Outcomes of Infants Born at 22 and 23 Weeks' Gestation

WHAT'S KNOWN ON THIS SUBJECT: The remarkable improvement in the survival of extremely premature infants has been well documented. However, there have been few cohort studies large enough to determine the neurodevelopmental outcomes of survivors born at 22 or 23 weeks.

WHAT THIS STUDY ADDS: The proportions of unimpaired or minimally impaired were 12.0% at 22 weeks (n = 75) and 20.0% at 23 weeks (n = 245). The outcomes were inferior compared with those for infants born at 24 and 25 weeks, but were improved compared with those in previous studies.

abstract

OBJECTIVE: To provide instructive information on death and neurodevelopmental outcomes of infants born at 22 and 23 weeks' gestational age.

METHODS: The study cohort consisted of 1057 infants born at 22 to 25 weeks in the Neonatal Research Network, Japan. Neurodevelopmental impairment (NDI) at 36 to 42 months' chronological age was defined as any of the following: cerebral palsy, hearing impairment, visual impairment, and a developmental quotient <70. A systematic review was performed by using databases of publications of cohort studies with neonatal and neurodevelopmental outcomes at 22 and 23 weeks.

RESULTS: Numbers and incidences (%) of infants with death or NDI were 60 (80%) at 22 weeks and 156 (64%) at 23 weeks. In logistic regression analysis, gestational ages of 22 weeks (odds ratio [OR]: 5.40; 95% confidence interval [CI]: 2.48–11.76) and 23 weeks (OR: 2.14; 95% CI: 1.38–3.32) were associated with increased risk of death or NDI compared with 24 weeks, but a gestational age of 25 weeks (OR: 0.65; 95% CI: 0.45–0.95) was associated with decreased risk of death or NDI. In the systematic review, the medians (range) of the incidence of death or NDI in 8 cohorts were 99% (90%–100%) at 22 weeks and 98% (67%–100%) at 23 weeks.

CONCLUSIONS: Infants born at 22 and 23 weeks' gestation were at higher risk of death or NDI than infants at born at 24 weeks. However, outcomes were improved compared with those in previous studies. There is a need for additional discussions on interventions for infants born at 22 or 23 weeks' gestation. *Pediatrics* 2013;132:62–71

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KEY WORDS

extremely preterm infants, neurodevelopmental, outcome of high-risk infants, cerebral palsy, cognitive impairment

ABBREVIATIONS

CI—confidence interval
CLD—chronic lung disease
CP—cerebral palsy
DQ—developmental quotient
GMFCS—Gross Motor Function Classification System
IVH—intraventricular hemorrhage
KSPD—Kyoto Scale of Psychological Development
NDI—neurodevelopmental impairment
OR—odds ratio
ROP—retinopathy of prematurity

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The remarkable improvement in the survival of extremely low birth weight infants has been well documented.[1,2] Increased extremely low birth weight infant survival rates have paralleled improvements in prenatal and neonatal care.[3] The outcomes after 24 weeks' gestational age have been well estimated and evaluated.[4–21]

There recently have been several notable reports on 22 and 23 weeks' gestational age; the short-term outcomes of these extremely premature infants seem to have improved, but the long-term outcomes are still unfavorable.[6–18] Decisions to initiate or withhold intensive care for these extremely premature infants are highly controversial, in contrast to those for infants born at 24 and 25 weeks' gestational age.[22–24] Physicians and parents contemplating the prognosis of extremely preterm infants require reliable information based on gestational age with which to plan care around the time of birth and thereafter.[4,25]

The aim of this study was to provide instructive information on death and neurodevelopmental outcomes of infants born at 22 and 23 weeks' gestational age and to compare them with those of infants born at 24 or 25 weeks from a large multicenter cohort and a systematic review.

METHODS

Study Subjects and Definitions

A total of 48 tertiary centers participated in a multicenter follow-up study of the Neonatal Research Network, Japan, in infants born at 22 to 25 weeks between January 1, 2003, and December 31, 2005.[5,6,26,27] Each center registered all very low birth weight infants who were admitted to the NICU within 28 days after birth, including infants transferred to the centers after birth (outborn). The infants who were born alive but died in the delivery room in the centers were registered. Infants who were recognized as born before 22 weeks 0 day were excluded.[6]

