JAMA®

Online article and related content
current as of June 2, 2009.

One-Year Survival of Extremely Preterm Infants After Active Perinatal Care in Sweden

The EXPRESS Group

JAMA. 2009;301(21):2225-2233 (doi:10.1001/jama.2009.771)

http://jama.ama-assn.org/cgi/content/full/301/21/2225

Correction	Contact me if this article is corrected.
Citations	This article has been cited 1 time. Contact me when this article is cited.
Topic collections	Pediatrics; Neonatology and Infant Care; Prognosis/ Outcomes Contact me when new articles are published in these topic areas.

Subscribe
http://jama.com/subscribe

Email Alerts
http://jamaarchives.com/alerts

Permissions
permissions@ama-assn.org
http://pubs.ama-assn.org/misc/permissions.dtl

Reprints/E-prints
reprints@ama-assn.org

Downloaded from www.jama.com at Univ Of North Carolina / Acquisitions srvcs on June 2, 2009

One-Year Survival of Extremely Preterm Infants After Active Perinatal Care in Sweden

The EXPRESS Group

Context Up-to-date information on infant survival after extremely preterm birth is needed for assessing perinatal care services, clinical guidelines, and parental counseling.

Objective To determine the 1-year survival in all infants born before 27 gestational weeks in Sweden during 2004-2007.

Design, Setting, and Patients Population-based prospective observational study of extremely preterm infants (707 live-born and 304 stillbirths) born to 887 mothers in 904 deliveries (102 multiple births) in all obstetric and neonatal units in Sweden from April 1, 2004, to March 31, 2007.

Main Outcome Measures Infant survival to 365 days and survival without major neonatal morbidity (intraventricular hemorrhage grade >2, retinopathy of prematurity stage >2, periventricular leukomalacia, necrotizing enterocolitis, severe bronchopulmonary dysplasia). Associations between perinatal interventions and survival.

Results The incidence of extreme prematurity was 3.3 per 1000 infants. Overall perinatal mortality was 45% (from 93% at 22 weeks to 24% at 26 weeks), with 30% stillbirths, including 6.5% intrapartum deaths. Of live-born infants, 91% were admitted to neonatal intensive care and 70% survived to 1 year of age (95% confidence interval [CI], 67%-73%). The Kaplan-Meier survival estimates for 22, 23, 24, 25, and 26 weeks were 9.8% (95% CI, 4%-23%), 53% (95% CI, 44%-63%), 67% (95% CI, 59%-75%), 82% (95% CI, 76%-87%), and 85% (95% CI, 81%-90%), respectively. Lower risk of infant death was associated with tocolytic treatment (adjusted for gestational age odds ratio [OR], 0.43; 95% CI, 0.36-0.52), antenatal corticosteroids (OR, 0.44; 95% CI, 0.24-0.81), surfactant treatment within 2 hours after birth (OR, 0.47; 95% CI, 0.32-0.71), and birth at a level III hospital (OR, 0.49; 95% CI, 0.32-0.75). Among 1-year survivors, 45% had no major neonatal morbidity.

Conclusion During 2004 to 2007, 1-year survival of infants born alive at 22 to 26 weeks of gestation in Sweden was 70% and ranged from 9.8% at 22 weeks to 85% at 26 weeks.

JAMA. 2009;301(21):2225-2233 www.jama.com

THE RATE OF PRETERM BIRTHS IS increasing worldwide and the associated neonatal morbidity contributes significantly to infant mortality. Without medical intervention, the number of deaths in those born extremely preterm would equal that of major causes of death in adults.[1] Advances in perinatal medicine have increased survival so that neonatal intensive care can today be life saving even for the most immature infants.[2-19] However, concerns about risks for later disability,[20] adverse developmental programming increasing the risk for hypertension and diabetes in later life, and high costs[21] make intensive care at the limits of viability controversial. Moreover, the evidence for improved outcomes among extremely immature infants, which is fundamental for decision making before, during, and after birth, has been questioned.[22-24] Conversely, misconceptions regarding outcomes may result in suboptimal perinatal care because chances for survival are underestimated.[25]

Objective estimates of survival for extremely preterm infants are difficult to establish because the more favorable outcomes, reported from centers of excellence,[4,7,8,19] may reflect some selection bias.[23] Population-based studies, considered to be most valid, may have limitations such as cohorts born before 2000,[2,9-13,26-28] stillbirths or delivery room deaths not accounted for,[2,9,11-13] survival data restricted to admitted infants,[6,13] or use of hospital discharge data.[9,10,13-17] Survival rates and morbidity often vary within countries and, to improve the outcome, centralization of care to centers of excellence is recommended.[17,29,30] However, strategies for better outcome, eg, more individualized management and decision making,[31] have not been evaluated on a population-based level. Accordingly, there is a need for up-to-date estimates of infant survival after extreme prematurity, both for assessing perinatal and neonatal care services and as a basis for clinical guidelines and parental counseling.

The objective of the national collaborative project Extremely Preterm Infants in Sweden Study (EXPRESS) was to evaluate the short- and long-term outcomes of infants born before 27 gestational weeks in Sweden during 2004-2007. The purpose of this report is to determine the 1-year survival with and without major neonatal morbidity among these infants.

Authors/EXPRESS Group members are listed at the end of this article.
Corresponding Author: Karel Maršál, MD, PhD, Department of Obstetrics and Gynecology, Lund University Hospital, S-221 85 Lund, Sweden (karel.marsal@med.lu.se).

©2009 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Univ Of North Carolina / Acquisitions srvcs on June 2, 2009

METHODS

The study population comprised all live-born (gestational age ≤26 weeks 6 days) and stillborn infants (gestational age 22 weeks 0 days–26 weeks 6 days) delivered extremely preterm in Sweden from April 1, 2004, to March 31, 2007. Terminations of pregnancy and infants born outside of Sweden and transferred to Sweden for neonatal care were excluded. All obstetric and pediatric departments in Sweden participated in the study and no infant fulfilling the eligibility criteria was excluded. The study was descriptive with no attempts in the study framework to standardize treatment.

In each of the 7 health care regions in Sweden, 1 obstetric and 1 pediatric study coordinator were responsible for data acquisition and quality control. Data on mothers and stillborn infants were collected at the time of delivery. Data on live-born infants were collected prospectively during the first 180 days of hospitalization or until discharge or death. Mother and infant data were cross-linked with the National Medical Birth Registry to ensure accuracy. Information on infant deaths after discharge home until 1 year was obtained from the National Population Registry. Data collection continued for all infants who were transferred between hospitals.

All data were collected by local staff on standard study forms in accordance with a manual defining the variables. Regional data were electronically transmitted to a central database and again checked for quality and completeness. Records with missing or obviously erroneous information were returned to the regional study coordinators. Missing data were traced until the investigators, after personal contact, concluded that data were unobtainable. During the study, 1 internal and 1 external data control were performed on a randomly selected subset of study patients.

The data set comprised 220 items, including demographic information, maternal medical and previous obstetric history, data on pregnancy, labor, and delivery, infant condition at birth and details on resuscitation, illness severity at admission to neonatal intensive care unit, selected neonatal procedures, and infant outcomes such as survival, neonatal morbidity, time of death, and use of hospital resources.

