A National Short-Term Follow-Up Study of Extremely Low Birth Weight Infants Born in Finland in 1996–1997

Viena Tommiska, MD*; Kirsti Heinonen, MD, PhD‡; Sami Ikonen, MD, PhD§; Pentti Kero, MD, PhD‖; Marja-Leena Pokela, MD, PhD¶; Martin Renlund, MD, PhD*#; Martti Virtanen, MD, PhD**; and Vineta Fellman, MD, PhD*

ABSTRACT. *Objectives.* The aims of this prospective nationwide investigation were to establish the birth rate, mortality, and morbidity of extremely low birth weight (ELBW) infants in Finland in 1996–1997, and to analyze risk factors associated with poor outcome.

Participants and Methods. The study population included all stillborn and live-born ELBW infants (birth weight: <1000 g; gestational age: at least 22 gestational weeks [GWs]), born in Finland between January 1, 1996 and December 31, 1997. Surviving infants were followed until discharge or to the age corresponding with 40 GWs. National ELBW infant register data with 101 prenatal and postnatal variables were used to calculate the mortality and morbidity rates. A total of 32 variables were included in risk factor analysis. The risk factors for death and intraventricular hemorrhage (IVH) of the live-born infants as well as for retinopathy of prematurity (ROP) and oxygen dependency of the surviving infants were analyzed using logistic regression models.

Results. A total of 529 ELBW infants (.4% of all newborn infants) were born during the 2-year study. The perinatal mortality of ELBW infants was 55% and accounted for 39% of all perinatal deaths. Of all ELBW infants, 34% were stillborn, 21% died on days 0 through 6, and 3% on days 7 though 28. Neonatal mortality was 38% and postneonatal mortality was 2%. Of the infants who were alive at the age of 4 days, 88% survived. In infants surviving >12 hours, the overall incidence of respiratory distress syndrome (RDS) was 76%; of blood culture-positive septicemia, 22%; of IVH grades II through IV, 20%; and of necrotizing enterocolitis (NEC) with bowel perforation, 9%. The rate of IVH grades II through IV and NEC with bowel perforation decreased with increasing gestational age, but the incidence of RDS did not differ significantly between GWs 24 to 29. A total of 5 infants (2%) needed a shunt operation because of posthemorrhagic ventricular dilatation. Two hundred eleven ELBW infants (40% of all and 60% of live-born infants) survived until discharge or to the age corresponding with 40 GWs. The oxygen dependency rate at the age corresponding to 36 GWs was 39%, and 9% had ROP stage III-V. Neurological status was considered completely normal in 74% of the surviving infants. The proportions of infants born at 22 to 23, 24 to 25, 26 to 27, and 28 to 29 GWs with at least one disability (ROP, oxygen dependency, or abnormal neurological status) at the age corresponding to 36 GWs were 100%, 62%, 51%, and 45%, respectively. Birth weight <600 g and gestational age <25 GWs were the independent risks for death and short-term disability. The primary risk factor for IVH grades II through IV was RDS. Low 5-minute Apgar scores predicted poor prognosis, ie, death or IVH, and antenatal steroid treatment to mothers with threatening premature labor seemed to protect infants against these. Some differences were found in the mortality rates between the 5 university hospital districts: neonatal mortality was significantly lower (25% vs 44%) in one university hospital area and notably higher (53% vs 34%) in another area. Furthermore, significant differences were also found in morbidity, ie, oxygen dependency and ROP rates. Differences in perinatal (79% vs 45%) and neonatal (59% vs 32%) mortality rates were found between secondary and tertiary level hospitals.

Conclusion. Our study shows that even with modern perinatal technology and care, intrauterine and early deaths of ELBW infants are common. The outcome of infants born at 22 to 23 GWs was unfavorable, but the prognosis improved rapidly with increasing maturity. The clear regional and hospital level differences detected in survival rates and in short-term outcome of ELBW infants emphasizes that the mortality and morbidity rates should be continuously followed and that differences should be evaluated in perinatal audit procedures. However, before the overall outcome of ELBW infants can be evaluated, the results of long-term follow-up and the effects of a premature birth on the family should be taken into consideration. *Pediatrics* 2001;107(1). URL: http://www.pediatrics.org/cgi/content/full/107/1/e2; *prematurity, perinatal mortality, neonatal morbidity, extremely low birth weight infants.*

ABBREVIATIONS. ELBW, extremely low birth weight; GW, gestational week; RDS, respiratory distress syndrome; SD standard deviation; SGA, small for gestational age; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity; CRIB, Clinical Risk Index for Babies; OR, odds ratio; CI, confidence interval; PDA, persistent ductus arteriosus.