Demographic, perinatal, and infant data were collected from each center by using previously described definitions.[5,6,26,27] Gestational age was determined in the following order: obstetric history based on last menstrual period, with confirmation or correction by obstetric examination by using ultrasonography at the health checkup for pregnant women during the first trimester, and postnatal physical examinations of neonates. Premature rupture of membranes was defined as rupture of membranes before the onset of labor. Antenatal steroid use was defined as administration of any corticosteroid to accelerate fetal lung maturity. Maternal transport meant only emergency transport. Respiratory distress syndrome was diagnosed by using clinical and radiographic findings. Chronic lung disease (CLD) was defined as the use of supplemental oxygen on the 28th day after birth, and 36-week CLD was defined when an infant received supplemental oxygen at the postmenstrual age of 36 weeks. Symptomatic patent ductus arteriosus was diagnosed on the basis of both echocardiographic findings and clinical evidence of volume overload because of left-to-right shunt. Intraventricular hemorrhage (IVH) was reported according to the classification of Papile et al.[28] Cystic periventricular leukomalacia was diagnosed by cranial ultrasound or head MRI scans. Sepsis was defined as culture-proven septicemia or bacteremia at any time during the NICU stay. Necrotizing enterocolitis was defined according to the classification of Bell et al[29] as stage II or higher. The treatment of retinopathy of prematurity (ROP) was laser coagulation, cryocoagulation therapy, or both.

Neurodevelopmental Assessments

A comprehensive neurodevelopmental assessment was performed on the surviving infants at 36 to 42 months' chronological age. The assessment consisted of neurologic assessment, functional classification of hearing and visual ability, developmental evaluation, growth assessment, medical and social history, and interviews at each participating center.

The neuromotor examinations were performed by a trained pediatrician, not necessarily blinded to the perinatal details. Cerebral palsy (CP) was defined as a nonprogressive, nontransient central nervous system disorder characterized by abnormal muscle tone in at least 1 extremity and abnormal control of movement and posture.[30] Profound CP was defined as a Gross Motor Function Classification System (GMFCS) level of 4 or 5.[31] Children with an unknown CP level were classified as having profound impairment. Children with any type of CP who were defined as GMFCS level 1 were excluded from the CP group and were included in the minimally impaired group.[13] Hearing impairment was defined as when amplification was required. Visual impairment was defined as blindness with no functional vision in 1 or both eyes.

The assessment of cognitive function was performed by using the Kyoto Scale of Psychological Development (KSPD) test.[32] This test was administered by experienced testers who were certified psychologists blinded to the perinatal details at each center. The developmental quotient (DQ) was derived by dividing developmental age by chronological age. A DQ score of 100.6 $\pm$ 13.4 represents the mean $\pm$ 1 SD at the time of standarization.[32] A DQ score $<$70 was interpreted as representing significantly delayed performance. If the KSPD assessment was not available, the pediatrician estimated the child's development level as delayed or not delayed. In cases judged as delayed, the developmental level was assumed as equivalent to a DQ score $<$50 in this study.

Neurodevelopmental impairment (NDI) was defined as any of the following: CP with a GMFCS level 2 to 5, hearing impairment, visual impairment, or a DQ score <70. Profound NDI was defined as profound CP and/or a DQ score <50.

Statistical Analyses

Characteristics by gestational age are described as means and SDs for continuous variables and as numbers and proportions for binary and categorical variables. Logistic regression was used to evaluate the relationship between risk factors and death or NDI at 3 years of age. We calculated odds ratios (ORs) and their 95% confidence intervals (CIs) by logistic regression using a reference of infants born at 24 weeks' gestational age. The selected biological and perinatal characteristics were gender, multiple birth, premature rupture of membranes, antenatal steroid use, maternal transport, being outborn, use of cesarean delivery, and gestational age because these were identified as variables associated with outcomes in previous follow-up studies.[7,33–38]

Systematic Review of Studies With Neonatal Outcomes at 22 and 23 Weeks' Gestation

The PubMed and Cochrane Library databases were searched by using a combination of the following words: extremely premature, infant, neurodevelopment, and outcome. The language was restricted to English. All potentially relevant titles and abstracts were retrieved and assessed for eligibility. The reference lists of relevant articles were reviewed, and relevant citations were retrieved if they had not been obtained in the primary search. Publications were selected for inclusion if they contained the following: (1) a publication date between January 1, 2000, and June 30, 2012; (2) outcomes of infants born during or after 1990; (3) the numbers of cases of death and NDI at 18 to 42 months for infants born at <28 weeks' gestational age; and (4) the numbers of evaluated infants at 18 to 42 months. For each eligible study, all reported components of death, NDI, and follow-up rates were extracted. The latest reports were chosen from the same cohorts or the same area.

RESULTS

During the study period, 1057 infants born at <26 weeks were registered with the Neonatal Research Network (Fig 1). Of these, 266 died in the NICU (25.2%), including 1 case not admitted to the NICU, and 791 (74.8%) survived to discharge. Nine infants died after discharge. Between January 2006 and December 2008, 562 of the 782 survivors visited a site for standardized follow-up assessment.

Demographic and perinatal characteristics, neonatal morbidities, and interventions were not different between infants evaluated and not evaluated, except that evaluated infants were more likely to require treatment of ROP (234 [41.7%] of evaluated infants, 73 [33.2%] of infants who were not evaluated), and were less likely to be outborn (47 [8.9%] of evaluated infants, 29 [13.2%] of infants who were not evaluated), experience neonatal seizure (30 [5.3%] of evaluated infants, 25 [11.4%] of infants who were not evaluated), and have grade 3–4 IVH (48 [8.6%] of evaluated infants, 30 [13.6%] of infants who were not evaluated).