The database was created in collaboration with the Swedish Perinatal Quality Register. MedSciNet (MedSciNet AB, Stockholm, Sweden) was responsible for the technical design of the study database and electronic transmission of data.

Sweden has a population of 9 million inhabitants and general health insurance coverage. Pregnancy care is standardized, free of charge, and virtually all pregnant women adhere to the routine antenatal care program starting in early pregnancy; 97% of all pregnant women have a routine ultrasound examination by specially trained personnel at 17 to 18 postmenstrual weeks. Each health region is served by a regional level III hospital. Births occur at 42 delivery facilities including 7 regional hospitals. The general policy is to centralize extremely preterm deliveries to regional hospitals.

Live birth and perinatal mortality were defined in accordance with the recommendations of the World Health Organization (WHO).[32] Perinatal mortality was defined as death in the perinatal period (comprising late pregnancy from 22 gestational weeks until birth, labor and delivery, and the first week of life) and includes stillbirths and early neonatal mortality. Intrapartum death was defined as stillbirth when the fetus was alive at the start of labor. The gestational age was recorded in completed weeks. In 860 pregnancies (95%), the gestational duration was based on ultrasound dating; in 16 pregnancies, on the date of last menstrual period (2%); and in 28 pregnancies, the dating method was not specified (3%). In 60 (10%) of the live-born infants with ultrasound estimation of gestational age, the expected date of delivery differed by at least –14 days from estimates according to the last menstrual period; 33 (13%) of the stillborn infants had a corresponding difference between the 2 estimation methods. Intrauterine growth was evaluated in accordance with the national fetal weight–based growth standard[33] and expressed as mean standard deviation scores (SDS; actual value minus mean/standard deviation). Infants with birth weight of more than 2 SDs below the mean were classified as small for gestational age (SGA).

Iatrogenic delivery was defined as delivery for maternal, fetal, or both indications, either after induced labor or as prelabor cesarean delivery.[34] Preterm premature rupture of membranes was defined as spontaneous rupture of the membranes at least 1 hour before the onset of contractions.[34] Mothers were considered to have received antenatal corticosteroids if they received 1 or 2 doses of betamethasone. Antenatal antibiotic treatment was defined as any antibiotic drug administered to the mother during hospitalization that resulted in delivery.

Intraventricular hemorrhage was graded in accordance with data from Papile et al.[35] Cystic periventricular leukomalacia was defined in accordance with data from de Vries et al,[36] retinopathy of prematurity in accordance with the International Classification for Retinopathy of Prematurity,[37] and necrotizing enterocolitis in accordance with staging by Bell et al.[38] Severe bronchopulmonary dysplasia was defined as the need for at least 30% oxygen at a time corresponding with 36 weeks of gestation.[39] Congenital anomalies were classified in accordance with the *WHO International Classification of Diseases, 10th Revision*; and luxations of the hip (Q65.0-Q65.5), balanic hypospadias (Q54.0), and patent ductus arteriosus (Q25.0) were not classified as anomalies.

The primary outcome was infant survival to 365 days based on all births including stillbirths and live-born infants. The secondary outcome was survival to at least 365 days without major neonatal morbidity, ie, survival without intraventricular hemorrhage grade greater than 2, retinopathy of prematurity stage greater than 2, periven-

©2009 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Univ Of North Carolina / Acquisitions srvcs on June 2, 2009

tricular leukomalacia, necrotizing enterocolitis, or severe bronchopulmonary dysplasia.

The study was approved by the Regional Research Ethics Board, Lund University, Lund, Sweden. The parents provided oral informed consent for data acquisition.

Statistical Analyses

Associations between gestational age and various dichotomized variables were analyzed using simple linear logistic regression either with gestational age as a continuous variable or as specified with gestational age converted to class variables. Overall survival was determined by standard Kaplan-Meier survival analysis. Dichotomized risk factors for infant death were evaluated using simple logistic regression analyses or, when specified, multiple logistic linear regression analyses adjusting for gestational age (entered as a continuous variable). The effect of perinatal interventions was analyzed in a multivariate model as specified. Goodness of fit was evaluated with Hosmer-Lemeshow test. All statistical analyses were performed using Gauss version 6.0 (Aptech Systems Inc, Black Diamond, Washington). All testing was 2-sided; *P* values of less than .05 were considered statistically significant.

RESULTS

During the 3-year study period, 305 318 infants were born in Sweden; of these, 1011 were extremely preterm infants (incidence, 3.3/1000 infants) born before 27 gestational weeks in 904 deliveries to 887 mothers. Of the infants in the study, 707 were live-born (70%; incidence, 2.3/1000 infants) and 304 stillborn (30%; incidence, 1.0/1000 infants). There were 102 multiple births (11.3%); 95 twin births (1 twin delivery before 22 weeks—only the live-born first twin included—and 1 delayed delivery after abortion of the first twin before 22 weeks); and 7 triplet births.

Maternal Characteristics

The mean age of mothers was 30.9 years (range, 14-46 years); 29 mothers were younger than 20 years of age (3.2%), 195 were 35 to 39 years old (22%), and 65 were aged 40 years or older (7.3%). There were 58% of mothers who were primiparae (520), 20% were non-Nordic (117/542 with available information), 14% were smokers (119/834), and 6.6% of pregnancies were the result of in vitro fertilization (59/904). In 36% of the pregnancies (325/904), clinical complications, eg, preeclampsia, antepartum hemorrhage, preterm premature rupture of membranes, or chorioamnionitis, were reported.

Characteristics of Live-Born Infants

The total number of infants and the number of live-born infants increased with gestational age (TABLE 1 and TABLE 2). There were 2 live-born infants reported before 22 gestational weeks; they died after 1 and 10 hours, respectively. Of the 707 live-born infants, 55% (n=388) were male, 22% (n=158) multiples, and 16% (114/703) were SGA (Table 1). The proportion of SGA infants increased with gestational age (odds ratio [OR] for 1-week increase, 1.47; 95% CI, 1.22-1.75; $P<.001$). The birth weights ranged from 266 g to 1500 g. Low Apgar scores (≤3) at 1 and 5 minutes in infants born at 22 weeks were 69% and 77%, respectively, and were more common than in more mature infants at 26 weeks (17% and 13%, respectively) (1-minute Apgar score OR, 11.07; 95% CI, 5.51-12.21; $P<.001$; and 5-minute Apgar score OR, 32.91; 95% CI, 14.63-74.04; $P<.001$). Congenital anomalies were reported in 12% of the infants.

Perinatal Interventions

Of all infants, 70% were born at level III hospitals (558 live-born and 145 stillborn). Of these infants, 75% and 42%, respectively, had been transferred in utero; 117 of 149 infants born alive at level II or at level I hospitals were transferred postnatally to a level III hospital for care (Table 1). Of all live-born infants, 509 were born after spontaneous onset of labor (72%) and 198 after iatrogenic deliveries for maternal or fetal indications or both (28%). In pregnancies with infants born alive after spontaneous onset of labor, tocolytics and antenatal corticosteroids were used significantly less at 22 weeks than at later gestational ages (tocolytic use OR, 0.34; 95% CI, 0.18-0.65; $P<.001$; and corticosteroid use OR, 0.06; 95% CI, 0.03-0.13; $P<.001$). Of 707 live-born infants, 356 (50%) were born by Cesarean delivery and of these, 172 (48%) were iatrogenic. Birth by cesarean delivery was 36% among infants of mothers with spontaneous onset of delivery and 88% among those with iatrogenic delivery.