With the development of antenatal and neonatal intensive care during the last 2 decades, the survival of the extremely low birth weight (ELBW) infant has improved significantly.[1–7] In the 1980s, the survival rate of these infants increased, while the incidence of neurological

and other major handicaps of especially those infants born at low gestational weeks (GWs), ie, 22 to 27 GWs, remained constant. Thus, the total number of children born extremely immature and surviving with long-term disability increased.[8,9] During the 1990s, new advances in care, such as antenatal steroid treatment to mothers with threatening premature labor, surfactant treatment to infants with respiratory distress syndrome (RDS), and new modes of respiratory support, all known to decrease the mortality of ELBW infants, have become widely used in developed countries. From this period, there are scarce data on long-term follow-up. Most studies on ELBW infants are based on neonatal intensive care unit patient material, and, thus, they include only live-born infants who were considered treatable. Although such studies provide a good regional reference, population-based studies including all stillborn and live-born infants are needed for more reliable and generalizable conclusions.

In Finland, all 5 university hospitals together with the National Center of Welfare and Health established in 1996 a register for all ELBW infants born in the country to prospectively assess the short- and long-term prognosis of these infants. Using this register, the aims of this investigation were to establish the birth rate, mortality, and short-term outcome in a comprehensive cohort of ELBW infants born during a 2-year period and to analyze the perinatal and neonatal risk factors associated with poor prognosis.

PARTICIPANTS AND METHODS

The study population consisted of all stillborn and live-born ELBW infants (defined as a birth weight <1000 g and a gestational age ≥22 GWs) born in Finland between January 1, 1996 and December 31, 1997. All maternity hospitals in the country ($n = 44$) participated in the study and no infants fulfilling the criteria were excluded.

The study was approved by the ethics committees of the Hospital for Children and Adolescents and the Departments of Obstetrics and Gynecology, Helsinki University Hospital and by the national Data Protection Ombudsman.

Data were collected in a form containing 101 variables with information about the pregnancy, delivery, neonatal morbidity, treatment, and the short-term outcome of the infant. The data were cross-linked with the Finnish National Birth Register, which also receives basic information on live-born and stillborn infants with a birth weight of 500 g or more or a gestational age of at least 22 weeks and on their mothers. The death certificates from the Central Statistical Office of Finland were cross-checked to confirm the causes of death. If the reports were contradictory or if complementary information was needed, the clarifications were obtained from patient records of each maternity hospital. Five infants born before 26 GWs had a birth weight over 1000 g and did not belong to the study population.

The gestational age was the best obstetrical estimation, based on ultrasound examination before the end of 20 GWs (73%) or on the last menstrual period. Infants with a birth weight below -2 SD according to Finnish intrauterine growth curves were classified as small for gestational age (SGA).[10]

Finnish maternity hospitals were classified into the following 4 levels based on the size, equipment, and staffing[11]: level III, university hospitals with a neonatal intensive care unit and a neonatologist available ($n = 5$); level II, all central hospitals and 2 local hospitals with an obstetrician available 24 hours a day and special wards for newborn infants with or without possibility to provide basic neonatal intensive care ($n = 18$); level Ib, local hospitals with equipment and staff primarily for healthy newborns. Obstetrician and pediatrician are usually not at the hospital outside office hours ($n = 20$); and level Ia, small local hospitals with no equipment for sick newborn infants, usually run by a general practitioner or consultant obstetrician ($n = 1$). Finland is geographically divided into 5 university hospital catchment areas, each served by 1 level III hospital. The 5 university hospitals with their catchment areas were labeled from A to E for outcome analysis.

The social class allocation was based on the mothers' education or occupation according to a classification into 4 categories, used by the Central Statistical Office of Finland and the National Research and Development Center for Welfare and Health.[12,13] In each hospital the same criteria were used for defining RDS,[14] necrotizing enterocolitis (NEC),[15] intraventricular hemorrhage (IVH),[16] and retinopathy of prematurity (ROP).[17] Neurological abnormalities were defined as seizures or muscular hypertonia or hypotonia. The diagnostic criterion for septicemia was a positive blood culture. To compare the patient populations in different hospitals, the Clinical Risk Index for Babies (CRIB) scores were calculated for live-born infants.[18] Survival was defined as the infant being alive at discharge or at the age corresponding to 40 GWs.

