Neurodevelopmental Follow-up of Very Preterm Infants after Proactive Treatment at a Gestational Age of ≥23 Weeks

Jochen Steinmacher, MD, Frank Pohlandt, MD, MS, Harald Bode, MD, Silvia Sander, MS, Martina Kron, PhD, and Axel R. Franz, MD

Objective To determine the long-term neurodevelopmental outcome in extremely preterm infants after offering life support to all infants ≥23 weeks gestation ("pro-active management").

Study design With parental consent, all infants born at 23 to 25 completed weeks gestation were treated proactively. Surviving infants born from July 1996 to June 1999 were assessed for standardized cognitive and neurological outcomes at 5 years corrected age.

Results 70 of 91 infants admitted to the neonatal intensive care unit survived until follow-up. 67 of the 70 surviving infants were examined at a median corrected age of 5.6 years; 12% had cerebral palsy and a Gross Motor Function Classification Scale score >2; 4% were blind; 1% required a hearing aid; and 12% had a Kaufmann Assessment Battery for Children mental processing composite <51, resulting in 18% sustaining a severe disability. 43% had normal results on a neurological examination, Gross Motor Function Classification Scale score = 0, mental processing composite >85, and had neither severe visual nor hearing impairment. 57% qualified for regular schooling.

Conclusion Improved survival was not associated with an increased risk of severe disability when compared with results of earlier publications. These findings may result from proactive management and are important for counseling patients at risk of imminent extremely preterm delivery. *(J Pediatr 2008;152:771-6)*

Preterm infants are at risk of brain injury and impaired neurocognitive and motor development.[1] Up-to-date information about neurocognitive and psychomotor development is important for appropriate counseling of parents at risk of imminent very preterm delivery[2] and for efforts to improve the care of these infants.

Most follow-up studies on preterm infants report the results of neurodevelopmental assessments at 18 to 24 months corrected age. These medium-term outcome results may not predict longer-term outcome and function.[3] Furthermore, the meaning of mental and physical developmental indices may not easily be explained to parents. At least for some parents, information on function (eg, the child can walk normally, the child qualifies for regular schooling, etc.) may be more informative.

Improved survival has been reported for extremely preterm infants in recent years.[4] However, some studies reported neonatal intensive care unit (NICU) mortality rates as high as 60% in infants of a gestational age between 23 and 25 completed weeks.[5,6] These results reflect life support policies, because as many as 80% of deaths occurred after a decision to withhold or withdraw therapy.[6] Differences in life support policies between centers and countries may not only affect survival,[7,8] but also long-term neurodevelopmental outcomes.[9,10] However, long-term outcome data are not available after explicitly proactive treatment of the most premature infants. The aim of this study was to determine the neurocognitive and motor development and function in a cohort of infants with gestational ages of 22 to 25 completed weeks at the age of school entry after offering life support to all extremely preterm infants with a gestational age ≥23 weeks.

METHODS

Study Subjects

The study was approved by the institutional review board, and written parental consent was obtained. All infants born at 22 to 25 completed weeks gestation (ie, at 22

GMFCS	Gross Motor Function Classification Scale	MPC	Mental processing composite
KABC	Kaufmann Assessment Battery for Children	NICU	Neonatal intensive care unit

From the Department of Pediatrics, Division of Neonatology and Pediatric Critical Care (J.S., F.P., A.F.), Department of Pediatrics, Division of Pediatric Neurology (J.S., H.B.), and Institute of Biometrics, University of Ulm, Ulm, Germany; and Center for Pediatrics, Department of Neonatology, University of Bonn, Bonn, Germany (A.F.).

Supported by the Else-Kröner-Fresenius Foundation (Bad Homburg, Germany) and the Rudolf and Clothilde Eberhardt Foundation (Ulm, Germany). The study sponsors were not involved in the design of the study, the collection and analysis of the data, and the writing of the manuscript.

Submitted for publication May 22, 2007; last revision received Sep 24, 2007; accepted Nov 2, 2007.

Reprint requests: Axel Franz, MD, Department of Neonatology, Center for Pediatrics, Sigmund-Freud-Strasse 25, 53105 Bonn, German. E-mail: axel.franz@ukb.uni-bonn.de.

0022-3476/$ - see front matter

10.1016/j.jpeds.2007.11.004

± 0/7 to 25 ± 6/7 weeks gestation) between July 1, 1996, and June 30, 1999, and admitted to the University of Ulm level 3 NICU on the first day of life were identified and followed up.

Neonatal Life Support Policy ("Proactive Management")

According to the current interdisciplinary German guideline for very preterm birth,[11] a basic policy was followed at the University of Ulm to provide life support immediately after birth to all preterm infants with a gestational age ≥23 completed weeks, provided that parents gave consent after having been informed about the potential survival and long-term outcome. This policy included intrauterine transfer, use of antenatal steroids, tocolysis, fetal monitoring and cesarean section of fetal indication, and attendance of a senior neonatologist at delivery.