A neonatologist attended 83% of the live births, 61% of the infants were intubated in the delivery room, and 72% received surfactant within 2 hours after birth (Table 1). The presence of a neonatologist and the administration of surfactant were less common at 22 weeks than at 23 to 26 weeks (neonatologist present OR, 0.15; 95% CI, 0.08-0.27; $P<.001$; and surfactant administration OR, 0.16; 95% CI, 0.08-0.31; $P<.001$). Intubation was less used at 26 weeks than at 23 to 25 weeks (OR, 0.25; 95% CI, 0.18-0.36; $P<.001$) (Table 1).

Mortality and Survival

The overall perinatal mortality was 45%, ranging from 93% at 22 gestational weeks to 24% at 26 weeks (Table 2). Of live-born infants, 152 (22%) died during the early neonatal period (0-6 days) including 58 (8.2%) who died in the delivery room; and 35 (5%) who died during the late neonatal period (7-27 days). Altogether, 210 live-born infants (30%) died before the age of 1 year. The proportion of stillbirths, delivery room deaths, neonatal deaths, and infant deaths decreased with gestational age (Table 2). There was no sex difference in mortality ($P=.77$), whereas SGA (OR, 1.69; 95% CI, 1.12-2.58; $P=.04$) and multiple birth (OR, 1.70; 95% CI, 1.04-2.77; $P=.01$) were associated with an increased risk of infant death (adjusted for gestational age).

Survival curves from birth to 365 days after birth for the 707 live-born infants according to gestational age at birth are shown in the FIGURE. Most of

©2009 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Univ Of North Carolina / Acquisitions srvcs on June 2, 2009

the deaths occurred early in the neonatal period. For infants who survived 24 hours, the chance of 1-year survival was significantly lower for those born at 22 weeks than for those born at 23 or 24 weeks (OR, 0.22; 95% CI, 0.06-0.71; $P=.01$), which in turn was lower than the corresponding survival for infants born at 25 or 26 weeks (OR, 0.50; 95% CI, 0.32-0.78; $P=.002$). For infants who survived 28 days, no significant association between gesta-

Table 1. Perinatal Characteristics of Live-Born Infants

Characteristic	No. With Event/No. in Group (%) by Gestational Age in Weeks[a]					
	≤22 (n = 51)[b]	23 (n = 101)	24 (n = 144)	25 (n = 205)	26 (n = 206)[c]	Total <27 wk (n = 707)
Male sex	27/51 (53)	55/101 (55)	78/144 (54)	120/205 (59)	108/206 (52)	388/707 (55)
Twins and triplets	21/51 (41)	16/101 (16)	32/144 (22)	38/205 (18)	51/206 (25)	158/707 (22)
1-min Apgar score ≤3	35/51 (69)	53/101 (53)	63/144 (44)	59/205 (29)	34/206 (17)	244/707 (35)
5-min Apgar score ≤3	39/51 (77)	47/101 (47)	47/144 (33)	42/205 (21)	27/206 (13)	202/707 (29)
Small for gestational age[d]	4/50 (8)	7/100 (7)	16/142 (11)	39/205 (19)	48/206 (23)	114/703 (16)
Birth weight, median (range), g[e]	508 (280 to 730)	590 (320 to 808)	674 (374 to 1070)	784 (266 to 1235)	920 (430 to 1500)	730 (266 to 1500)
Birth weight standard deviation score, median (interquartile range)[f]	–0.07 (–0.88 to –0.51)	–0.44 (–0.60 to 0.19)	–0.59 (–1.36 to 0.02)	–0.76 (–1.50 to –0.02)	–0.87 (–1.87 to –0.16)	–0.67 (–1.47 to 0.06)
Obstetric intervention						
Iatrogenic preterm delivery	4/49 (8)	8/99 (8)	27/137 (20)	59/201 (29)	74/196 (38)	172/682 (25)
Tocolytic treatment[g]	28/45 (62)	71/90 (78)	93/110 (84)	117/142 (82)	104/122 (85)	413/509 (81)
Antenatal steroids	20/49 (40)	85/99 (85)	130/137 (95)	176/198 (89)	180/193 (93)	591/676 (87)
Cesarean delivery	3/51 (6)	17/101 (16)	67/144 (46)	128/205 (62)	141/206 (68)	356/707 (50)
Delivery at level III hospital	24/51 (47)	79/101 (78)	129/144 (90)	166/205 (81)	160/206 (78)	558/707 (79)
Neonatal intervention						
Neonatologist attending at birth	24/50 (48)	83/100 (83)	130/142 (92)	180/205 (88)	170/206 (83)	587/703 (83)
Intubation at birth	13/22 (59)	68/84 (81)	113/142 (80)	126/202 (62)	80/206 (39)	400/656 (61)
Surfactant administration within 2 hours after birth	14/43 (33)	72/95 (76)	120/140 (86)	153/203 (75)	138/205 (67)	497/686 (72)
Admission for neonatal care						
All live-born infants	19/50 (38)	81/100 (81)	132/142 (93)	200/205 (98)	206/206 (100)	638/703 (91)
Outborn infants[h]	6/19 (32)	13/81 (16)	15/132 (11)	37/200 (19)	46/206 (22)	117/638 (18)
Transport to level III care[i]	6/51 (12)	13/101 (13)	15/144 (10)	37/205 (18)	46/206 (22)	117/707 (17)

[a] Number in group denotes the number of infants with available relevant information.
[b] Category denotes gestational age of 22 weeks 0 days to 22 weeks 6 days but also includes 1 infant born at 21 weeks 5 days and 1 infant born at 21 weeks 6 days.
[c] Category denotes gestational age of 26 weeks 0 days to 26 weeks 6 days.
[d] Birth weight smaller than 2 SDs below the mean of the Swedish standard for intrauterine growth.[33]
[e] Reported numbers of infants by gestational age for 22 weeks or younger, 23 weeks, 24 weeks, 25 weeks, and 26 weeks are 50, 100, 142, 205, and 206, respectively.
[f] Standard deviation scores (mean minus actual value/standard deviation) are based on the Swedish standard for intrauterine growth.
[g] Tocolytic treatment in the subgroup with spontaneous preterm labor only.
[h] Percent outborn infants of all live-born infants admitted to level III hospitals.
[i] Infants born at level I or level II hospitals and transported postnatally to level III care as proportion of all admitted live-born infants.