All statistical analysis were made by SPSS program (SPSS, Chicago, IL). Mantel-Haenzel and Pearson's χ^2 test, Fisher's exact test, and Student's t test were used as appropriate to distinguish the outcome differences between the gestational age groups or the university hospital districts. The outcome results of each university hospital area were compared with the combined mean value of the other areas. Logistic regression analysis was used to detect risk factors for death and IVH grades II through IV of live-born infants, as well as for oxygen dependency and retinopathy at the age corresponding to 36 GWs of surviving infants. Birth weight, gestational age, Apgar score at 5 minutes of age, and maternal age were dichotomized. All analyzed variables are listed in Table 1 with definition of risk for each variable. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for statistically significant variables. P values <.05 were considered significant.

RESULTS

Mothers

During the 2-year study, 529 ELBW infants (.4% of all newborn infants) were delivered to 480 mothers with a mean age of 31.1 years (range: 16.1–48.5 years): 3% of the mothers ($n = 15$) were younger than 20 years of age and 7% ($n = 33$) were older than 40 years of age. One half of the mothers ($n = 239$) were primipara. The occurrence of pregnancy complications diagnosed before delivery was 58% ($n = 280$): 19% ($n = 92$) had preeclampsia; 19% ($n = 93$), premature rupture of membranes; 30% ($n = 143$), infection at the time of delivery; and 7% ($n = 33$), abruption of placenta. In addition, 3% of the mothers ($n = 16$) had either gestational or insulin-dependent diabetes mellitus. Antenatal steroid treatment was administered to 66% of the mothers ($n = 207$) of live-born infants; the frequency increased with increasing gestational age and was 24%, 68%, 75%, and 82% at 22 to 23, 24 to 25, 26 to 27, and 28 to 29 GWs, respectively. The distribution of the mothers of ELBW infants in social classes 1, 2, 3, and 4 was 12%, 45%, 18%, and 21%, respectively, and corresponds with the social class distribution of all Finnish mothers.[19,20] Twenty percent of the mothers ($n = 65$) smoked during the pregnancy; of these, 8% ($n = 5$) stopped before the end of the first trimester.

Infants

The basic data on ELBW infants and on all infants[19,20] born during the study are summarized in Table 2. The mean gestational ages were 26.0 GWs (range: 21.0–39.0 GWs) in stillborn and 26.4 GWs (range: 22.0–34.9 GWs) in live-born ELBW infants, and the mean birth weights were 601 g (range: 89–

TABLE 1. Variables Included in Logistic Regression Analysis for Risk Factors*

Variables Used in the Risk Factor Analysis	Definition/Unit
Pregnancy data	
Parity	Primiparity
Multiple pregnancy	Yes
Preeclampsia	Yes
Diabetes	Yes
Maternal infection	Yes
Abruption of placenta	Yes
Premature rupture of membranes	Yes
Antenatal steroid treatment	Yes
Hyperstimulation/ in vitro fertilization	Yes
Maternal age	<20 or >40 y
Social classes (1–4)	Yes
Smoking	Yes
Birth data	
Birth in secondary or primary level hospital	Yes
Birth in hospitals belonging to the catchment area of respective tertiary level hospitals	Yes
Maternal transport before delivery	Yes
Vaginal delivery	Yes
1-, 5-, and 10-min Apgar scores	5-min Apgar score <4
Gestational age	<25 GW
Birth weight, length, and head circumference	Weight <600 g
Intrauterine growth retardation	<−2 SD for GW
Infant's gender	Male
Neonatal morbidity	
Anomalies	Yes
RDS	Yes
Septicemia	Yes
NEC	Yes
IVH	Grades II–IV
Neonatal treatment	
† Duration of respirator support	Days
† Supplementary oxygen amount	Percents
† Supplementary oxygen duration	Days
Surfactant treatment	Yes
At the age corresponding to 36 GWs	
Oxygen dependency	Yes
ROP	Grades III–V

* The definition of positive dichotomized value for each risk factor is indicated in the right column.
† Variables that were analyzed in continuous form. For these variables, the unit of analysis is indicated in the right column.

995 g) and 750 g (range: 290–995 g), respectively. The proportion of ELBW infants at each GW is shown in Fig 1.[19,20] Forty percent of the infants (n = 209) were classified as SGA. The birth weights of 3 stillborn infants were <150 g: 2 of them were twins delivered at 25 and 39 GWs with the other surviving twin. A total of 27% of the infants (n = 140) were born from multiple pregnancies. In 48% of twin pregnancies, 1 twin weighed >1000 g and was not included the study population. Of all ELBW infants, 13% (n = 68) were born after assisted reproduction using hyperstimulation or in vitro fertilization.

