates surviving the neonatal intensive care unit were compared with those not surviving with respect to the distribution of clinical and demographic variables. Group comparisons for continuous variables were made using the Student's *t* test. The Mann-Whitney test was used for nonparametric continuous variables. χ^2 or Fisher's exact tests were used for categorical variables. A comparison of neonates receiving and not receiving delivery room CPR was performed using Kaplan-Meier analysis. Multiple logistic regression models on the likelihood of survival to hospital discharge were adjusted for variables that were known before or shortly after birth, including preterm PROM, birth weight, sex, 1-minute Apgar score 3 or less, cesarean delivery, two doses antenatal corticosteroids, "first era," chorioamnionitis, fetal growth restriction, delivery room CPR, and prolonged intubation sequence. In the multivariate analysis, variables with univariate *P* values <.05 were entered with a maximum of four to prevent overfitting of the model. Results are expressed as crude odds ratio (OR) and adjusted OR with 95% confidence interval. Data on children not examined at 18–22 months were not included in analysis of neurodevelopmental impairment. A *P* value of <.05 was used to denote statistical significance. All statistical calculations were performed with SAS 9.1.3.

RESULTS

Among 152 neonates born at 23 weeks of gestation, 51 (34%) did not receive proactive obstetric and neonatal care and were excluded from data analysis. Excluded neonates had a mean gestational age of 23.4 weeks and a birth weight of 522 g; 45% were female; 35% received antenatal corticosteroids; 16% were delivered by cesarean; and 72% received neonatal resuscitation. Among neonates not offered proactive care, 32% survived to discharge. Of the excluded neonates, 33% (17/51) died in the delivery room and 31% (16/51) survived to hospital discharge. Only 12 of the 18 (67%) survivors in the group not receiving proactive care were evaluated at 18–22 months, and 10 (83%) had evidence of neurodevelopmental impairment.

Obstetric diagnosis antecedent to delivery was preterm labor in the majority (53%) of cases (Table 1). Cesarean delivery occurred in 62 of 101 patients (62%) and of these, 52 of 62 (84%) were classical or vertical uterine incisions and 10 of 62 (16%) were transverse incisions.

Among 101 neonates who received proactive care, 100 (99%) survived the delivery room and 60 (59%) survived to hospital discharge (Table 2). All neonates were exposed to at least one dose of antenatal corticosteroids, and 62% (63/101) received two

Table 1. Maternal Characteristics

Characteristic	Cohort (N=101)
Maternal age (y)	25.9±5.5
Race–ethnicity*	
White	75
Black	21
Hispanic	4
Other	1
Prenatal care	92 (91)
Enrolled in private insurance	43 (43)
Type 1 diabetes mellitus	4 (4)
Chorioamnionitis	11 (11)
Preterm labor	54 (53)
Preterm PROM	24 (24)
Indications for cesarean delivery†	
Preterm labor with noncephalic fetal presentation	14 (23)
Severe preeclampsia or eclampsia	15 (24)
Nonreassuring fetal status	14 (42)
Placental abruption	12 (36)
Prolapsed umbilical cord	5 (15)
Suspected uterine rupture	2 (6)
Type of cesarean delivery†	
Vertical uterine incision	52 (84)
Transverse uterine incision	10 (16)

PROM, premature rupture of membranes; vertical incision, classical or low vertical incisions.
Data are mean±standard deviation, n, or n (%).
* Race and ethnic group were self-reported.
† Percentages based on those undergoing cesarean delivery.

Table 2. Neonatal Characteristics

Characteristic	Cohort (N=101)
Female sex	39 (39)
1-min Apgar score 3 or less	75 (74)
5-min Apgar score less than 7	35 (35)
Birth weight (g)*	588 (412–678)
Gestational age (wk)	23 4/7 (23 0/7–23 6/7)
Fetal growth restriction*	14 (14)
Umbilical artery pH†	7.21±0.11
Delivery room CPR	16 (16)
Prolonged intubation sequence	35 (35)
Surfactant in delivery room	81 (80)
Exposure to antenatal corticosteroids	
1 dose	38 (38)
2 doses	63 (62)

CPR, cardiopulmonary resuscitation (chest compressions±epinephrine).
Data are n (%), median (range), or mean±standard deviation.
Prolonged intubation sequence, greater than three intubation attempts before successful placement of endotracheal tube.
* Information on fetal growth restriction status was not available in 13 patients.
† Data on umbilical artery pH was available for 78% (79/101) of the neonates.