Table 2. Mortality by Gestational Age for All Infants and Live-Born Infants

	No. (%) of Infants by Gestational Age, wk					
	≤22[a]	23	24	25	26[b]	Total <27 wk
All infants	(n=142)	(n=183)	(n=191)	(n=250)	(n=245)	**(N=1011)**
Perinatal death	132 (93)	121 (66)	77 (40)	68 (27)	58 (24)	456 (45)
Stillbirth	91 (64)	82 (45)	47 (25)	45 (18)	39 (16)	304 (30)
Intrapartum death	40 (28)	19 (10)	2 (1)	3 (1.2)	2 (0.8)	66 (6.5)
Live-born infants	(n=51)	(n=101)	(n=144)	(n=205)	(n=206)	**(N=707)**
Neonatal death	45 (88)	46 (46)	41 (29)	29 (14)	26 (13)	187 (26)
Early neonatal death, 0-6 days	41 (80)	39 (39)	30 (21)	23 (11)	19 (9.2)	152 (22)
Delivery room death	28 (55)	16 (16)	10 (6.9)	4 (2)	0	58 (8.2)
Late neonatal death, 7-27 days	4 (7.8)	7 (6.9)	11 (7.6)	6 (2.9)	7 (3.4)	35 (5)
Infant death, 0-365 days	46 (90)	48 (48)	48 (33)	38 (19)	30 (15)	210 (30)

[a] Category denotes gestational age of 22 weeks 0 days to 22 weeks 6 days but also includes 1 infant born at 21 weeks 5 days and 1 infant born at 21 weeks 6 days.
[b] Category denotes gestational age of 26 weeks 0 days to 26 weeks 6 days.

©2009 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Univ Of North Carolina / Acquisitions srvcs on June 2, 2009

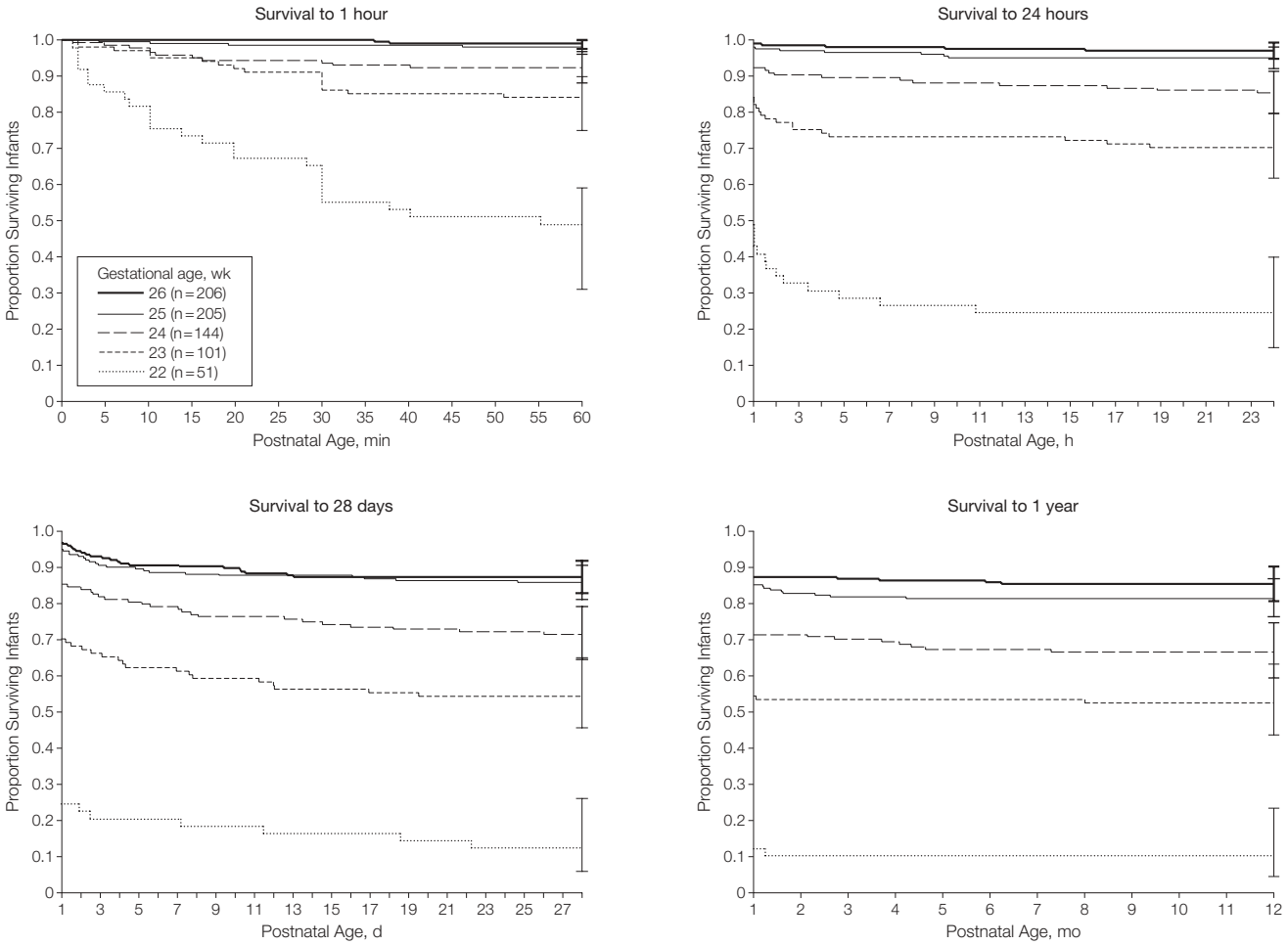
tional age at birth and 1-year survival could be detected ($P=.08$).

Overall survival at 1 year of age for infants born alive was 70%: for those born at 22 weeks it was 9.8%; at 23 weeks 53%; at 24 weeks 67%; at 25 weeks 82%; and at 26 weeks 85% (absolute numbers in TABLE 3). The overall survival including stillbirths in the denominator was 49% and for 22, 23, 24, 25, and 26 weeks, it was 3.5%, 29%, 50%, 67%, and 72%, respectively. Of the 104 deaths occurring at least 24 hours after admission to a neonatal intensive care unit, 42 (40%) involved a decision to withdraw intensive care due to anticipated poor long-term prognosis. The percentages of death due to intensive care withdrawal ranged from 57% at 22 weeks to 29% at 26 weeks.

Of 497 infants who survived to 1 year, 5.6% (28) had cystic periventricular leukomalacia, 5.8% (29) had necrotizing enterocolitis, 10% (50 of 493 with available information) had intraventricular hemorrhage (> grade 2), 34% (169 of 493) had retinopathy of prematurity (> stage 2), and 25% (113 of 452) had severe bronchopulmonary dysplasia. Among these same survivors, 226 (45%) had been discharged from the hospital without major neonatal morbidity (Table 3). The percentages ranged from 20% at 22 weeks to 63% at 26 weeks; the association with gestational age was statistically significant (OR for 1-week increase, 2.17; 95% CI, 1.67-2.78; $P<.001$).

Antenatal treatment with tocolytics, corticosteroids, or both; surfactant treatment within 2 hours after birth; and birth at a level III hospital were significantly associated with lower risk of infant death, before and after adjustment for gestational age (TABLE 4). Cesarean delivery was not associated with a significantly increased chance of survival after adjustment for gestational age. Birth at a level III hospital, which was associated with a lower risk of infant death in the univariate analysis and in the analysis with adjustment for gestational age, was not found

Figure. Survival Curves for Infants Born Alive According to Gestational Age



All surviving infants were followed up for 365 days; therefore, only the initial numbers of infants at risk are shown. Error bars are 95% Kaplan-Meier survival estimates at 60 minutes, 24 hours, 28 days, and 12 months.

©2009 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Univ Of North Carolina / Acquisitions srvcs on June 2, 2009

to be significantly protective in the multivariate analysis.