During the study, 31% of all deliveries took place in tertiary level and one half in secondary level hospitals.[19,20] ELBW infant births occurred in 33 of all the 44 maternity hospitals in Finland. Most ELBW infants (n = 379; 72%) were born in university clinics, ie, tertiary level, 24% (n = 125) in secondary level, and 5% in primary level hospitals. Of the 25 ELBW infants born in primary level hospitals, 64% (n = 16)

were stillborn, 24% (n = 6) died during the first 12 hours, and 12% (n = 3) died during the first 3 days; no infant survived. The overall cesarean section rate in the whole study population was 37% (n = 195) and in live-born ELBW infants was 53% (n = 185). The cesarean section rate of live-born infants increased with increasing maturity; at 22 to 23, 24 to 25, 26 to 27, and 28 to 29 GWs, the rates were 4%, 33%, 68%, and 87%, respectively.

Mortality

Perinatal mortality in relation to gestational age is shown in Fig 2. The overall perinatal mortality in Finland in 1996–1997 was $6^0/_{00}$ (756/121330): $4^0/_{00}$ (n = 485) were stillborn and $2^0/_{00}$ (n = 271) died during the first 6 days.[19,20] The perinatal mortality of ELBW infants was 55% (293/529) and accounted for 39% of all perinatal deaths. Of the stillborn infants, 72% (n = 128) died before and 19% (n = 33) during the delivery, the time of death was unknown in 9% (n = 17) of cases. A total of 88% of live-born infants (n = 309) were admitted to neonatal intensive care. Of the 115 ELBW infants who died during the first week, 60% (n = 68) died during the first 12 hours and 96% (n = 110) during the first 3 days. The ages at death in relation to gestational age are summarized in Fig 3. Neonatal mortality was 38% (n = 133); 18 infants died during the neonatal period after the first 6 days.

Autopsy was performed to 83% of stillborn (n = 147) and to 74% of live-born (n = 103) infants (Table 3). When autopsy was not performed, the causes of death were based on clinical information on the child and mother. Of the 90 stillborn infants with unknown cause of death, 52% (n = 47) had underlying factors not alone sufficient to cause death, such as maternal preeclampsia (n = 5); chronic illness (n = 9) or infection (n = 8); or functional or constitutional disturbances of placenta (n = 21), cervix (n = 2), or umbilical cord (n = 2). The second most common reported cause of death was immaturity (Table 3), and 92% of these infants were born at 22 to 24 GWs. During the first week of life, the reported leading causes of death were RDS and immaturity. During the following 3 weeks, the order of reported causes of death was NEC, RDS, and IVH grades III through IV (Table 3). After the neonatal period during the follow-up until 40 GWs, 7 infants died because of NEC or bronchopulmonary dysplasia.

Neonatal Morbidity

Of live-born infants born at 22 to 23, 24 to 25, 26 to 27, and 28 to 29 GWs, 44%, 90%, 94%, and 92%, respectively, were mechanically ventilated. The incidence of RDS, NEC, septicemia, and IVH grades II through IV of the infants surviving >12 hours (n = 283) are shown in Fig 4. The total incidence of RDS in these infants was 76% and surfactant was administered to 88%, 73%, 71%, and 71%, in the respective gestational age groups.

In infants surviving >12 hours, the incidence of NEC of was 22% (n = 62), when the diagnosis was based on either clinical signs (14%) or verified bowel perforation (9%). A total of 22% (n = 63) had blood

TABLE 2. Birth Characteristics of ELBW Infants and All Newborn Infants Delivered During the Two-Year Study

	Stillborn n (%)	ELBW Infants Live-Born n (%)						All Infants Born in 1996–1997 n (%)
		ALL	22 to 23 GWs	24 to 25 GWs	26 to 27 GWs	28 to 29 GWs	≥30 GWs	
n	178	351	57	95	111	61	27	121 330
Male sex	92 (52)	173 (49)	33 (58)	56 (59)	51 (46)	22 (36)	11 (41)	61 951 (51)
SGA	88 (49)	121 (35)	6 (11)	13 (14)	33 (30)	42 (70)	27 (100)	Not available
Multiple birth infants	38 (21)	102 (29)	14 (25)	32 (34)	34 (31)	14 (23)	8 (30)	3865 (3)
Cesarean section	10 (6)	185 (53)	2 (4)	31 (33)	75 (68)	53 (87)	24 (89)	18 704 (16)
Born in level III hospital	91 (51)	288 (82)	37 (65)	79 (83)	98 (88)	54 (89)	20 (74)	37 631 (31)
Mean birth weight*	601 (±205)	750 (±159)	567 (±102)	715 (±132)	793 (±142)	826 (±125)	914 (±79)	