As shown in Table 1, stratifying demographic and perinatal characteristics according to gestational weeks, infants with a birth weight <400 g were particularly common at 22 weeks. The use of antenatal steroids, maternal transport, being outborn, and cesarean delivery increased with increasing gestational weeks. Among neonatal morbidities, proportions of respiratory distress syndrome, neonatal seizure, IVH grades 3–4, and sepsis tended to decrease with increasing gestational weeks. Proportions of CLD at 36 weeks' corrected gestational age, ligation for patent ductus arteriosus, cystic periventricular leukomalacia, necrotizing enterocolitis, and ROP requiring any treatment were low in infants born at 22 weeks.

Table 2 shows neurodevelopmental outcomes grouped by gestational weeks of the evaluated infants. Seventy-five (13.7%) infants had CP,

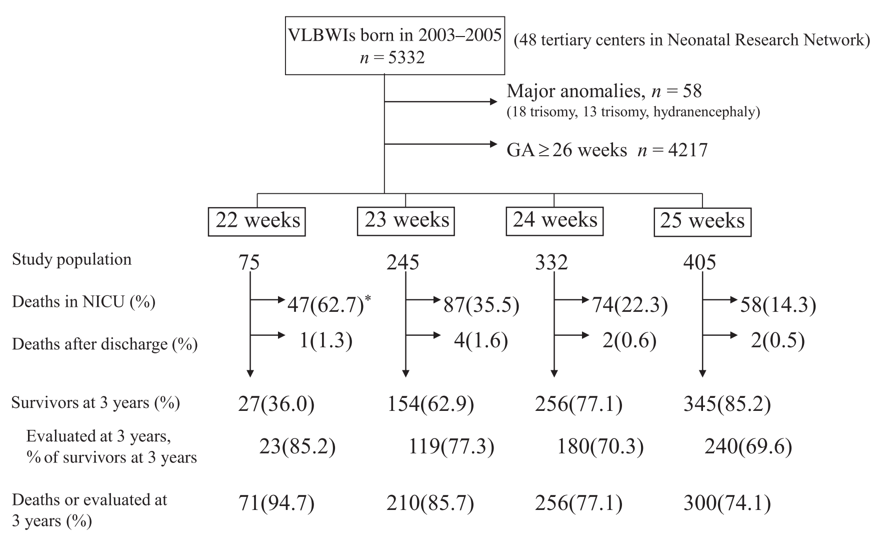

FIGURE 1
Study subjects by gestational age groups. *Includes 1 case born alive but not admitted to the NICU. GA, gestational age; VLBWI, very low birth weight infants.

TABLE 1 Characteristics of Study Cohort

	Gestational Age				
	22 Weeks (n = 75)	23 Weeks (n = 245)	24 Weeks (n = 332)	25 Weeks (n = 405)	Total N =1057
Demographic and perinatal characteristics					
BW, mean ± SD, g	488 ± 72	575 ± 80	634 ± 103	741 ± 137	651 ± 137
BW <400 g, *n*/*N* (%)	7/75 (9.3)	3/245(1.2)	7/332(2.1)	9/405(2.2)	26/1057 (2.5)
Male, *n*/*N* (%)	32/75 (42.7)	133/244[a] (54.5)	163/332 (49.1)	219/403[a] (54.3)	547/1054[a] (51.9)
Multiple birth, *n*/*N* (%)	16/75 (21.3)	60/245 (24.5)	61/332 (18.4)	82/405 (20.2)	219/1057 (20.7)
Preterm rupture of membranes, *n*/*N* (%)	36/75 (48.0)	96/245 (39.2)	140/332 (42.2)	148/405 (36.5)	420/1057 (39.7)
Antenatal steroid use, *n*/*N* (%)	16/75 (21.3)	79/245 (32.2)	137/332 (41.3)	177/405 (43.7)	409/1057 (38.7)
Maternal transport, *n*/*N* (%)	38/75 (50.7)	151/245 (61.6)	207/331[a] (62.5)	247/402[a] (61.4)	643/1053[a] (61.1)
Outborn, *n*/*N* (%)	6/75 (8.0)	20/245 (8.2)	31/332 (9.3)	41/405 (10.1)	98/1057 (9.3)
Cesarean delivery, *n*/*N* (%)	18/75 (24.0)	104/245 (42.4)	218/332 (65.7)	297/405 (73.3)	637/1057 (60.3)
In-hospital morbidities and interventions, *n*/*N* (%)					
RDS diagnosed	60/74[a] (81.1)	191/245 (78.0)	251/332 (75.6)	309/405 (76.3)	811/1056[a] (76.8)
CLD at 36 weeks[b]	15/71[a] (21.1)	71/236[a] (30.1)	121/319[a] (37.9)	133/392[a] (33.9)	340/1018[a] (33.4)
PDA ligation	4/72[a] (5.6)	34/238[a] (14.3)	50/316[a] (15.8)	41/389[a] (10.5)	129/1015[a] (12.7)
Neonatal seizure	11/74[a] (14.9)	28/245 (11.4)	40/331[a] (12.1)	30/405 (7.4)	109/1055[a] (10.3)
IVH grade 3–4	18/74[a] (24.3)	52/241[a] (21.6)	48/328[a] (14.6)	49/403[a] (12.2)	167/1046[a] (16.0)
Cystic PVL	2/74[a] (2.7)	10/244[a] (4.1)	13/331[a] (3.9)	22/405 (5.4)	47/1054[a] (4.5)
Sepsis	17/74[a] (23.0)	58/244[a] (23.8)	73/331[a] (22.1)	59/405 (14.6)	207/1054[a] (19.6)
Necrotizing enterocolitis	1/74[a] (1.4)	16/245 (6.5)	10/331[a] (3.0)	15/405 (3.7)	42/1055[a] (4.0)
ROP requiring treatment	15/75[a] (20.0)	73/245 (29.8)	102/331[a] (30.8)	128/405 (31.6)	318/1056[a] (30.1)