Determination of Gestational Age

Gestational age was determined on the basis of the date of fertilization in the case of assisted reproduction, the results of the first trimester ultrasound scan, or the last menstrual period when dates determined by ultrasound scanning were not available.

Standardized Follow-up Assessment

The neurological examination was performed by an experienced pediatric neurologist (J.S.). The child was rated as normal, mildly abnormal (in the presence of minor neurological signs such as broad gait, dysdiadochokinesis, or dysmetria), and severely abnormal (in the presence of any paresis with or without spasticity, any cerebral nerve palsy, or any ataxia).

For evaluation of mobility, the Gross Motor Function Classification Scale (GMFCS)[12] was employed. A score of 0 represents normal mobility, 1 represents mild abnormality (ie, walking, running, and jumping are possible but somewhat reduced in precision and velocity), and 2 represents obviously impaired mobility. A score of 3 or 4 represent severely impaired mobility and lack of mobility, resulting from disabling cerebral palsy in these children.

To evaluate cognitive function, the Kaufmann Assessment Battery for Children (KABC) was applied. The KABC comprises a summative scale, the mental processing composite (MPC), a global measure of cognitive ability with 2 subscales, sequential processing and simultaneous processing. The range of possible scores is 40 to 150. The test was last standardized in 1992 to a mean of 100 and a SD of 15 in a German reference population.[13] The MPC can be interpreted similarly to the results of an intelligence test. Children whose severe cognitive impairment or disability precluded the use of this assessment tool were assigned a score of 30 when minimal speech and the ability for minimal communication with the parents were present (n = 4) and a score of 20 when no speech was present but at least minimal sensory or motor achievements were elicited (n = 1).

Assessment of visual impairment was based on ophthalmological records and classified as severely impaired in the presence of a refractory error in at least 1 eye of more than ± 10 diopter or any amblyopia with a best-corrected visual acuity of less than 20/40. A visual acuity after best-possible correction for ametropia of <20/200 was defined as blindness.

To assess the children for behavioral abnormalities, the parents were asked to complete the Child Behavior Check List for 4- to 18-year-old children in its German adaptation.[14] Parents completed a questionnaire about their child's performance in games, activities, chores, and the quality of relationships with friends and family. 113 items related to behavior had to be scored on a 3-point scale (not true = 0, somewhat true = 1, often true = 2). A total problem score was obtained by sum of all items. Raw scores were converted to age-standardized scores ("T scores" having a mean = 50 and a SD = 10). T scores >70 and >63 defined abnormal behavior in each subscale and in the broader scales of internalizing and externalizing behavior, respectively.

Outcome Criteria

Composite outcome criteria were defined by matching previous reports[15] as closely as possible to enable comparisons of outcomes.

Severe disability was defined as any cerebral palsy resulting in a severely impaired mobility (GMFCS >2), severe cognitive impairment (mental processing composite < 51), hearing loss requiring amplification, or blindness. Provided that none of the aforementioned criteria were met, moderate disability was defined as any abnormal neurological examination associated with a moderate impairment of mobility (GMFCS = 2), cognitive impairment (mental processing composite 51-70), or any severe impairment of vision. Provided that none of the aforementioned criteria were met, mild disability was defined as any abnormal neurological examination with normal or mildly impaired mobility (GMFCS <2), a mental processing composite of 71 to 85, or both. The absence of significant impairment (without disability) was defined as normal neurological examination results, normal mobility (GMFCS = 0), normal cognitive development (mental processing composite >85), and the absence of severe hearing and visual impairment.

Recommendations for school assignment were made by J.S. on the basis of the aforementioned evaluations and the ability to compensate impairments (ie, everyday functioning of the children). In general, a mental processing composite >85 and the absence of any severe impairment were required. When impairments were present, they had to be compensated.

Statistical Analyses

Absolute and relative frequencies (including exact 95% CIs) were calculated for qualitative data. Mean and SD and median, minimum, and maximum were calculated for quantitative data. Associations between risk factors and outcome (here: moderate/severe disability and cognitive impairment),

Table I. Demographic and neonatal morbidity data

	Follow-up (n = 67)	Lost to follow-up (n = 3)	Died (n = 21)
Gestational age, weeks*	24.9 ± 0.6	25.2 ± 0.4	24.3 ± 0.8
	25.1 (22.9-25.7)	25.1 (24.9-25.6)	24.4 (22.9-25.6)
Birth weight, g*	675 ± 153	697 ± 180	588 ± 166
	690 (320-1020)	780 (490-820)	580 (330-1000)
Birth weight <3rd percentile, n (%)	8/67 (12%)	0/3 (0%)	4/21 (19%)
Female sex, n (%)	42/67 (63%)	2/3 (67%)	14/21 (67%)
Any antenatal steroids, n (%)	61/67 (91%%)	3/3 (100%)	17/20 (85%)
*CRIB score**	7.7 ± 3.5		9.7 ± 2.9
	8 (1-16)		9 (5-15)
<3, n (%)	5/59 (8%)	0	0
3-7, n (%)	21/59 (36%)	1/1 (100%)	2/11 (18%)
8-12, n (%)	29/59 (49%)	0	6/11 (55%)
>12, n (%)	4/59 (7%)	0	3/11 (27%)
IVH/PVH ≥grade 3, n (%)	9/67 (13%)	1/3 (33%)	9/19 (47%)
ROP ≥grade 3, n (%)	23/67 (34%)	0/3 (0%)	1/21 (5%)
NEC ≥Bell stage 2, n (%)	6/67 (9%)	1/3 (33%)	3/21 (14%)
CLD (FiO_2 > 0.21 at 36 weeks), n (%)	39/66 (59%)	2/3 (67%)	6/7 (86%)