* Mean birth weight in grams (± SD).
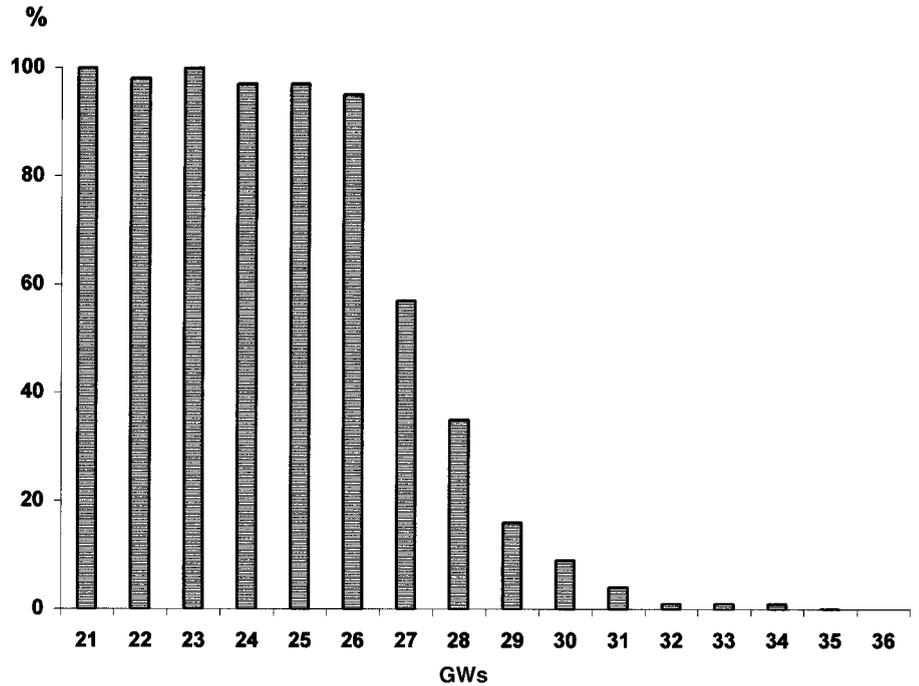
Fig 1. Proportion of ELBW infants of all infants born at different GWs during the 2-year study.

culture-positive septicemia. The incidence of IVH decreased steadily with increasing gestational age: 59%, 33%, 30%, 16%, and 4% of the infants born at 22 to 23, 24 to 25, 26 to 27, 28 to 29, and ≥30 GWs, respectively, had intraventricular bleeding. The mean rate of any IVH was 27% and of grades II through IV was 20%. Persistent ductus arteriosus (PDA) was detected at the age of 5 days in 46% (n = 129) of infants surviving 12 hours or more, and 20% of these (n = 26; 9% of all infants) needed surgical closure. A total of 2% of infants (n = 5) needed a shunt operation because of posthemorrhagic ventricular dilatation.

Short-Term Outcome

A total of 211 ELBW infants survived until discharge or to the age corresponding to 40 GWs. Of these infants 39% (n = 83) were oxygen-dependent at the age corresponding to 36 GWs and 9% (n = 19) had ROP stages III through V. Neurological status was considered completely normal in 74% of the infants (n = 155) and clearly abnormal only in 2% (n = 5). The incidences of ROP, oxygen dependency,

and abnormal neurological status of surviving infants are summarized in Fig 5. The proportions of infants born at 22 to 23, 24 to 25, 26 to 27, and 28 to 29 GWs with at least one of these disabilities at the age corresponding to 36 GWs were 100%, 62%, 51%, and 45%, respectively.

Hospital Differences

No significant differences were found in the mean gestational age or birth weight of ELBW infants among the 5 university hospital areas. Some differences were, however, found in the mortality and morbidity rates: neonatal mortality was significantly lower (25% vs 44%; P < .001) in the university hospital area C and notably higher (53% vs 34%; P = .002) in area A. Furthermore, the incidence of ROP stages III through V was higher (19% vs 6%; P = .006) and the use of supplementary oxygen at the age corresponding to 36 GWs more frequent (59% vs 36%; P = .01) in university hospital area D than in the rest of the country. In area B, the oxygen dependency rate was notably lower (12% vs 43%; P = .002). Clear differences in perinatal (79% vs 45%; P < .001) and