COMMENT

This study showed 45% perinatal mortality, and 1-year survival of 70% of live-born extremely preterm infants. As expected, live-born infants had considerable morbidity in the neonatal period. Studies on their long-term neurodevelopmental outcome are therefore warranted and in progress.

The strengths of this study include the population-based and prospective enrollment representing a large number of births occurring extremely preterm, including antenatal and intrapartum stillbirths and infants born alive. Population-based data are essential for planning of health care, for determining temporal trends, and for comparisons with other results. Patients were recruited over a 3-year period reflecting present perinatal practice in Sweden. The cohort was stratified by gestational age estimated by ultrasound in practically all pregnancies. Infant survival was determined at several time points ending at 1 year of age, which provided detailed data for parental

Table 3. One-Year Survival, Major Neonatal Morbidity Among Survivors, and Survival Without Major Neonatal Morbidity

	No. With Event/No. in Group (%)					
	Gestational Age, wk					
	≤22[a]	23	24	25	26[b]	Total <27 wk
Survival 365 days						
All infants including stillbirths	5/142 (3.5)	53/183 (29)	96/191 (50)	167/250 (67)	176/245 (72)	497/1011 (49)
Live-born infants	5/51 (9.8)	53/101 (53)	96/144 (67)	167/205 (82)	176/206 (85)	497/707 (70)
Infants admitted to neonatal intensive care unit	5/19 (26)	53/81 (65)	96/132 (73)	167/200 (84)	176/204 (86)	497/636 (78)
Survival 365 days with major neonatal morbidity[c]						
Intraventricular hemorrhage grade >2	1/5 (20)	10/53 (19)	10/96 (10)	20/166 (12)	9/173 (5.2)	50/493 (10)
Retinopathy of prematurity stage >2	4/5 (80)	33/53 (62)	45/94 (48)	54/167 (32)	33/174 (19)	169/493 (34)
Severe bronchopulmonary dysplasia	2/5 (40)	13/49 (26)	27/87 (31)	45/153 (29)	26/158 (17)	113/452 (25)
Periventricular leukomalacia	0/5 (0)	5/53 (9.4)	6/96 (6.2)	9/167 (5.4)	8/176 (4.5)	28/497 (5.6)
Necrotizing enterocolitis	0/5 (0)	1/53 (1.9)	9/96 (9.4)	10/167 (6.0)	9/176 (5.1)	29/497 (5.8)
Survival 365 days without major neonatal morbidity[d]						
Live-born infants	1/51 (2)	9/101 (8.9)	30/144 (21)	75/205 (37)	111/206 (54)	226/707 (32)
Survivors at 1 year	1/5 (20)	9/53 (17)	30/96 (31)	75/167 (45)	111/176 (63)	226/497 (45)

[a] Category denotes gestational age of 22 weeks 0 days to 22 weeks 6 days but also includes 1 infant born at 21 weeks 5 days and 1 infant born at 21 weeks 6 days.
[b] Category denotes gestational age of 26 weeks 0 days to 26 weeks 6 days.
[c] Infants with known information in denominator.
[d] Survival without any of the major neonatal morbidities (intraventricular hemorrhage, retinopathy of prematurity, severe bronchopulmonary dysplasia, periventricular leukomalacia, or necrotizing enterocolitis) as described. Denominators are for all infants, including 21 infants without reported morbidity but with some information missing.

Table 4. Association Between Perinatal Interventions and Risk of Death to Age 1 Year Among Live-Born Infants

	Live-Born Infants		Odds Ratio (95% Confidence Interval)[a]		
	All (n = 707), No.[b]	Dead at 0-364 d (n = 210), No. (%)	Crude	Adjusted[c]	Multivariate Model[d]
Tocolytic treatment					
Yes	413	110 (27)	0.36 (0.23-0.57)	0.43 (0.36-0.52)	0.60 (0.39-0.94)
No	96	48 (50)	1 [Reference]	1 [Reference]	1 [Reference]
Antenatal corticosteroids					
Yes	591	144 (24)	0.31 (0.18-0.54)	0.44 (0.24-0.81)	0.41 (0.20-0.81)
No	85	55 (65)	1 [Reference]	1 [Reference]	1 [Reference]
Cesarean delivery					
Yes	356	75 (21)	0.43 (0.31-0.60)	0.89 (0.60-1.32)	0.98 (0.62-1.52)
No	351	135 (39)	1 [Reference]	1 [Reference]	1 [Reference]
Surfactant administered within 2 hours after birth					
Yes	497	116 (23)	0.47 (0.33-0.68)	0.47 (0.32-0.71)	0.48 (0.31-0.74)
No	189	74 (39)	1 [Reference]	1 [Reference]	1 [Reference]
Born at level III hospital					
Yes	558	145 (26)	0.45 (0.31-0.66)	0.49 (0.32-0.75)	0.78 (0.45-1.35)
No	149	65 (44)	1 [Reference]	1 [Reference]	1 [Reference]

[a] Odds ratios were obtained from logistic regression analysis (simple and adjusted for gestational age) and from a multivariate model including gestational age and all evaluated interventions listed in the table.
[b] All live-born infants with available information.
[c] Adjusted for gestational age at birth.
[d] Only 659 infants with all available information were included in the model (of these, 185 [28%] died at 0-364 days); evaluated with Hosmer-Lemeshow goodness of fit test ($P = .27$).

©2009 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Univ Of North Carolina / Acquisitions srvcs on June 2, 2009

counseling and decision making at various points in time. Accordingly, this study fulfills all criteria for realistic survival figures as previously proposed.[22]

One limitation, shared with other studies using ultrasonography for estimating gestational age, is that some infants with early intrauterine growth restriction might have been assigned a falsely low gestational age. Such erroneous correction of gestational age done only a few weeks before birth might also explain the found increase in SGA percentages with gestational age; possibly at higher gestational weeks, the process of intrauterine growth restriction has continued for a longer time, thus causing more fetuses to become SGA. Furthermore, because of the observational design of the study, associations between interventions and outcome should be interpreted with caution. Some data could not be retrieved and the numbers of live-born infants at 22 weeks of gestational age, as well as in some subgroups, were small. Because the purpose of this report is to provide survival data, neonatal morbidity has not been reported in detail.

In a Swedish cohort born between 1990 and 1992 and comprising all infants with a birth weight of 1000 g or less (n=931), care was less interventional.[26] Half of the infants were delivered at a level III hospital, one-fifth received antenatal steroids, and one-fourth were treated with surfactant. Among infants born at 23 and 24 weeks of gestation, many were stillborn and a majority of those born alive died in the delivery room. The survival to 1 year was only 8% and 28%, respectively.[26] Patient management followed national guidelines to refrain from care of infants delivered at less than 25 weeks gestational age because of anticipated poor outcome. In 2001, the National Board of Health and Welfare published an expert report on perinatal management of extreme prematurity, which stressed centralization of perinatal services for women delivering extremely preterm. It also encouraged individualized evaluation of the mother and infant, departing from previous recommendations based on gestational age thresholds alone. We believe that the endorsement of these guidelines has contributed to the higher survival rates reported in this study.