CRIB, Clinical Risk Index for Babies[16]; *IVH/PVH*, intraventricular and periventricular hemorrhage; *ROP*, retinopathy of prematurity; *NEC*, necrotizing enterocolitis; *CLD*, chronic lung disease.
*Mean ± SD, median (minimum-maximum).

were described by crude odds ratios with exact 95% CIs and *P* values with the Fisher exact test. Because of the small sample size of infants (n = 67), a meaningful multiple logistic regression analysis of risk factors for adverse outcome was not possible.

RESULTS

70 of the 91 infants (77%) admitted to the NICU survived to follow-up. 67 of 70 (96%) surviving children born at <26 weeks of gestation completed the follow-up assessment at a median age of 5.6 years (range, 4.9-6.7 years). The demographic data and neonatal morbidities of these 67 infants, of the 21 infants who died, and of the 3 infants who were lost to follow-up are summarized in Table I.

Because life support policy may influence long-term outcome, delivery, resuscitation, and survival data are combined in Table II. 4 of the 17 NICU deaths occurred despite intensive medical care. In 13 infants, intensive care was withdrawn. In 9 of these 13 infants, death was clearly inevitable. In 3 infants, intensive therapy was likely to be futile, and the prognosis was thought to be poor. In 1 infant, intensive care was withdrawn because of anticipated poor neurological outcome after severe bilateral parenchymal hemorrhages.

8 of 67 children (12%; 95% CI, 5%-22%) had severe cerebral palsy resulting in a GMFCS > 2, 8 children (12%; 95% CI, 5%-22%) had a severe cognitive deficit with a MPC < 51, 3 children (4%; 95% CI, 1%-13%) were blind, and 1 child (1%; 95% CI, 0%-8%) required a hearing aid. 12 children (18%; 95% CI, 10%-29%) were severely disabled. 29 children (43%; 95% CI, 31%-56%) were without significant impairment, and 38 children (57%; 95% CI, 44%-69%) qualified for regular schooling. Table III (available at www.jpeds.com) summarizes the complete neurological, psychomotor, cognitive, and behavioral outcome data according to gestational age at birth.

Results of the analysis of risk factors for moderate or severe disability and for cognitive impairment are summarized in Table IV as crude odds ratios.

For comparison, we reviewed recently published survival and outcome of infants born in Europe and North America at 23 to 25 completed weeks.[5,6,15,17-21] At a gestational age of 23, 24, and 25 completed weeks, NICU survival rates in live-born infants vary from 6% to 46%, from 26% to 63%, and from 44% to 82%, respectively. The rates of infants who survive without severe disability among those who survived NICU varied from 48% to 71%, from 36% to 88%, and from 41% to 89%, respectively (Table V; available at www.jpeds.com). The higher rates of survival in our patients were not associated with higher rates of severely disabled children.

DISCUSSION

We describe neurocognitive and motor developmental outcomes at a median corrected age of 5.6 years for a 3-year cohort of extremely preterm infants. The results confirm earlier reports of impaired neurodevelopmental outcome in extremely preterm infants,[1,15,22-24] stressing the need for further efforts to improve long-term outcome in this vulnerable population.

This information is helpful for counseling parents with imminent extremely preterm delivery. First, both the frequency of recommendations for normal schooling and the frequency of normal motor functioning (GMFCS = 0) are easy to understand and more meaningful to parents than a mental or a physical developmental index. Second, the results of neurodevelopmental assessments at the age of school entry provided in this study predict longer-term outcome and func-

Table II. Resuscitation and survival data according to gestational age in extremely preterm infants born between July 1996 and June 1999

Gestational age, completed weeks*	22	23	24	25
Number of still births	7	5	5	2
Number of live births not attended by a neonatologist	1	0	0	0
Number of deliveries attended by a neonatologist (only live births)	3	13	31	48
Number of NICU admissions	3	12	31	45
Survivors to discharge, n (% of NICU admissions)	1 (33%)[1%-91%]	9 (75%)[43%-95%]	23 (74%)[55%-88%]	41 (91%)[79%-98%]
Long-term survivors, n (% of NICU admissions)	1 (33%)[1%-91%]	8 (66%)[35%-90%]	21 (68%)[49%-83%]	40 (89%)[76%-96%]
Follow-up completed, n (% of long-term survivors)	1 (100%)[3%-100%]	8 (100%)[63%-100%]	20 (95%)[76%-100%]	38 (95%)[83%-99%]

95% CI shown in brackets.
*For example, infants born at 23 completed weeks gestation included infants born at 23 + 0/7 weeks to 23 + 6/7 weeks gestation.