BW, birth weight; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome.

[a] There were cases without data on this characteristic.

[b] CLD at 36 weeks was defined when an infant received supplemental oxygen at the postmenstrual age of 36 weeks.

TABLE 2 Neurodevelopmental Outcomes at 3 Years of Age According to Gestational Age

	Gestational Age				
	22 Weeks	23 Weeks	24 Weeks	25 Weeks	Total
Evaluated at 3 years, *n*	23	119	180	240	562
CP, *n*/*N* (%)[a]	5/23 (21.7)	21/118[b] (17.8)	14/173[b] (8.1)	35/234[b] (15.0)	75/548 (13.7)
Profound CP	4/23 (17.4)	12/118[b] (10.2)	9/173[b] (5.2)	20/234[b] (8.5)	45/548 (8.2)
Hearing impairment, *n*/*N* (%)[a]	0/23 (0.0)	4/119 (3.4)	2/168[b] (1.2)	3/234[b] (1.3)	9/544 (1.7)
Visual impairment, *n*/*N* (%)[a]	2/23 (8.7)	12/118[b] (10.2)	6/175[b] (3.4)	5/231[b] (2.2)	25/547 (4.6)
Cognitive delay, *n*/*N* (%)[a]	12/21[b] (57.1)	55/110[b] (50.0)	49/152[b] (32.2)	58/208[b] (27.9)	174/491 (35.4)
KSPD DQ of 50–69	5/11 (45.5)	12/58 (20.7)	27/104 (26.0)	31/145 (21.4)	75/318 (23.6)
KSPD DQ of <50	0/11 (0.0)	7/58 (12.1)	11/104 (10.6)	17/145 (11.7)	35/318 (11.0)
Judgment of delay by pediatrician	7/10 (70.0)	36/52 (69.2)	11/48 (22.9)	10/63 (15.9)	64/173 (37.0)
NDI, *n*/*N* (%)[a]	12/23 (52.2)	65/114[b] (57.0)	53/142[b] (37.3)	78/212[b] (36.8)	208/491 (42.4)
Profound NDI	7/23 (30.4)	45/114[b] (39.5)	23/142[b] (16.2)	36/212[b] (17.0)	111/491 (22.6)
Death or NDI, *n*/*N* (%)[c]	60/75 (80.0)	156/245 (63.7)	129/332 (38.9)	138/405 (34.1)	483/1057 (45.7)
Death or Profound NDI	55/75 (73.3)	136/245 (55.5)	99/332 (29.8)	96/405 (23.7)	386/1057 (36.5)
Unimpaired/minimally impaired, *n*/*N* (%)[c]	9/75 (12.0)	49/245 (20.0)	89/332 (26.8)	134/405 (33.1)	281/1057 (26.6)

Profound CP was defined as a GMFCS level of 4 or 5. Children who were defined as GMFCS level 1 were excluded and were included in the minimally impaired group. Hearing impairment was defined as requiring amplification. Visual impairment was defined as blind with no functional vision in 1 or both eyes. Cognitive delay was defined as a DQ score <70; if the child was unable to complete the KSPD assessment, the pediatrician estimated the child's developmental level as delayed or not. In cases judged as delayed, the developmental level was assumed to be equivalent to a KSPD DQ of <50. NDI was defined as any of the following: CP with a GMFCS level of 2 to 5, hearing impairment, visual impairment, or DQ score <70. Profound NDI was defined as profound CP and/or a DQ score of <50. Children with an unknown CP level were classified into profound impairment.

[a] (%): percentage of infants with data of the assessment.

[b] There were cases without the assessment.