As expected, 1-year survival of 70% for extremely preterm infants was lower than has been reported for preterm infants born at higher gestational ages. In Sweden from 1992 to 1998, 93% of singleton infants born alive to primiparous mothers after 28 to 31 weeks of gestation survived to 1 year of age.[2]

Few population-based studies published in 2000 or later have reported stillbirths when reporting on extremely preterm delivery.[5,14-17] When the stillbirth rate in this study was expressed as a percentage of all births, it was similar to the rate in other Nordic countries.[14,17] However, in non-Nordic countries, stillbirths are reported to be more prevalent.[5,15] This could partly be explained by differences in rates of intrapartum deaths. In 2 European studies,[5,15] the reported intrapartum death rates varied from 40% to 97% at 22 weeks, 20% to 75% at 23 weeks, 12% to 36% at 24 weeks, and 5% to 22% at 25 weeks, whereas corresponding figures in this study were 44%, 16%, 1%, and 1%, respectively.

The most important finding in this study is the high survival of extremely preterm infants born alive. Survival rates at hospital discharge in recent population-based studies have been reported as 0% at 22 weeks, 6% to 26% at 23 weeks, and 29% to 55% at 24 weeks.[5,14-17] In comparison, the 1-year survival rates in our study for infants born at 22, 23, and 24 weeks were 10%, 53%, and 67%, respectively. In this context, we note that the case-mix, ie, the proportions of infants with known risk factors for adverse outcome such as male sex (55%), pregnancy of multiples (22%), SGA (16%), and 5-minute Apgar score of 3 or less (29%), were similar to those reported from other countries.[9,14,31]

The wide variation in admission for neonatal intensive care in different parts of Europe, ranging from 0% to 80% in infants alive at onset of delivery and born before 24 weeks of gestation,[16] clearly indicates that a large proportion of variation in infant survival reflects differences in care management around birth. In our study, the percentage of delivery room deaths in infants born alive (8.2%) was lower than the percentage reported by other studies.[5,14,15,17] In this study, survival rates based on the number of admitted patients were comparatively high and are thought to reflect the quality of neonatal intensive care in Sweden. In a recent study from Great Britain,[15] the survival rates of admitted infants at 22, 23, 24, and 25 weeks were 0%, 18%, 41%, and 63%, respectively, compared with 26%, 65%, 73%, and 84%, respectively, in this study. Here, 40% of deaths occurring at least 24 hours after admission to the neonatal intensive care unit involved a decision to withdraw intensive care on the basis of anticipated poor long-term prognosis. The practice of withdrawal of neonatal intensive care is known to vary significantly among countries and regions[40] and might partly explain variations in survival rates.

This study revealed high rates of interventions reflecting a proactive approach to perinatal and neonatal care. Of infants born alive, 4 out of 5 were delivered at level III hospitals and the use of tocolytic treatment, administration of antenatal corticosteroids, attendance of a neonatologist at delivery, intubation at birth, and administration of surfactant were frequent. At 24 weeks, almost half of the infants were delivered by cesarean section and the number increased further with advancing gestational age. Of infants born alive at 23 to 26 weeks of gestation, 95% were admitted for neonatal intensive care. However, at 22 weeks of gestation, our findings reflect a more selective use of perinatal interventions

Although observational, this study sheds some light on the effectiveness of perinatal interventions in extremely short gestations that have not been or are unlikely to be tested in randomized trials. Tocolysis, antenatal steroids, and surfactant administration before 2 hours of postnatal age were

©2009 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Univ Of North Carolina / Acquisitions srvcs on June 2, 2009

independently associated with a reduced risk for infant death. However, in contrast to the findings of a recent and larger study,[41] cesarean delivery was not associated with survival advantages. Also, we could not show that the attendance of a neonatologist in the delivery room and intubation at birth were associated with significantly lower mortality. These findings might be explained by methodological flaws, but they may also reflect the fact that delivery room care is neither standardized nor evidence based.[42,43] Extremely preterm infants born at level I or level II hospitals had an almost doubled mortality (44%), as compared with infants born at level III hospitals (26%). This excess mortality risk for extremely preterm infants born in general hospitals has been previously described[17,29,30] and found to be unchanged even after acute obstetric complications are taken into account.[2] However, when adjusted for the use of perinatal interventions, birth at a level III hospital was no longer associated with a reduced risk, implying that the survival advantage of birth at a level III hospital was related to the use of interventions.

The goal of neonatal intensive care is survival without unacceptable severe morbidity. Major neonatal morbidity, such as periventricular leukomalacia, severe degrees of intraventricular hemorrhage, retinopathy of prematurity, and bronchopulmonary dysplasia, are of significant concern because they are associated with an increased risk for poor long-term outcome.[44] The proportion of surviving infants who were free of major neonatal morbidity was 45% in the total cohort. One-year survival without any major neonatal morbidity exhibited a strong correlation with gestational age ranging from 20% at 22 weeks to 63% at 26 weeks of gestation (Table 3). Before a complete assessment of outcome can be made, the morbidity rates found in this study require further analyses of early prognostic indicators and risk factors, as well as a careful follow-up of survivors. In other studies that used broadly similar definitions, percentages without major neonatal morbidity varied from 19% to 79% among survivors.[6,14]

Population differences in Sweden vs other countries must be considered when interpreting our results. In Sweden, the general health of the population has been good for more than 2 generations and the health policy is egalitarian—contraception is subsidized for teenagers and abortion legislation is liberal. Adherence with the antenatal health care program is nearly universal. These factors may have contributed to a lower risk of extremely preterm delivery. However, the effect on improved survival once an infant has been delivered remains to be clarified. We believe that the results can be generalized to countries with universal access to health care and active perinatal programs.

In summary, overall 1-year survival was 70% in extremely preterm infants born alive at 22 to 26 weeks of gestation in Sweden during 2004-2007. Proactive perinatal management is likely to have contributed to this outcome. Therefore, noninitiation or withdrawal of intensive care for extremely preterm infants cannot be based solely on a notion of unlikely survival. This is not to suggest that all extremely preterm liveborn infants should be kept alive at any cost. The prognosis, based on an individual assessment, including early and subsequent morbidities, and parental desires are still the most important factors in decision making.[44]

Whether survival is in the best interest of the infant and family will have to be continuously reassessed. Long-term health of survivors, with focus on neurodevelopment and cognition, is being investigated in a follow-up study at 30 months of corrected age.