Table IV. Crude odds ratios of risk factors for moderate or severe disability and for cognitive impairment (mental processing composite [IQ] <71)

		Moderate or severe disability		MPC < 71	
Risk factor	**n**	**OR [95% CI]**	***P* value†**	**OR [95% CI]**	***P* value†**
GA,22-23 versus 24-25 completed weeks	67	1.5 [0.3-7.9]	.711	0.8 [0.1-4.6]	1.0
SGA, yes versus no	67	3.5 [0.6-24.5]	.124	1.8 [0.24-10.3]	.672
IVH/PVH, ≥ grade 3 versus < grade 3	67	8.4 [1.4-88.2]	.008	15.0 [2.3-157.7]	<.001
PVL, yes versus no	64	(1,22,0,41)*	.359	(1,16,0,47)*	.266
ROP, ≥ grade 3 versus < grade 3	67	5.3 [1.6-18.3]	.003	2.5 [0.7-8.8]	.147
MV, yes versus no	67	(24,0,36,7)*	.044	(18,0,42,7)*	.176
Duration of MV, ≥7 days versus <7 days	67	(24,0,27,16)*	<.001	(18,0,33,16)*	.004
Maternal language, others versus German	67	2.7 [0.6-7.9]	.161	3.1 [0.8-11.5]	.065
Maternal occupation, no versus yes	65	3.5 [0.9-16.5]	.055	5.4 [1.0-52.9]	.036
Highest academic degree of mother, none or lowest degree‡ versus higher degrees	62	4.1 [1.2-15.1]	.015	5.9 [1.4-28.7]	.007

OR, Odds ratio; *GA*, gestational age; *SGA*, small for gestational age (ie, weight at birth <3rd percentile); *PVL*, periventricular leukomalacia; *MV*, mechanical ventilation.
*Frequencies of 2-by-2 tables (outcome/riskfactor: yes/yes, yes/no, no/yes, no/no) instead of odds ratios because of zero cells.
†Fisher exact test.
‡Lowest level of the 3 level German school system, qualifies for non-academic education.

tion more accurately than the results of assessments at 18 months corrected age.[3] Third, although an alarming number of preterm infants sustained severe disability, half the infants qualified for regular schooling, although birth occurred at 23 to 25 weeks gestation.

Although we confirmed the role of certain prenatal and perinatal risk factors for severe disability, every attempt to estimate the prognosis for an individual child on the basis of these variables would leave parents and physicians with a high degree of uncertainty. Furthermore, the most important risk factors for impaired neurocognitive development will only become apparent after birth (eg, severe intraventricular or periventricular hemorrhage, need for prolonged mechanical ventilation; Table IV). An attempt to predict outcome prenatally, on the basis of gestational age alone, would be even more uncertain. Most importantly, normal neurocognitive outcome occurred in some of the most premature infants. Although the rates of cognitive deficits or impaired mobility do not increase substantially with decreasing gestational age among survivors with a gestational age <26 weeks in our population (Table III), the actual prevalences of these disabilities cannot be estimated with confidence because of the small number of infants in each gestational age group. There does not seem to be an obvious cutoff value in gestational age groups of 23 to 25 weeks, below which normal neurodevelopment will not occur.

Severe intraventricular and periventricular hemorrhage and the need for prolonged ventilation were the 2 variables most strongly associated with impaired neurodevelopmental outcome, as previously described.[25] Therefore, reducing the need for prolonged mechanical ventilation (eg, by early surfactant administration and early extubation to nasal continuous positive airway pressure)[26] and reducing the incidence of severe intraventricular and periventricular hemorrhage (eg, with prophylactic indomethacin[27] and with yet-unknown

measures to stabilize cerebral perfusion[28]) may help to further improve neurodevelopmental outcome.

Social and environmental factors including maternal level of education and primary language spoken were associated with impaired cognitive outcome (Table IV), as previously reported.[3,24,29-31] These findings suggest that improving post-discharge supportive interventions may further improve long-term outcomes, especially in infants in under-privileged families.[31] However, post-discharge interventions so far only have been effective in the short term in very low birth weight infants.[32,33]

In contrast to our results, earlier European studies on outcome in extremely preterm infants born at <26 weeks of gestation reported higher mortality rates at delivery and in the NICU.[5,6,15,17,34] These higher mortality rates probably not only reflect differences in perinatal morbidity, but also differences in parental choices and perinatal management strategies. As many as 80% of perinatal and neonatal deaths are reported to occur after a decision to withhold or withdraw therapy.[6] In our study, the parents of almost all infants delivered at 22 and 23 weeks chose life support instead of palliative care for their infants. We speculate that the local outcome data provided to the parents and the general offer of life support may have contributed more to these decisions than parental cultural characteristics.