Fig 2. Perinatal mortality in Finland in 1996–1997 at different completed gestational weeks. Black part of the bar indicates stillborn infants; gray part, infants who died on days 0 to 6.
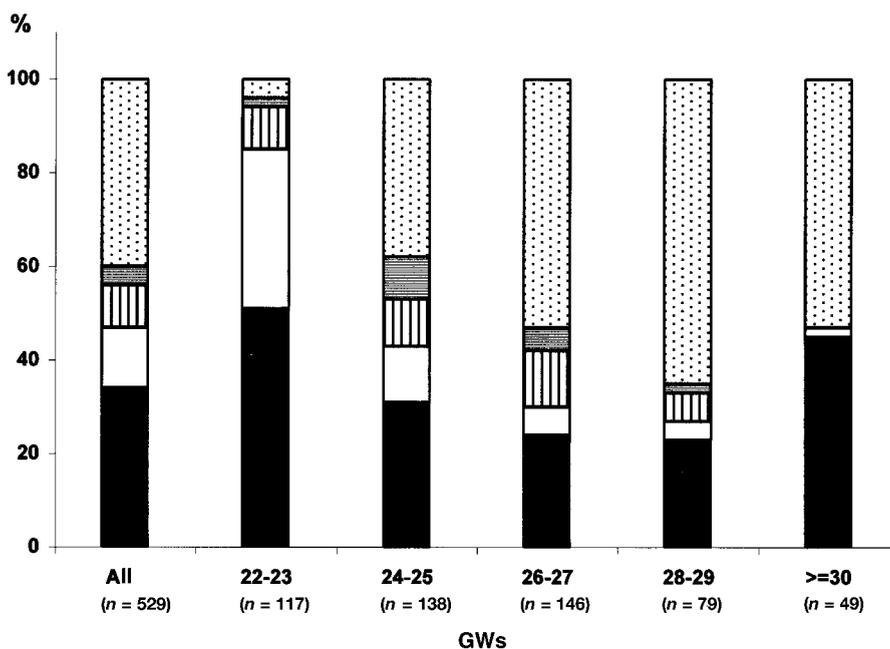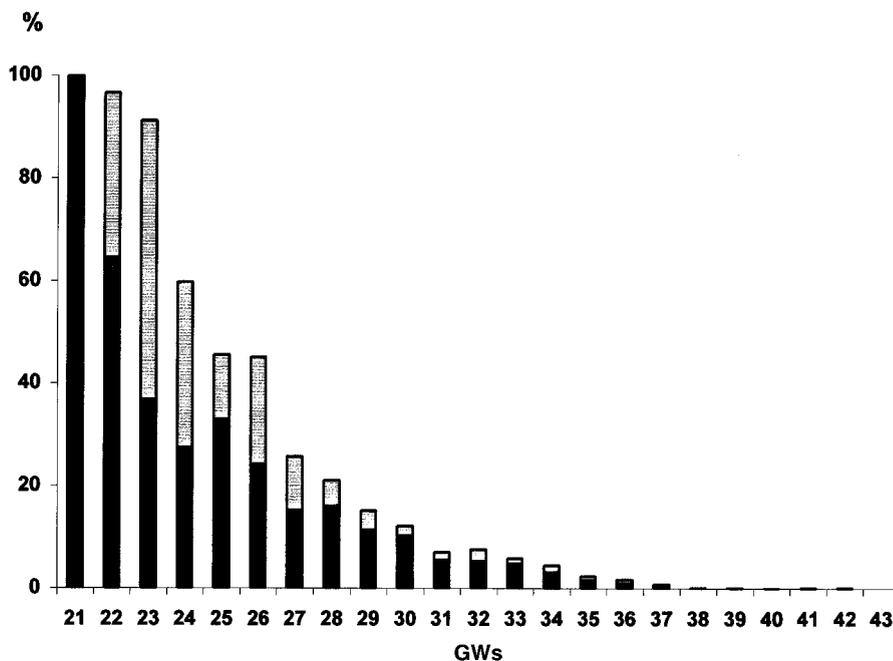
Fig 3. The percentages of stillborn ELBW infants (black), ELBW infants who died during the first 12 hours (white), during the first week (striped), after the first week (dark gray), and those who survived (spotted), in relation to gestational age.

neonatal (59% vs 32%; $P < .001$) mortality rates were also found between secondary and tertiary level hospitals.