Authors/EXPRESS Group Members: Mats Blennow, MD, PhD, Department of Pediatrics, Karolinska University Hospital, Huddinge, and Department of Clinical Investigation, Intervention, & Technology, Karolinska Institutet, Stockholm, Sweden; Uwe Ewald, MD, PhD, Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden; Tomas Fritz, MD, Department of Obstetrics and Gynecology, Sahlgrenska University Hospital, Göteborg, Sweden; Per Åke Holmgren, MD, PhD, Department of Clinical Sciences, Obstetrics, and Gynecology, Umeå University, Umeå, Sweden; Annika Jeppsson, MD, PhD, Department of Obstetrics and Gynecology, Linköping University, Linköping, Sweden; Eva Lindberg, MD, Department of Pediatrics, Örebro University, Örebro, Sweden; Anita Lundqvist, PhD, Department of Health Sciences, Lund University, Lund, Sweden; Solveig Nordén Lindeberg, MD, PhD, Department of Obstetrics and Gynecology, Uppsala University; Elisabeth Olhager, MD, PhD, Department of Pediatrics, Linköping University; Ingrid Östlund, MD, PhD, Department of Obstetrics and Gynecology, Örebro University Hospital, Örebro; Marija Simic, MD, Department of Obstetrics and Gynecology, Karolinska University Hospital Solna, Stockholm; Gunnar Sjörs, MD, PhD, Department of Pediatrics, Uppsala University; Lennart Stigson, MD, Department of Pediatrics, Sahlgrenska University Hospital. *Writing committee members:* Vineta Fellman, MD, PhD, Department of Pediatrics, Clinical Sciences Lund, Lund University; Lena Hellström-Westas, MD, PhD, Department of Women's and Children's Health, Uppsala University; Mikael Norman, MD, PhD, Department of Pediatrics, Karolinska University Hospital, Huddinge and Department of Clinical Investigation, Intervention & Technology, Karolinska Institutet, Stockholm; Magnus Westgren, MD, PhD, Department of Obstetrics and Gynecology, Karolinska University Hospital Huddinge. *Expert group members:* Gerd Holmström, MD, PhD, Department of Ophthalmology, Uppsala University; Ricardo Laurini, MD, PhD, Department of Pathology, Nordland Hospital, Bodö, Norway; Karin Stjernqvist, PhD, Department of Psychology, Lund University. *Steering group and writing committee members:* Karin Källén, PhD, Centre of Reproductive Epidemiology, Lund University; Hugo Lagercrantz, MD, PhD, Department of Women and Child Health, Karolinska Institute, Stockholm, Astrid Lindgren Children's Hospital, Stockholm; Karel Maršál, MD, PhD, Department of Obstetrics and Gynecology, Clinical Sciences Lund, Lund University; Fredrik Serenius, MD, PhD, Department of Clinical Sciences, Pediatrics, Umeå University; Margareta Wennergren, MD, PhD, Department of Obstetrics and Gynecology, Sahlgrenska University Hospital. *Steering group members:* Tore Nilstun, PhD, Department of Medical Ethics, Lund University; Petra Otterblad Olausson, PhD, Centre of Epidemiology, The National Board of Health and Welfare, Stockholm; Bo Strömberg, MD, PhD, Department of Pediatrics, Uppsala University.

Author Contributions: Drs Maršál, principal investigator, and Källén had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Blennow, Ewald, Fellman, Hellström-Westas, Holmgren, Holmström, Jeppsson, Källén, Lagercrantz, Laurini, Lindberg, Lundqvist, Maršál, Nilstun, Nordén Lindeberg, Norman, Olhager, Olausson, Östlund, Serenius, Stjernqvist, Strömberg, Wennergren, Westgren.

Acquisition of data: Blennow, Ewald, Fellman, Fritz, Hellström-Westas, Holmgren, Holmström, Jeppsson, Källén, Lagercrantz, Laurini, Lindberg, Lundqvist, Maršál, Nordén Lindeberg, Norman, Olhager, Östlund, Serenius, Simic, Sjörs, Stigson, Stjernqvist, Strömberg, Wennergren, Westgren.

Analysis and interpretation of data: Blennow, Ewald, Fellman, Fritz, Hellström-Westas, Holmgren, Holmström, Jeppsson, Källén, Lagercrantz, Laurini, Lindberg, Maršál, Nordén Lindeberg, Norman, Olhager, Olausson, Östlund, Serenius, Simic, Sjörs, Stigson, Stjernqvist, Strömberg, Wennergren, Westgren.

Drafting of the manuscript: Fellman, Hellström-Westas, Källén, Lagercrantz, Maršál, Norman, Serenius, Wennergren, Westgren.

Critical revision of the manuscript for important intellectual content: Blennow, Ewald, Fellman, Fritz, Hellström-Westas, Holmgren, Holmström, Jeppsson, Källén, Lagercrantz, Laurini, Lindberg, Lundqvist, Maršál, Nilstun, Nordén Lindeberg, Norman, Olhager, Olausson, Östlund, Serenius, Simic, Sjörs, Stigson, Stjernqvist, Strömberg, Wennergren, Westgren.

Statistical analysis: Källén.

 ©2009 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Univ Of North Carolina / Acquisitions srvcs on June 2, 2009

Obtained funding: Blennow, Källén, Norman, Maršál, Serenius.
Financial Disclosures: None reported.
Funding/Support: This study was supported by Swedish Research Council grant 521-2006-3858; and by grants from the Swedish National Board of Health and Welfare and from Grants to Researchers in the Public Health Care from the Swedish government. The grants were administered by Lund University and Umeå University and used to compensate the 2 research administrators working part time with conduct of the study and collection and management of the data. Karin Källén, PhD, reported grant support from the Evy and Gunnar Sandberg Foundation.
Role of the Sponsor: None of the sponsors had any role in the design of the study; analysis and interpretation of the data; or in the preparation, review, or approval of the manuscript.
Additional Contributions: The administrative support by Kerstin Nordstrand, RN, the Swedish National Board of Health and Welfare, and the technical assistance with data collection by Ingrid Hansson, laboratory assistant, and Grozda Pajic, Lund University, are gratefully acknowledged. We thank Stellan Håkansson, MD, PhD, main coordinator of National Perinatal Quality Registry, and Marius Kublickas, MD, PhD, for valuable help in building the study database. The English language of the manuscript was revised by Nancy Lea Eik-Nes, PhD. Ms Hansson and Ms Pajic were paid by study grants administered by Lund University. Dr Kublickas, Ms Nordstrand, Dr Hakansson, and Dr Eik-Nes were not compensated.