Table 3. Outcomes of Neonatal Intensive Care Unit Survivors

Outcome	NICU Survivors (n=60)
PDA	53 (88)
Surgical PDA ligation	32 (53)
Bacterial sepsis	31 (52)
Fungal infection	4 (7)
NEC stage 2 or greater	7 (12)
Intraventricular hemorrhage (grades 1–4)	32 (53)
Severe intraventricular hemorrhage (grades 3–4)	16 (27)
PVL	13 (22)
Severe ROP (stage 3 or greater)	22 (37)
BPD	60 (100)
Severe BPD	20 (33)
Length of hospital stay (d)*	131 (76–386)
Mechanical ventilation (d)	52 (23–313)
No. of major comorbidities†	
0	23 (38)
1	18 (30)
2	9 (15)
3	5 (8)

NICU, neonatal intensive care unit; PDA, patent ductus arteriosus; NEC, necrotizing enterocolitis; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; BPD, bronchopulmonary dysplasia.
Data are n (%) or median (range).
Bacterial sepsis defined as positive blood or urine culture and receipt of 3 days or more of antibiotic treatment; NEC stage 2 or greater, following Bell's criteria[28] for severe intraventricular hemorrhage on head ultrasonography at day of life 30[29]; PVL was defined as cystic PVL detected on ultrasonographic examination; severe ROP was defined as stage 3 or greater.
* Length of hospital stay reflects days at tertiary care hospital only; some neonates were transferred to an outside hospital before discharge home.
† Defined as severe BPD, ROP stage 3 or greater, severe intraventricular hemorrhage, PVL, or all of these.

doses of antenatal corticosteroids before delivery. The duration of antenatal corticosteroids before delivery was 0–12 hours in 22%, 12–24 hours in 16%, and greater than 24 hours in 61%. In one case, two doses of betamethasone were provided at an outside institution before transfer, but the timing of the dose relative to delivery was unknown.

Among neonates who survived to hospital discharge, 62% had at least one major morbidity during their hospitalization (Table 3). Infection rates in surviving neonates were relatively high, and 7% of neonatal intensive care unit survivors had documented fungal infections and received treatment. All surviving neonates had BPD, and one third had severe BPD. Marked variability in the length of hospital stay was observed.

Less than half of neonates who survived to hospital discharge were intubated in the delivery room on the first attempt (Table 4). An attending neonatologist was present for 76% (77/101) of deliveries. The need for prolonged intubation sequences was not lower among cases in which an attending neonatologist was present in the delivery room than in cases in which an attending neonatologist was not present. Umbilical artery pH was available in 78% of the deliveries, and no differences between survivors and nonsurvivors were observed. We observed no differences in survival according to "early" or "late" 23-week gestations (23/42 [55%] compared with 38/59 [64%], $P=.41$) or between in neonates born during the "early era" or during the "late era" (20/38 [53%] compared with 41/63 [65%], $P=.29$). Because several of the variables have low sample sizes, conclusions on the results are limited as a result of lack of statistical power.

A majority of infant deaths (32/41 [78%]) occurred in the first 30 days of life (median 9 days, range 1–225 days). Infants who died were more likely to have received delivery room CPR than survivors (Fig. 1; log-rank test, $P<.01$).

Of the children who received delivery room CPR, 94% (15/16) had prolonged intubation sequence. Of the five (31%) children who received delivery room CPR and survived to hospital discharge, all had evidence of neurodevelopmental impairment. In the logistic regression model, preterm PROM and fetal growth restriction were associated with lower neonatal survival as were delivery room CPR and prolonged intubation sequence (Table 5).

Table 4. Neonatal Intensive Care Unit Survivors Compared With Neonatal Intensive Care Unit Deaths

Study Characteristic	NICU Survivors (n=60)	NICU Deaths (n=41)	*P*
Obstetric variables			
Prenatal care	55 (92)	37 (90)	.81
Enrolled in private insurance	28 (47)	15 (37)	.31
Chorioamnionitis	8 (13)	3 (7)	.52
Preterm labor	31 (52)	23 (56)	.66
Preterm PROM	8 (13)	16 (39)	<.01
Cesarean delivery	35 (58)	27 (66)	.58
Neonatal variables			
Female sex	21 (35)	18 (44)	.37
1-min Apgar score 3 or less	44 (73)	31 (75)	.79
5-min Apgar score less than 7	20 (33)	15 (37)	.74
Birth weight (g)	582 (412–642)	571 (443–678)	.54
Gestational age (wk)	23 3/7 (23 0/7–23 6/7)	23 3/7 (23 3/7–23 6/7)	.63
Fetal growth restriction*	4 (7)	10 (24)	.02
Surfactant in delivery room	50 (83)	31 (76)	.34
Delivery room CPR	3 (5)	13 (32)	<.01
Prolonged intubation sequence	12 (20)	23 (56)	<.01
Neonatal attending present	47 (78)	30 (73)	.55
Two doses of antenatal corticosteroid	40 (67)	23 (56)	.28