[c] (%): percentage of the study population.

including 45 (8.2%) with profound CP. Profound CP was more often found in infants born at 22 weeks than in those born at the other weeks. There was no obvious association between hearing impairment and increasing gestational weeks. The proportions with visual impairment were equally high at 22 and 23 weeks. Cognitive delay was found in 174 (35.4%) of the 491 evaluated infants, 75 (15.3%) with a DQ between 50 and 69, and 99 (20.2%) with a DQ ≤50. Of the 318 infants assessed by the KSPD, 20 (6.3%) had a DQ <50 and 75 (23.6%) had a DQ of 50 to 70. In infants with 22 and 23 weeks' gestational age, those whose cognitive function was assessed by pediatricians were more likely to have blindness (19%) or CP (37%) than infants assessed by the KSPD (3% for blindness and 9% for CP). A total of 208 (42.4%) fully evaluated infants had NDI, with 111 (22.6%) having profound NDI. The incidences of both death or NDI and death or profound NDI were clearly related to gestational weeks. Overall, 281 (26.6%) of the 1057 subjects were unimpaired or minimally impaired at 3 years of age: 9 (12.0%) of whom were born at 22 weeks' gestational age, 49 (20.0%) of whom were born at 23 weeks' gestational age, 89 (26.8%) of whom were born at 24 weeks' gestational age, and 134 (33.1%) of whom were born at 25 weeks' gestational age.

In logistic regression after adjusting for biological and perinatal variables, being born at 22 weeks (OR: 5.40; 95% CI: 2.48–11.76) and 23 weeks (OR: 2.14; 95% CI: 1.38–3.32) in comparison with the reference (24 weeks) increased the risk of death or NDI, but being born at 25 weeks (OR: 0.65; 95% CI: 0.45–0.95) decreased the risk of death or NDI. When infants with birth weights <400 g were excluded from the model to eliminate the effect of severe growth restriction, a gestational age of 22 weeks (OR: 5.77; 95% CI: 2.55–13.04) and 23 weeks (OR: 2.22; 95% CI: 1.43–3.44) compared with a gestational age of 24 weeks similarly increased the risk of death or NDI.

From the systematic review, 46 publications reporting outcomes and follow-up rates were identified, 30 of which described outcomes at 18 to 42 months; however, only 12 included the numbers of cases of death and NDI at 18 to 42 months for a total of 15 different cohorts. Eight of these 15 cohorts contained data that met the definition of NDI in this study. The numbers of cases of death, NDI, and evaluated infants were reported for a total of 9717 extremely premature infants at 18 to 42 months for all 8 publications.[7–18] Year, country of birth, and type of study cohort are summarized in Table 3 and 4 by gestational weeks. Mortality rates ranged from 64% to 100% in infants born at 22 weeks' gestation, from 37% to 100% at 23 weeks' gestation, and from 19% to 65% at 24 to 27 weeks' gestation. Follow-up rates ranged from 0% to 100% for 22 and 23 weeks' gestation and from 70% to 99% for 24 to 27 weeks' gestation (Table 3). The incidence of death or NDI ranged from 80% to 100% for 22 weeks' gestational age, from 64% to 100% for 23 weeks' gestational age, and from 36% to 82% for 24 to 27 weeks' gestational age (Table 4).

DISCUSSION

In a large cohort of extremely preterm infants born at <26 weeks' gestational age, we found that 50% to 60% of survivors born at 22 and 23 weeks' gestational age and ~30% of survivors at 24 and 25 weeks' gestational age had disability at 3 years of age in terms of mental and psychomotor development. On the other hand, nearly half of the infants born even at 22 or 23 weeks, and who had survived to 3 years of age, were unimpaired or minimally impaired, although these proportions were lower than those for infants born at 24 or 25 weeks. The incidence of death or NDI was clearly related to gestational weeks, consistent with many previous studies.[3,5–21] Among the survivors, however, the incidence of NDI for those born at 22 weeks was nearly equal to that for those born at 23 weeks. This result was probably affected by the high mortality for 22 weeks, meaning that the most severe cases born at 22 weeks died early in life. In addition, the proportion of NDI at 22 weeks should be interpreted with caution because the number of survivors in this category was low.

The strengths of our study include the relatively large population with a lower mortality rate of infants born at 22 and 23 weeks than in previous studies, as shown in Table 3. As a result, more infants survived and could be evaluated at 3 years of age.