REFERENCES

1. Martin JA, Kung HC, Mathews TJ, et al. Annual summary of vital statistics: 2006. *Pediatrics*. 2008; 121(4):788-801.
2. Johansson S, Montgomery SM, Ekbom A, et al. Preterm delivery, level of care, and infant death in Sweden: a population-based study. *Pediatrics*. 2004; 113(5):1230-1235.
3. Håkansson 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(1):58-64.
4. 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 tertiary centres, part 2: infant survival. *Acta Paediatr*. 2004;93(8):1081-1089.
5. Vanhaesebrouck P, Allegaert K, Bottu J, et al; Extremely Preterm Infants in Belgium Study Group. The EPIBEL study: outcomes to discharge from hospital for extremely preterm infants in Belgium. *Pediatrics*. 2004; 114(3):663-675.
6. Chan K, Ohlsson A, Synnes A, Lee DS, Chien LY, Lee SK; Canadian Neonatal Network. Survival, morbidity, and resource use of infants of 25 weeks' gestational age or less. *Am J Obstet Gynecol*. 2001; 185(1):220-226.
7. 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(1):16-22.
8. 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(5):616-622.
9. Costeloe K, Hennessy E, Gibson AT, Marlow N, Wilkinson AR. The EPICure study: outcomes to discharge from hospital for infants born at the threshold of viability. *Pediatrics*. 2000;106(4):659-671.
10. Larroque B, Breart G, Kaminski M, et al; Epipage study group. Survival of very preterm infants: Epipage, a population based cohort study. *Arch Dis Child Fetal Neonatal Ed*. 2004;89(2):F139-F144.
11. Holmgren PA, Hogberg U. The very preterm infant—a population-based study. *Acta Obstet Gynecol Scand*. 2001;80(6):525-531.
12. Doyle LW; Victorian Infant Collaborative Study Group. Outcome at 5 years of age of children 23 to 27 weeks' gestation: refining the prognosis. *Pediatrics*. 2001;108(1):134-141.
13. Cust AE, Darlow BA, Donoghue DA; Australian and New Zealand Neonatal Network (ANZNN). Outcomes for high risk New Zealand newborn infants in 1998-1999: a population based, national study. *Arch Dis Child Fetal Neonatal Ed*. 2003;88(1):F15-F22.
14. Markestad T, Kaaresen PI, Ronnestad A, et al; Norwegian Extreme Prematurity Study Group. Early death, morbidity, and need of treatment among extremely premature infants. *Pediatrics*. 2005;115(5):1289-1298.
15. Field DJ, Dorling JS, Manktelow BN, Draper ES. Survival of extremely premature babies in a geographically defined population: prospective cohort study of 1994-9 compared with 2000-5. *BMJ*. 2008;336 (7655):1221-1223.
16. Draper ES, Zeitlin J, Fenton AC, et al; MOSAIC Birth Cohort. Investigating the variations in survival rates for very preterm infants in 10 European regions: the MOSAIC birth cohort [published online ahead of print September 19, 2008]. *Arch Dis Child Fetal Neonatal Ed*. 2009;94(3):F158-F163. doi: 10.1136/adc.2008.141531.
17. Tommiska V, Heinonen K, Lehtonen L, et al. No improvement in outcome of nationwide extremely low birth weight infant populations between 1996-1997 and 1999-2000. *Pediatrics*. 2007;119(1):29-36.
18. Effer SB, Moutquin JM, Farine D, et al. Neonatal survival rates in 860 singleton live births at 24 and 25 weeks gestational age: a Canadian multicenter study. *BJOG*. 2002;109(7):740-745.
19. Hoekstra RE, Ferrara TB, Couser RJ, Payne NR, Connett JE. Survival and long-term neurodevelopmental outcome of extremely premature infants born at 23-26 weeks' of gestational age at a tertiary center. *Pediatrics*. 2004;113(1 pt 1):e1-e6.
20. Marlow N, Wolke D, Bracewell MA, Samara M; EPICure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. *N Engl J Med*. 2005;352(1):9-19.
21. Schmitt SK, Sneed L, Phibbs CS. Costs of newborn care in California: a population-based study. *Pediatrics*. 2006;117(1):154-160.
22. Levene M. Is intensive care for very immature babies justified? *Acta Paediatr*. 2004;93(2):149-152.
23. Evans DJ, Levene MI. Evidence of selection bias in preterm survival studies: a systematic review. *Arch Dis Child Fetal Neonatal Ed*. 2001;84(2):F79-F84.
24. Pignotti MS, Donzelli G. Perinatal care at the threshold of viability: an international comparison of practical guidelines for the treatment of extremely preterm births. *Pediatrics*. 2008;121(1):e193-e198.
25. Morse SB, Haywood JL, Goldenberg RI, Bronstein J, Nelson KG, Carlo WA. Estimation of neonatal outcome and perinatal therapy use. *Pediatrics*. 2000; 105(5):1046-1050.
26. Finnström O, Olausson PO, Sedin G, et al. The Swedish national prospective study on extremely low birthweight (ELBW) infants. Incidence, mortality, morbidity and survival in relation to level of care. *Acta Paediatr*. 1997;86(5):503-511.
27. Kamper J, Feilberg Jorgensen N, Jonsbo F, Pedersen-Bjergaard L, Pryds O; Danish ETFOL Study Group. The Danish national study in infants with extremely low gestational age and birthweight (the ETFOL study): respiratory morbidity and outcome. *Acta Paediatr*. 2004;93(2):225-232.
28. Sutton L, Bajuk B; New South Wales Neonatal Intensive Care Unit Study Group. Population-based study of infants born at less than 28 weeks' gestation in New South Wales, Australia, in 1992-3: New South Wales Neonatal Intensive Care Unit Study Group. *Paediatr Perinat Epidemiol*. 1999;13(3):288-301.
29. Rautava L, Lehtonen L, Peltola M, et al; PERFECT Preterm Infant Study Group. The effect of birth in secondary- or tertiary-level hospitals in Finland on mortality in very preterm infants: a birth-register study. *Pediatrics*. 2007;119(1):e257-e263.
30. Lee SK, McMillan DD, Ohlsson A, et al. The benefit of preterm birth at tertiary care centers is related to gestational age. *Am J Obstet Gynecol*. 2003; 188(3):617-622.
31. Tyson JE, Parikh NA, Langer J, Green C, Higgins RD; National Institute of Child Health and Human Development Neonatal Research Network. Intensive care for extreme prematurity–moving beyond gestational age. *N Engl J Med*. 2008;358(16):1672-1681.
32. World Health Organization. The World Health Report 2005: make every mother and child count. http://www.who.int/whr/2005/whr2005_en.pdf. Accessed April 19, 2009.
33. Marsál K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr*. 1996;85(7):843-848.
34. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet*. 2008;371(9606):75-84.
35. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr*. 1978;92 (4):529-534.
36. de Vries LS, Eken P, Dubowitz LM. The spectrum of leukomalacia using cranial ultrasound. *Behav Brain Res*. 1992;49(1):1-6.
37. International Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of prematurity revisited. *Arch Ophthalmol*. 2005;123(7):991-999.
38. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis: therapeutic decisions based upon clinical staging. *Ann Surg*. 1978;187(1): 1-7.
39. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2001;163(7):1723-1729.
40. Cuttini M, Nadai M, Kaminski M, et al; EURONIC Study Group. End-of-life decisions in neonatal intensive care: physicians' self-reported practices in seven European countries: EURONIC Study Group. *Lancet*. 2000;355(9221):2112-2118.
41. Malloy MH. Impact of cesarean section on neonatal mortality rates among very preterm infants in the United States, 2000-2003. *Pediatrics*. 2008; 122(2):285-292.
42. Vento M, Aguar M, Leone TA, et al. Using intensive care technology in the delivery room: a new concept for the resuscitation of extremely preterm neonates. *Pediatrics*. 2008;122(5):1113-1116.
43. Vanpée M, Walfridsson-Schultz U, Katz-Salamon M, Zupancic JA, Pursley D, Jonsson B. Resuscitation and ventilation strategies for extremely preterm infants: a comparison study between two neonatal centers in Boston and Stockholm. *Acta Paediatr*. 2007; 96(1):10-16.
44. Schmidt B, Aszalos EV, Roberts RS, et al; Trial of Indomethacin Prophylaxis in Preterms (TIPP) Investigators. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely-low-birth-weight infants at 18 months: results from the trial on indomethacin prophylaxis in preterms. *JAMA*. 2003;289(9):1124-1129.
45. Bell EF; American Academy of Pediatrics Committee on Fetus and Newborn. Noninitiation or withdrawal of intensive care for high-risk newborns. *Pediatrics*. 2007;119(2):401-403.

©2009 American Medical Association. All rights reserved.

Downloaded from www.jama.com at Univ Of North Carolina / Acquisitions srvcs on June 2, 2009