University hospital area C with the lowest mortality rate differed from the other areas in that the proportion of live-born infants born outside of the tertiary center was lowest (8% vs 23%; $P = .001$), whereas it was highest (33% vs 15%; $P = .002$) in area D with the highest morbidity rate. The mean CRIB score of the infants born in university hospital area A with the highest mortality rate was significantly higher than the mean score of the infants born in the rest of the country (10.0 vs 7.0; $P < .001$). No differences were found in CRIB scores of the infants born in tertiary or secondary level hospitals (7.7 vs 6.2; $P = .19$).

Risk Factors Associated With Poor Outcome

In the risk factor analysis, 32 perinatal and neonatal variables (Table 1) were included and 6 of them were found significant for death (Table 4). The significant risk factors for IVH, need for supplementary oxygen, and ROP are listed in Table 4.

DISCUSSION

Studies on mortality and outcome of ELBW infants are usually based on neonatal intensive care unit patient cohorts, and, thus, they do not represent the complete birth cohort. Another common epidemiologic problem is an underestimation of birth rate of especially stillborn infants because of variation in the limit between an abortion and a stillbirth ranging

TABLE 3. Causes of Death of ELBW Infants According to Official Death Certificates in Groups Defined by the Time of Death*

	Stillborn	Live-Born		
		Death at Age		
		0 to 12 Hours	>12 Hours, <7 Days	7 to 27 Days
n	178	68†	47	18
Autopsy rate	147 (83)	48 (71)	41 (87)	12 (67)
Unknown cause of intrauterine death	90 (51)			
Immaturity	26 (15)	33 (49)	1 (2)	
Asphyxia	20 (11)	3 (5)	0 (0)	
Anomalies	24 (13)	2 (3)	2 (4)	1 (6)
Infection	4 (2)	9 (13)	2 (4)	1 (6)
IVH (grades III–IV)	3 (2)	1 (2)	16 (34)	3 (17)
RDS		12 (18)	22 (47)	4 (22)
NEC				8 (44)
Other specific causes	9 (5)	8 (12)	4 (9)	1 (6)

* Numbers of infants are given with percent in brackets.
† Forty-two infants (62%) died in the delivery room and were not admitted to neonatal intensive care.

Fig 4. Gestational age-specific rates of respiratory distress syndrome (filled circle), IVH grades II through IV (triangles), septicemia (open circles), and NEC with bowel perforation (crosses) of infants surviving >12 hours.
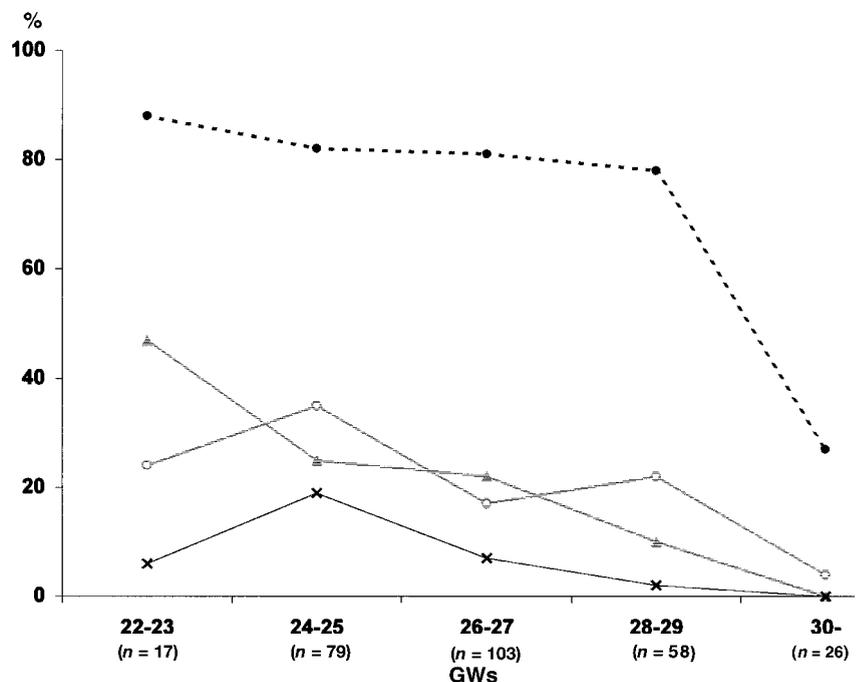
from 22 to 28 GWs.[21,22] At the border of viability, there is also a risk for nonoptimal prenatal treatment resulting in stillbirth. Furthermore, there is a gray zone between stillborn and live-born ELBW infants: infants with a 1-minute Apgar score of zero may be resuscitated, as was the case in 3 infants of our study population. Population-based studies including all stillborn and live-born infants provide a more reliable basis for international epidemiologic comparisons and for evaluating the prognosis of most immature neonates.