In the evaluated infants, the proportions of CP, hearing impairment, visual impairment, and a DQ <70 were similar to those in previous studies.[7,11,15,19] The incidence of profound CP was slightly higher than in a report from the NICHD, especially at 22 and 23 weeks.[7] One reason for this was that we classified the infants with an unknown CP level as having profound impairment. We decided to choose the strictest judgment for NDI because the judgment might have a major impact on the conclusion of the study. If the infants with an unknown CP level were excluded from the profound impairment group, the incidence of profound CP decreased to 2 (8.7%) for those born at 22 weeks and to 10 (8.5%) for those born at 23 weeks, which is equal to the incidence in the NICHD data.[7]

The proportion of infants with a DQ <70 was higher than the proportions with other impairments. Approximately half of the infants born at 22 and 23 weeks' gestation were found to have cognitive delay, but the corresponding proportion was one-third at 24 and 25 weeks' gestation. Infants at 22 and 23 weeks were more likely to be judged by a pediatrician and they more often had other handicaps such as blindness or CP. These impairments might prevent completion of the KSPD test.[13] Because pediatricians were not always blinded to perinatal and neonatal morbidities and interventions, judgment by a pediatrician without a test could result in overestimation of the proportion of cognitive delay in infants at 22 and 23 weeks' gestational age. A higher incidence of impaired cognitive development in infants born at very low gestational ages has been described in several reports.[7,11,13,15–21,25] Although

TABLE 3 Survival and Neurodevelopmental Outcomes of Infants Born at 22 and 23 Weeks' Gestation From the Systematic Review

Study Name (Reference) (Location, Age at Follow-up, Year of Birth, Type of Study)	22 Weeks			23 Weeks			24–27 Weeks		
	Mortality,[a] n/Live Births (%)	Evaluated, n/Survivors at 3 Years (%)	Death or NDI, n/Study Cohort (%)	Mortality,[a] n/Live Births (%)	Evaluated, n/Survivors at 3 Years (%)	Death or NDI, n/Study Cohort (%)	Mortality,[a] n/Live Births (%)	Evaluated, n/Survivors at 3 Years (%)	Death or NDI, n/Study Cohort (%)
NICHD (7) (US, 18–24 mo, 2002–2004, multicenter)	309/322 (96)	—	—	342/441 (78)	22–23 weeks; 104/112 (93)	22–23 weeks; 750/763 (98)	24 weeks; 294/632 (47)	22–24 weeks; 405/450 (90)	24 weeks; 489/632 (77)
VON (8) (US, 18–24 mo, 1998–2003, multicenter)	<23 weeks; 504/528 (96)	<23 weeks; 15/21 (71)	<23 weeks; 515/528 (98)	567/916 (62)	214/298 (72)	679/916 (74)	24–25 weeks; 906/3033 (30)	24–25 weeks; 1229/1702 (72)	24–25 weeks; 1401/3033 (46)
Victoria (9,10) (Australia, 24 mo, 2005, population-based)	32/33 (97)	—	—	28/35 (80)	—	—	24–27 weeks; 56/220 (25)	22–27 weeks; 163/172 (95)	22–27 weeks; 196/288 (68)
EPIBEL (11,12) (Belgium,30–42 mo, 1999–2000, population-based)	28/28 (100)	0/0 (0)	28/28(100)	40/41 (98)	1/1(100)	40/41 (98)	24–26 weeks; 91/182 (50)	24–26 weeks; 88/91 (97)	24–26 weeks; 142/182 (78)
EPICure (13,14) (UK, 30 mo median, 1995, population-based)	136/138 (99)	2/2 (100)	137/138(99)	216/241 (90)	25/25(100)	230/241 (95)	24–25 weeks; 525/806 (65)	24–25 weeks; 279/281 (99)	24–25 weeks; 661/806 (82)
EPIPAGE (15,16) (France, 24 mo, 1997, population-based)	16/16 (100)	0/0 (0)	16/16(100)	30/30 (100)	0/0 (0)	30/30 (100)	24–27 weeks; 224/549 (41)	—	—
Essen (17) (Germany, 24–30 mo, 2000–2004, hospital-based)	8/10 (80)	2/2 (100)	9/10(90)	12/18 (67)	5/6 (83)	12/18(67)	24–25 weeks; 16/55 (29)	24–25 weeks; 34/39 (87)	24–25 weeks; 22/55 (40)
ETFOL (18) (Denmark, 24 mo, 1994–1995, population-based)	—	—	—	<24 weeks; 37/37 (100)	<24 weeks; 0/0 (0)	< 24 weeks; 37/37 (100)	24–27 weeks; 154/349 (44)	24–27 weeks; 183/195 (94)	24–27 weeks; 206/349 (59)
Current study (Japan, 36 mo median, 2003–2005, multicenter)	48/75 (64), 43/69 (62)[b]	23/27 (85)	60/75(80)	91/245 (37), 82/225 (36)[b]	119/154 (77)	156/245 (64)	24–25 weeks; 139/737 (19), 127/605(19)[b]	24–25 weeks; 420/601 (70)	24–25 weeks; 267/737 (36)

EPIBEL, Extremely Preterm Infants in Belgium Study Group; EPICure, study for all infants born before 26 completed weeks of gestational age in the United Kingdom and the Republic of Ireland in 1995; EPIPAGE, The Etude Epidémiologique sur les Petits Ages Gestationnels study; VON, Vermont Oxford Network; —, data was not shown.

[a] Mortality included cases who died in the delivery room, died in the NICU, or died after discharge until evaluation, but not cases who died intrapartum.