NICU, neonatal intensive care unit; PROM, premature rupture of membranes; CPR, cardiopulmonary resuscitation (chest compressions±epinephrine); prolonged intubation sequence, greater than intubation attempts before successful placement of endotracheal tube.
Data are n (%) or median (range).
* Information on fetal growth restriction status was not available in 13 patients.

Outcome data for neurodevelopmental impairment were available in 83% (50/60) of patients. We observed no difference in the proportion of preterm PROM, fetal growth restriction, delivery room CPR, or prolonged intubation sequence between the 50 evaluated survivors and the 10 with incomplete follow-up data. Among 50 survivors with assessment at 18–22 months, six (12%) were unimpaired, 20 (40%) had mild impairment, and 24 (48%) had neurodevelopmental impairment. Moderate or severe cerebral palsy was observed in 14% (7/50) of the neurodevelopmental impairment group. Half of the children with moderate or severe neurodevelopmental impairment (12/24 [50%]) were walking independently at 18–22 months. The number of impairments in the children with neurodevelopmental impairment ranged from one to greater than three. Of the children with neurodevelopmental impairment, 42% were classified on the basis of a single factor, 33% were classified on the basis of two factors, and 25% on the basis of three or more factors. Of the mildly impaired group, 60% were classified on the basis of a single factor, 15% on the basis of two factors, and 25% on the basis of three or more factors. The majority (17/20 [85%]) of children in the mildly impaired group were walking independently at 18–22 months.

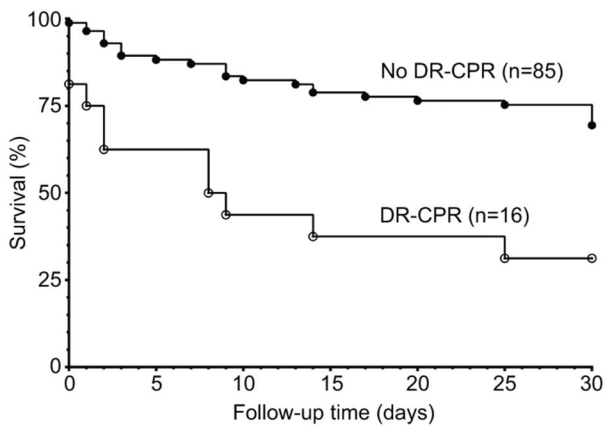

Fig. 1. Kaplan-Meier survival plot stratified according to receipt of delivery room cardiopulmonary resuscitation (DR-CPR, n=16) or no delivery room cardiopulmonary resuscitation (no DR-CPR, n=85). DR-CPR defined as chest compressions±epinephrine. *P*<.01.

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DISCUSSION

We found that 95% of neonates born at 23 weeks of gestation provided proactive care survived the first 24 hours of life and exhibited rates of survival and survival without neurodevelopmental impairment greater than those reported by the Vermont Oxford Network[3] and the NICHD.[5] We offer a number of potential explanations for these observed differences. Although previous studies have defined active treatment as neonatal resuscitation and intensive care

Table 5. Factors Associated With In-Hospital Survival

Variable	OR	95% CI	*P*
Univariate estimates			
Preterm PROM	0.31	0.12–0.77	.01
Birth weight (g)	1.10	0.99–1.20	.13
Female sex	0.70	0.31–1.58	.39
1-min Apgar 3 or less	1.04	0.22–4.91	.90
Cesarean delivery	0.79	0.31–1.83	.58
2 doses of antenatal corticosteroid	1.47	0.62–3.47	.38
"First era" (2004–2008)	1.48	0.67–3.32	.33
Chorioamnionitis	0.61	0.26–1.40	.24
Fetal growth restriction	0.23	0.10–0.94	.04
Delivery room CPR	0.10	0.05–0.20	<.01
Prolonged intubation sequence	0.11	0.04–0.27	<.01
Multivariate estimates*			
Preterm PROM	0.29†	0.09–0.94	.04
Fetal growth restriction	0.16†	0.03–0.89	.03
Delivery room CPR	0.07†	0.02–0.32	<.01
Prolonged intubation sequence	0.15†	0.05–0.45	<.01