In comparison with these European studies[5,6,15,17,34] from countries where life support is not offered universally to infants with a gestational age <26 weeks, we report higher NICU admission, survival to discharge, and long-term survival rates without increases in the rates of adverse outcomes. The rates of severe disability in infants who survived were 12 of 67 (18%) in this study versus 53 of 241 (22%) in the Epicure study.[15] These outcome differences may in part result from proactive treatment of these extremely preterm infants, as previously suggested,[7] and are in contrast to older reports suggesting that improved survival, because of a more active life support, may result in higher proportions of disabled children.[9,10]

Our results could be biased because some obstetricians may had chosen to refer only what they considered to be the most viable fetuses and to treat less viable pregnancies as late spontaneous abortions.

These are results from a single institution and may not have general validity. At least we show what can be achieved when a consistent policy of life support is applied in all extremely preterm infants with a gestational age ≥23 weeks. The validity of our results is supported by reports of similar survival to discharge and survival without disability rates from other institutions.[7,8,19,21]

REFERENCES

1. Hack M, Taylor HG, Klein N, Eiben R, Schatschneider C, Mercuri Minich N. School-age outcomes in children with birth weights under 750 g. N Engl J Med 1994;331:753-9.
2. Blanco F, Suresh G, Howard D, Soll RF. Ensuring accurate knowledge of prematurity outcomes for prenatal counseling. Pediatrics 2005;115:e478-87.
3. Hack M, Taylor HG, Drotar D, Schluchter M, Cartar L, Wilson-Costello D, et al. Poor predictive validity of the Bayley Scales of Infant Development for cognitive function of extremely low birth weight children at school age. Pediatrics 2005;116:333-41.
4. Lemons JA, Bauer CR, Oh W, Korones SB, Papile LA, Stoll BJ, et al. Very low birth weight outcomes of the National Institute of Child health and human development neonatal research network, January 1995 through December 1996. Pediatrics 2001; 107:E1.
5. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. N Engl J Med 2000;343:378-84.
6. Larroque B, Breart G, Kaminski M, Dehan M, Andre M, Burguet A, et al. Survival of very preterm infants: Epipage, a population based cohort study. Arch Dis Child Fetal Neonatal Ed 2004;89:F139-44.
7. Hakansson S, Farooqi A, Holmgren PA, Serenius F, Hogberg U. Proactive management promotes outcome in extremely preterm infants: a population-based comparison of two perinatal management strategies. Pediatrics 2004;114:58-64.
8. Herber-Jonat S, Schulze A, Kribs A, Roth B, Lindner W, Pohlandt F. Survival and major neonatal complications in infants born between 22 0/7 and 24 6/7 weeks of gestation (1999-2003). Am J Obstet Gynecol 2006;195:16-22.
9. Lorenz JM, Paneth N, Jetton JR, den Ouden L, Tyson JE. Comparison of management strategies for extreme prematurity in New Jersey and the Netherlands: outcomes and resource expenditure. Pediatrics 2001;108:1269-74.
10. Emsley HC, Wardle SP, Sims DG, Chiswick ML, D'Souza SW. Increased survival and deteriorating developmental outcome in 23 to 25 week old gestation infants, 1990-4 compared with 1984-9. Arch Dis Child Fetal Neonatal Ed 1998;78:F99-104.
11. German Society of Gynecology and Obstetrics, German Society of Pediatrics and Adolescent Medicine, German Society of Perinatal Medicine and Society of Neonatology and Pediatric Intensive Care Medicine. [Premature delivery in borderline viability of the infant. A recommendation.] Z Geburtshilfe Neonatol 1998;202:261-3.
12. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997;39:214-23.
13. Melchers P, Preuss U. [Adaptation of the Kaufman Assessment Battery for Children for German-speaking areas. Part 1: Introduction of the battery]. Z Kinder Jugendpsychiatr 1992;20:85-93.
14. Dopfner M, Schmeck K, Berner W, Lehmkuhl G, Poustka F. [Reliability and factorial validity of the Child Behavior Checklist—an analysis of a clinical and field sample]. Z Kinder Jugendpsychiatr 1994;22:189-205.
15. Marlow N, Wolke D, Bracewell MA, Samara M. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med 2005;352:9-19.
16. The CRIB (clinical risk index for babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. Lancet 1993;342: 193-8.
17. Vanhaesebrouck P, Allegaert K, Bottu J, Debauche C, Devlieger H, Docx M, et al. The EPIBEL study: outcomes to discharge from hospital for extremely preterm infants in Belgium. Pediatrics 2004;114:663-75.
18. Markestad T, Kaaresen PI, Ronnestad A, Reigstad H, Lossius K, Medbo S, et al. Early death, morbidity, and need of treatment among extremely premature infants. Pediatrics 2005;115:1289-98.
19. El Metwally D, Vohr B, Tucker R. Survival and neonatal morbidity at the limits of viability in the mid 1990s: 22 to 25 weeks. J Pediatr 2000;137:616-22.
20. Chan K, Ohlsson A, Synnes A, Lee DS, Chien LY, Lee SK. Survival, morbidity, and resource use of infants of 25 weeks' gestational age or less. Am J Obstet Gynecol 2001;185:220-6.
21. Serenius F, Ewald U, Farooqi A, Holmgren PA, Hakansson S, Sedin G. Short-term outcome after active perinatal management at 23–25 weeks of gestation. A study from two Swedish perinatal centres. Part 3: neonatal morbidity. Acta Paediatr 2004;93:1090-7.
22. Wolke D, Meyer R. Cognitive status, language attainment, and prereading skills of 6-year-old very preterm children and their peers: the Bavarian Longitudinal Study. Dev Med Child Neurol 1999;41:94-109.
23. Gross SJ, Mettelman BB, Dye TD, Slagle TA. Impact of family structure and stability on academic outcome in preterm children at 10 years of age. J Pediatr 2001;138:169-75.
24. Vohr BR, Allan WC, Westerveld M, Schneider KC, Katz KH, Makuch RW, et al. School-age outcomes of very low birth weight infants in the indomethacin intraventricular hemorrhage prevention trial. Pediatrics 2003;111:e340-6.
25. Ment LR, Allan WC, Makuch RW, Vohr B. Grade 3 to 4 intraventricular hemorrhage and Bayley scores predict outcome. Pediatrics 2005;116:1597-8.
26. Stevens TP, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. Cochrane Database Syst Rev 2004;CD003063.
27. Ment LR, Vohr BR, Makuch RW, Westerveld M, Katz KH, Schneider KC, et al. Prevention of intraventricular hemorrhage by indomethacin in male preterm infants. J Pediatr 2004;145:832-4.
28. Kluckow M, Evans N. Low superior vena cava flow and intraventricular haemorrhage in preterm infants. Arch Dis Child Fetal Neonatal Ed 2000;82:F188-94.