[b] Mortality excluding the infants transferred after birth to the participating centers from cases in footnote a.

the reason is unclear, various factors affect cognitive development, such as socioeconomic, environmental, and nutritional factors.[8,19,20,34,37] It could be assumed that extreme prematurity of the brain itself is critical for later brain functions.[39–41] Cognitive delay judged by pediatricians may have overestimated the number of infants with a DQ <50.

The most important result in this study was the proportion of unimpaired/minimally impaired infants: 9 (12.0%) of those born at 22 weeks and 49 (20.0%) of those born at 23 weeks. The risks of death or NDI were 5 times higher at 22 weeks' gestational age and 2 times higher at 23 weeks' gestational age than in those born at 24 weeks in a logistic regression model. Resuscitation or intensive care of infants born at 22 or 23 weeks is a very controversial issue.[2,4,7,10,12,20] There is widespread consensus that the aim of neonatal resuscitation should be the qualitatively acceptable survival of the child. However, the guidelines for resuscitation of these infants have not been unified across countries or institutions.[4,22–25,42,43] There could be differences in medical behavior and attitudes associated with the different cultural, social, and legal backgrounds of each country; this could affect the survival and morbidity data of infants born at the threshold of viability. Comparing death or NDI with that in other cohorts, the mortality rate in this study was lower, especially at 22 and 23 weeks, although eligibility and exclusion criteria and the follow-up rate of the study cohorts were not all the same. The incidence of death or NDI was also low, meaning that the proportion of survivors with NDI at 3 years of age was not higher. The follow-up rate, however, may have affected the proportion of NDI, the same as in studies of Mercier et al[8] and Kutz et al.[17] We chose the strictest criteria

TABLE 4 CP and Cognitive Delay of the Evaluated Infants Born at 22 and 23 Weeks' Gestation From the Systematic Review

Study Name (Reference) (Location, Age at Follow-up, Year of Birth, Type of Study)	22 Weeks			23 Weeks			24–27 Weeks		
	CP, *n*/Evaluated Infants (%)	Cognitive Delay, *n*/Evaluated Infants (%)	NDI, *n*/Evaluated Infants (%)	CP, *n*/Evaluated Infants (%)	Cognitive Delay, *n*/Evaluated Infants (%)	NDI, *n*/Evaluated Infants (%)	CP, *n*/Evaluated Infants (%)	Cognitive Delay, *n*/Evaluated Infants (%)	NDI, *n*/Evaluated Infants (%)
NICHD (7) (US, 18–24 mo, 2002–2004, multicenter)	—	—	—	22–23 weeks; 28/105 (27)	22–23 weeks; MDI <70: 63/102 (62); PDI <70: 46/104 (44)	22–23 weeks; 72/103 (70)	24 weeks; 57/298 (19)	24 weeks; MDI <70: 133/282 (47); PDI <70 88/280 (31)	24 weeks; 155/284 (55)
VON (8) (US, 18–24 mo, 1998–2003, multicenter)	<23 weeks CP and/or cognitive delay; 11/15(73)		<23 weeks; 11/15 (13)	CP and/or cognitive delay; 112/214 (52)		112/214 (52)	24–25 weeks CP and/or cognitive delay; 495/1499 (33)		24–25 weeks; 495/1229 (40)
Victoria (9,10) (Australia, 24 mo, 2005, population-based)	—	—	—	—	—	—	22–27 weeks; 16/163 (10)	22–27 weeks; 26/163 (16)	24–27 weeks; 80/163 (49)
EPIBEL (11,12) (Belgium, 30–42 mo, 1999–2000, population-based)	(All cases dead)	(All cases dead)	(All cases dead)	0/1 (0)	0/1 (0)	0/1 (0)	24–26 weeks; 19/77 (25)	24-26 weeks; MDI <70: 22/77 (29); PDI <70: 37/77 (48)	24–26 weeks; 51/88 (58)
EPICure 1 (13,14) (UK, 30 mo median, 1995, population-based)	—	—	1/2 (50)	—	22–23 weeks; 7/26 (27)	14/25 (56)	22–25 weeks; 50/306 (16)	24–25 weeks; 78/257 (30)	24–25 weeks; 136/279 (49)
EPIPAGE (15,16) (France, 24 mo, 1997, population-based)	(All cases dead)	(All cases dead)	(All cases dead)	(All cases dead)	(All cases dead)	(All cases dead)	—	—	—
Essen (17) (Germany, 24–30 mo, 2000–2004, hospital-based)	—	—	1/2 (50)	—	—	0/5 (0)	—	—	24-25 weeks; 6/34 (18)
ETFOL (18) (Denmark, 24 mo, 1994–1995, population-based)	—	—	—	(All cases dead)	(All cases dead)	(All cases dead)	24–27 weeks; 5/53 (9)	24–27 weeks; 9/53 (17)	24–27 weeks; 52/183 (28)
Current study (Japan, 36 mo median, 2003–2005, multicenter)	5/23 (22)	12/21 (57)	12/23 (52)	21/118 (18)	55/110 (50)	65/114 (57)	24–25 weeks; 49/407 (12)	24–25 weeks; 107/360 (30)	24–25 weeks; 131/354 (37)