OR, odds ratio; CI, confidence interval; PROM, premature rupture of membranes; CPR, cardiopulmonary resuscitation.
Prolonged intubation sequence, greater than three intubation attempts before successful placement of endotracheal tube.
* Adjusted OR.
† Adjusted for preterm PROM, fetal growth restriction, delivery room CPR, prolonged intubation sequence.

only,[2] we describe outcomes of neonates provided comprehensive and coordinated obstetric and neonatal care. Tyson et al[19] showed that singleton birth, exposure to antenatal corticosteroids, and neonatal intensive care were each associated with reductions in mortality similar to those associated with 1-week increases in gestational age. Thus, our sample is not representative of all live births at 23 weeks of gestation and likely represents subgroups of mother–neonate dyads in "best case" circumstances. Care planning consensus among patients, families, and health care providers was achieved and required time for predelivery counseling. Although we do not have data on how or when decisions were made regarding treatment, differences in outcomes anticipated by health care workers were likely determinants of whether to provide proactive care.

Once a decision is made to provide proactive perinatal care for neonates at 23 weeks of gestation, data to guide clinicians on the optimal mode of delivery are limited.[21] Evidence to support routine planned cesarean delivery to improve outcomes for extremely premature neonates, compared with planned vaginal delivery, is lacking. Although a recent joint statement from the NICHD, the American College of Obstetricians and Gynecologists, the Society for Maternal-Fetal Medicine, and the American Academy of Pediatrics supported cesarean delivery for fetal indications at 23 weeks of gestation,[22] this practice remains controversial. Because cesarean delivery is associated with maternal morbidity[11] and may alter the care of subsequent pregnancies,[23] risk–benefit profiles to the mother and the fetus should be balanced when counseling families. Notably, 84% of the cesarean deliveries done in our cohort were vertical or classical uterine incisions, which largely mandate all future deliveries to be delivered by cesarean in the late preterm or early term timeframe. Interestingly, Bottoms et al observed that, among neonates born between 22 and 25 weeks of gestation, willingness to perform a cesarean delivery, rather than mode of delivery, was a primary determinant of neonatal outcomes.[24]

Other studies have reported relatively few unimpaired survivors among extremely premature neonates receiving CPR in the delivery room.[17] However, lack of standardization for the indications and conduct of delivery room CPR make these results difficult to interpret. The multiple (greater than three) intubation attempts required for the majority of neonates who received delivery room CPR suggest that cardiac compressions may have been given before establishment of effective ventilation, raising concerns as to whether CPR was needed. The higher mortality among neonates receiving multiple intubation attempts reinforces that efficient airway management is paramount, and minimizing the number of intubation attempts may improve outcomes.

This study has several important limitations. Although the present study suggests that a proactive approach should be considered, it is not possible to conclude that this approach increases survival and survival without neurodevelopmental impairment because of potential selection bias and other confounding variables in a retrospective study design. Additionally, outcomes associated with specific interventions (antenatal corticosteroids, cesarean delivery) were not examined. Further studies, either randomized controlled trials or comparative effectiveness research, are needed to identify optimal treatments for extremely preterm neonates born at 23 weeks of gestation.

Differences in the definitions of neurodevelopmental impairment across studies limit comparisons and should be considered in parental counseling and decision-making. Whereas previous studies compared children with neurodevelopmental impairment with those with mild or no impairment,[19] we

distinguished between those with mild and no impairment. Outcomes at 18–22 months-corrected gestational age may not fully predict developmental outcomes later in childhood,[25] and more robust assessments of neurodevelopmental outcomes at school age are needed. Outcomes reported here may not be applicable to centers without trained neonatal care personnel. Furthermore, errors in assessing pregnancy length are recognized.[26] During the study period, NICHD recommendations on definitions and interpretation of electronic fetal monitoring changed.[27] Although preterm PROM was a risk factor for adverse neonatal outcomes, duration of latency between membrane rupture and delivery was unknown.

In conclusion, proactive, interdisciplinary care enabled more than half of the neonates born at 23 weeks of gestation to survive, and approximately half of children evaluated at 18 months exhibited no or mild impairment. This information should be considered when providing prognostic advice to families with threatened preterm birth at 23 weeks of gestation. Although increasing survival to discharge is a first step, increasing survival without neurodevelopmental impairment is the ultimate goal.[22] The relatively small numbers of patients born at the limits of viability dictate that multicenter collaborations are needed to identify best practices for these vulnerable neonates.

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