29. Vohr BR, Wright LL, Dusick AM, Perritt R, Poole WK, Tyson JE, et al. Center differences and outcomes of extremely low birth weight infants. Pediatrics 2004;113:781-9.
30. Kilbride HW, Thorstad K, Daily DK. Preschool outcome of less than 801-gram preterm infants compared with full-term siblings. Pediatrics 2004;113:742-7.
31. Fily A, Pierrat V, Delporte V, Breart G, Truffert P. Factors associated with neurodevelopmental outcome at 2 years after very preterm birth: the population-based Nord-Pas-de-Calais EPIPAGE cohort. Pediatrics 2006;117:357-66.
32. The Infant Health and Development Program Study Group. Enhancing the outcomes of low birth weight, premature infants. A multisite, randomized trial. JAMA 1990;263:3035-42.
33. McCormick MC, Brooks-Gunn J, Buka SL, Goldman J, Yu J, Salganik M, et al. Early intervention in low birth weight premature infants: results at 18 years of age for the Infant Health and Development Program. Pediatrics 2006;117:771-80.
34. Bucher HU, Ochsner Y, Fauchere JC. Two years outcome of very pre-term and very low birthweight infants in Switzerland. Swiss Med Wkly 2003;133:93-9.

50 Years Ago in *The Journal of Pediatrics*

Narcotic withdrawal symptoms in the newborn infant resulting from maternal addiction

Schneck H. J Pediatr 1958;52:584-87

No longer does one need to go to a medical journal to read about drug abuse and addiction; the lay media reports on the drug culture, drug lifestyle, drug cartels, drug gangs, drug connections, death from drugs, and drug rehabilitation. Our vocabulary has special meaning with reference to drugs; we routinely speak of "highs," "cold turkey," "speed," "crack," and "mainlining," to name only a few terms. The 2004 National Survey on Drug Use and Health estimates that 19.1 million Americans age 12 years and older use illicit drugs.[1] We hear and read of people in high profile professions (eg, entertainers, athletes, politicians) who succumb to drugs, confront the law, and seek medical intervention. Actually, the problem of drug addiction cuts across all demographic boundaries of society, affecting even the most vulnerable and helpless—the newborn and unborn.

Fifty years ago, Dr Schneck reported on an infant born to a mother addicted to heroin. Today we are dealing with dependence on an array of drugs including narcotics, hallucinogens, barbiturates, benzodiazepines, amphetamines, methamphetamine, cocaine, marijuana, alcohol, nicotine, inhalants, and antidepressants, and combinations of these drugs. The signs of withdrawal in the newborn described by Schneck have been expanded and systematized to guide evaluation and treatment. The principles of care for the withdrawing newborn are primarily supportive and have not changed much in 50 years. Treatment drugs should match the class of agents from which the infant is withdrawing. The aim of pharmacologic therapy is to make the infant comfortable but not obtunded. Weaning from the drug should be gradual.

In the past, mortality was secondary to diarrhea, vomiting, fever, and fluid and electrolyte imbalance as a consequence of withdrawal. Today, death is rare but can result from complications of abuse during pregnancy, such as prematurity, low birth weight, meconium aspiration, sepsis, and cerebral infarction. Laboratory analysis of meconium, hair, and urine can confirm drug exposure.