EPIBEL, Extremely Preterm Infants in Belgium Study Group; EPICure, study for all infants born before 26 completed weeks of gestational age in the United Kingdom and the Republic of Ireland in 1995; EPIPAGE, The Etude Epidémiologique sur les Petits Ages Gestationnels study; MDI, mental developmental index; PDI, psychomotor developmental index; VON, Vermont Oxford Network; —, data was not shown.

for NDI, meaning that impairments having CP or cognitive delay without assessment of degrees were considered as profound impairments. When discussing intervention and treatment of infants at the threshold of viability, we should not do opportunistic assessment because severe impairments would have a major impact on the surviving infants and their parents for life. This strictest criteria for NDI could provide overestimated impairments and the possible-worst outcome. Although there is no definite consensus regarding what probability of survival without profound impairment justifies intensive care,[44] the results of this study provide important information to consider in current treatment.

There are several limitations to this study. The first concerns the follow-up rate, which was ∼70% in infants born at 24 and 25 weeks' gestation. It is unclear how the follow-up rate affects the true incidence of severe disability.[45,46] Several reports on attrition in follow-up programs suggest that infants with serious developmental delays or disabilities are more likely to drop out of follow-up.[47–49] Coincident with this, the nonevaluated group had a higher percentage of IVH grade 3–4 than did the evaluated group. This could be relevant and confer a higher risk of NDI in the infants.

The second limitation is a lack of registration of stillbirth and clear classifications of withdrawing/withholding intensive care in the delivery room, which are important when we compare the survival rate with those in other cohort studies.[21] The network defines stillbirth as an infant who does not show any cardiac pulse under vigorous resuscitation after 22 weeks of gestational age regardless of birth weight, although the number of stillbirths was not collected, which remained almost constant at <1% of the total number of infants registered each year.[6] The numbers of stillbirths or deaths in the delivery room in hospitals other than the participating centers were also not collected. The mortality rate, however, did not change after excluding the outborn infants in this study, as shown in Table 3.

The last limitation concerns the use of the KSPD test for cognitive evaluation. Although the KSPD test is written only in Japanese, it is a validated and standardized developmental test battery available for all centers participating in the follow-up study in Japan.[32] KSPD assessment is not comparable to, for instance, the Bayley Scales of Infant Development III, which is widely used for cognitive evaluation at this age.[50] Additionally, we could not collect socioeconomic information, which is known to be associated with infants' future developmental state.[51] The quality of life of the infants, their later neurologic outcomes, and academic and social achievements into adulthood should also be elucidated in future studies.

CONCLUSIONS

Infants born at 22 and 23 weeks' gestation were at higher risk of death or NDI than infants born at 24 and 25 weeks' gestation, but outcomes were improved compared with those in previous studies from a systematic review. There is a need for additional discussions on interventions for infants born at 22 or 23 weeks' gestation.

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A GLANCE INTO THE FUTURE: FECAL TRANSPLANTS FOR WEIGHT LOSS: *Each day I am bombarded with information about how to lose weight. There seems to be an almost endless array of diet or exercise recommendations and oodles of gadgets "guaranteed" to work. In the past few months, one of my relatives has tried to lose weight following the South Beach diet, then a Paleolithic diet, and most recently using a smart phone application. Maybe she should try a fecal transplant. As reported in* The New York Times *(Health: March 28, 2013), the bacterial flora in our guts may be at least partially responsible for weight loss or gain. Researchers have never quite understood all the reasons why people lose weight following gastric bypass surgery. However, in a recent study conducted in mice, researchers concluded that approximately 20% of the weight loss is most likely due to a change in bacterial flora. Fattened mice that underwent gastric bypass surgery lost weight and had altered intestinal flora. Mice that underwent a sham surgery where the intestine was simply severed and re-anastomosed did not lose weight and the microbiota did not change. Next, intestinal contents from each group were transplanted into mice lacking intestinal flora. The mice that received material from the bypass surgery group lost weight while the mice receiving material from the sham group did not. In a study conducted in adults with potential gastrointestinal disorders, researchers found that indirect evidence of the presence of* Methanobrevibacter smithii *in the gut was directly related to body mass. The individuals with the highest levels of methane and hydrogen on breath tests were more likely to have more body fat. One possible explanation for this finding is that* M. smithii *may contribute to the breakdown of foodstuffs, making more calories available. The general dieter may not be ready for a fecal transplant to help increase weight loss, but the more we learn about our gut and the bacteria that inhabit it, the more we realize how intertwined we are.*

Noted by WVR, MD

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Outcomes of Infants Born at 22 and 23 Weeks' Gestation

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