Data on long-term outcomes include delayed physical and mental development, learning disabilities, and hyperactivity. Other risks include ongoing exposure to illicit drugs (either passively or by accidental ingestion), abuse, and sudden infant death syndrome.

We are faced with a national drug problem of epidemic proportions and pediatricians care for some of its unwitting victims. We need to be vigilant, compassionate, and effective in our management of the infant and the drug-dependent mother.

Eugene E. Cepeda, MD
Enrique M. Ostrea Jr, MD
Department of Pediatrics
Wayne State University
Hutzel Women's Hospital
Detroit, Michigan
10.1016/j.jpeds.2007.11.028

REFERENCE

1. Substance Abuse and Mental Health Services Administration (2005). Results from the 2004 National Survey on Drug Use and Health: National Findings (Office of Applied Studies, NSDUH Series H-28, DHHS Publication No. SMA 05-4082). Rockville, MD.

Table III. Neurocognitive, psychomotor, and behavioral outcome in extremely preterm infants according to gestational age at birth

Gestational age, completed weeks*	All (22-25)	22	23	24	25
Survivors with full follow-up, n	67	1	8	20	38
Neurological examination results					
Normal, n (%), [95%CI]	37 (55%)[43%-67%]	0	6 (75%)[35%-97%]	6 (30%)[12%-54%]	25 (66%)[49%-80%]
Severely abnormal, n (%), [95%CI]	12 (18%)[10%-29%]	0	0 (0%)[0%-37%]	5 (25%)[9%-49%]	7 (18%)[8%-34%]
Mobility					
GMFCS = 0, n (%), [95%CI]	47 (70%)[58%-81%]	1	7 (88%)[47%-100%]	10 (50%)[27%-73%]	29 (76%)[60%-89%]
GMFCS > 2, n (%), [95%CI]	8 (12%)[5%-22%]	0	0 [0%-37%]	3 (15%)[3%-38%]	5 (13%)[4%-27%]
Cognitive development					
Mean MPC±SD (Kaufmann ABC)	82 ± 23	101	89 ± 16	79 ± 23	82 ± 25
Median MPC (minimum-maximum)	90 (20-122)	101	94 (65-105)	84 (30-111)	91 (20-122)
MPC < 51, n (%), [95%CI]	8 (12%)[5%-22%]	0	0 (0%)[0%-37%]	2 (10%)[1%-32%]	6 (16%)[6%-31%]
MPC 51-70, n (%), [95%CI]	10 (15%)[7%-26%]	0	2 (25%)[3%-65%]	4 (20%)[6%-44%]	4 (11%)[3%-25%]
MPC 71-85, n (%), [95%CI]	11 (16%)[8%-27%]	0	1 (13%)[0%-53%]	4 (20%)[6%-44%]	6 (16%)[6%-31%]
MPC > 85, n (%), [95%CI]	38 (57%)[44%-69%]	1	5 (63%)[24%-91%]	10 (50%)[27%-73%]	22 (58%)[41%-74%]
Composite outcome variables					
Severe disability, n (%), [95%CI]	12 (18%)[10%-29%]	0	0 (0%)[0%-37%]	4 (20%)[6%-44%]	8 (21%)[10%-37%]
Moderate disability, n (%), [95%CI]	12 (18%)[10%-29%]	0	4 (50%)[16%-84%]	3 (15%)[3%-38%]	5 (13%)[4%-28%]
Mild disability, n (%), [95%CI]	14 (21%)[12%-33%]	1	2 (25%)[3%-65%]	7 (35%)[15%-59%]	4 (11%)[3%-25%]
Without disability, n (%), [95%CI]	29 (43%)[31%-56%]	0	2 (25%)[3%-65%]	6 (30%)[12%-54%]	21 (55%)[38%-71%]
School recommendation					
Qualified for regular schooling, n (%), [95%CI]	38 (57%)[44%-69%]	1	5 (63%)[24%-91%]	9 (45%)[23%-68%]	23 (61%)[43%-76%]
Behavioral outcome, n†	59	1	7	18	33
Attention problems (ie, T > 70 in CBCL subscale), n (%), [95%CI]	4 (6%)[2%-16%]	0	0 (0%)[0%-41%]	1 (6%)[0%-27%]	3 (9%)[2%-24%]
Abnormal behavior (ie, T > 70 in ≥1 subscale of the CBCL), n (%), [95%CI]	7 (12%)[5%-23%]	0	0 (0%)[0%-41%]	2 (11%)[1%-35%]	5 (15%)[5%-32%]
Internalizing problems (ie, T > 64 in summary scale), n (%), [95%CI]	7 (12%)[5%-23%]	0	1 (14%)[0%-58%]	1 (6%)[0%-27%]	5 (15%)[5%-32%]
Externalizing problems (ie, T > 64 in summary scale), n (%), [95%CI]	6 (10%)[4%-20%]	0	1 (14%)[0%-58%]	1 (6%)[0%-27%]	4 (12%)[3%-28%]

GMFCS, Gross motor function classification scale; *T*, T-score of the Child Behavior Check List (CBCL); MPC, mental processing composite.
*Infants born at 23 completed weeks gestation included infants born at 23 + 0/7 weeks − 23 + 6/7 weeks gestation.
†Behavioral data is only available in 59 patients, of whom the parents completed the Child Behavior Check List (CBCL).

Table V. Survival and long-term outcome of extremely preterm infants (23-25 weeks) in several recent European and North American studies

Study		EPICure short-term[5]	EPICure long-term[16]	Epipage[6]	EPIBel[18]	Canadian NICUs[21]	Norway[19]	Providence[20]	North Sweden[22]	Ulm
	Years of birth	1995	1995	1997	1999-2000	1996-1997	1999-2000	1993-1997	1992-1998	1996-1999
23 weeks										
All births	[n]			137	71		55	56		18
All live births	[n]	241	241	30	18	150	35	41	40	13
NICU admissions	[n (% of life births)]	131 (54%)	131 (54%)	6 (20%)	13 (73%)	73 (49%)	23 (66%)	39 (95%)	40 (100%)	12 (92%)
Survivors to discharge	[n (% of NICU adm.) (% of all life births)]	26 (20%) (11%)	26 (20%) (11%)	0	1 (8%) (6%)	25 (34%) (17%)	9 (39%) (26%)	19 (49%) (46%)	17 (43%) (43%)	9 (75%) (69%)
Survivors without severe disability	[n (% of NICU surviv.) (% of all life births)]	17 (65%) (7%)	17 (65%) (7%)			12 (48%) (8%)	5 (56%) (14%)	11 (58%) (27%)	12 (71%) (30%)	8 (89%) (62%)
24 weeks										
All births	[n]			115	101		80	73		36
All live births	[n]	382	382	42	65	242	64	61	70	31
NICU admissions	[n (% of life births)]	298 (78%)	298 (78%)	27 (64%)	54 (83%)	187 (77%)	58 (91%)	54 (89%)	70 (100%)	31 (100%)
Survivors to discharge	[n (% of NICU adm.) (% of all life births)]	100 (34%) (26%)	100 (34%) (26%)	13 (48%) (31%)	19 (35%) (29%)	107 (57%) (44%)	35 (60%) (55%)	36 (67%) (59%)	44 (63%) (63%)	23 (74%) (74%)
Survivors without severe disability	[n (% of NICU surviv.) (% of all life births)]	73 (73%) (19%)	52 (52%) (14%)		10 (53%) (15%)	39 (36%) (21%)	23 (66%) (36%)	32 (88%) (52%)	32 (73%) (46%)	16 (70%) (52%)
25 weeks										
All births	[n]			204	115		83	94		50
All live births	[n]	424	424	119	90	302	71	87	103	48
NICU admissions	[n (% of life births)]	357 (84%)	357 (84%)	95 (79%)	90 (100%)	266 (88%)	69 (97%)	87 (93%)	103 (100%)	45 (95%)
Survivors to discharge	[n (% of NICU adm.) (% of all life births)]	186 (52%) (44%)	186 (52%) (44%)	59 (63%) (50%)	50 (56%) (56%)	205 (77%) (68%)	55 (80%) (77%)	71 (82%) (82%)	79 (77%) (77%)	41 (91%) (85%)
Survivors without severe disability	[n (% of NICU surviv.) (% of all life births)]	142 (76%) (33%)	118 (63%) (28%)		29 (58%) (32%)	85 (41%) (32%)	44 (80%) (62%)	56 (79%) (64%)	70 (89%) (68%)	29 (71%) (60%)

In EPICure, short-term[5] survivors without severe disability were NICU survivors at median corrected age of 30 months without a disability that was likely to put the child in need of physical assistance to perform daily activities.
In EPICure, long-term[16] survivors without severe disability were survivors at a median age of 6.3 years with absence of all the following items: non-ambulatory cerebral palsy, IQ >3 SD below the mean (applying contemporary classmates as a reference group), profound sensorineural hearing loss, and blindness. 78% of long-term survivors were examined and reported.
For the Canadian NICUs,[21] only inborn infants are reported in this table. Survivors without severe disability were short-term NICU survivors without chronic lung disease, necrotizing enterocolitis, >grade 2 intraventricular hemorrhage, or > grade 2 retinopathy of prematurity.
In Markestad,[19] survivors without severe disability were short-term NICU survivors without > grade 2 intraventricular/periventricular hemorrhage, periventricular leukomalacia with >2 cysts, ventricular dilation requiring a shunt, clinical signs of brain damage at discharge, deafness, retinopathy > grade 3 or cryotherapy.
In El Metwally,[20] survivors without severe disability were short-term NICU survivors without grade 3 intraventricular hemorrhage or periventricular hemorrhage.
In Serenius,[22] survivors without severe disability were short-term NICU survivors without > grade 2 intraventricular hemorrhage and without > grade 2 retinopathy of prematurity.