Our inclusion criterion was a birth weight <1000 g, and, thus, this study focuses on the most immature infants because the study population includes virtually all infants born before the 27th GW. A birth weight-based inclusion criterion is often criticized, because mortality and morbidity are more related to gestational age than to weight, but the commonly used birth weight-based criterion facilitates compar-

isons with other studies and is applicable for a nationwide study including tens of hospitals.

Although a relatively small group, the ELBW infant deaths account for more than one third of total perinatal mortality. The high stillbirth rate in our study (34%) was similar to that of the Swedish national report[21] (32%) but higher than in the studies by Emsley et al[9] (22%) and Battin et al[23] (14%). The majority of postnatal deaths occur during the first 3 days. The survival rate after the third day (88%) was comparable to other studies.[24] The current antenatal treatment and neonatal intensive care in Finland did not seem to excessively prolong the suffering of those infants who eventually died. Although the autopsy rate was high, in the official death certificates the unspecified causes of death were common in the stillborns and in those infants who died during the first 12 hours. Specific causes of death should be registered also for the most immature infants. The
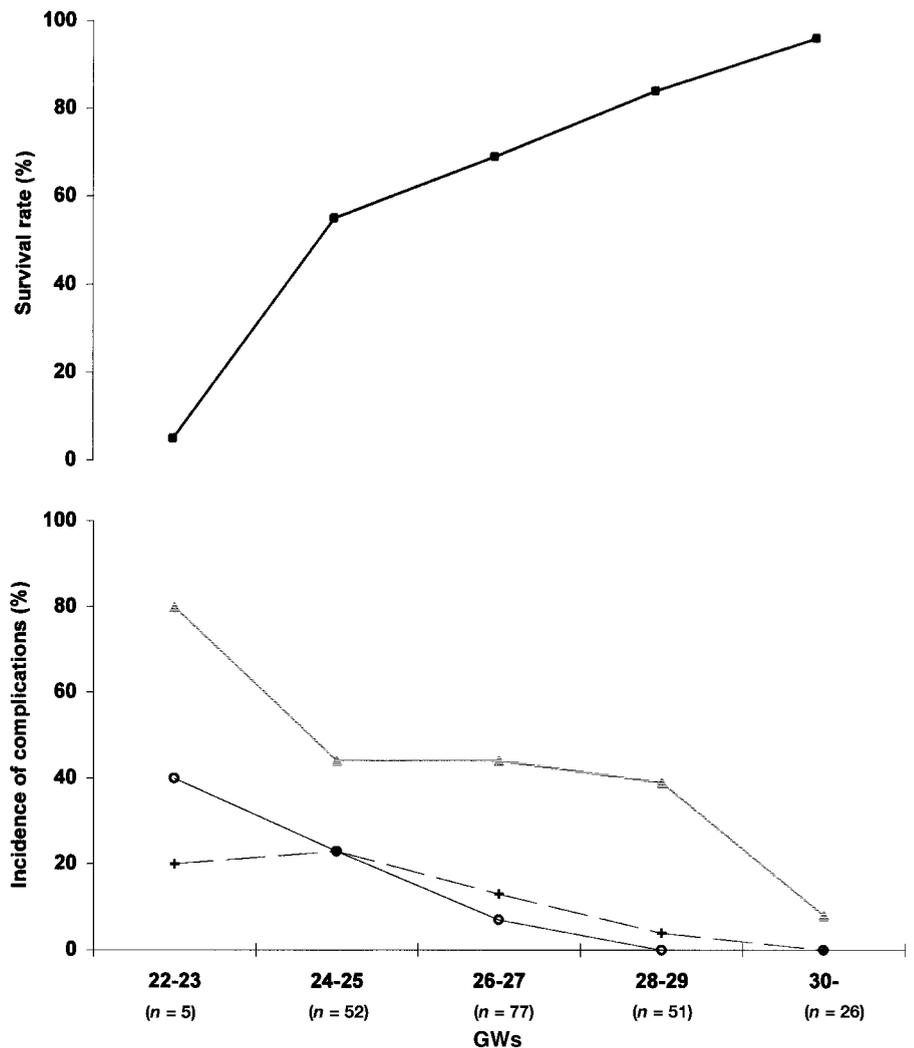
Fig 5. Upper panel: the survival rate of live-born infants. Lower panel: the incidence of oxygen dependency (triangles), ROP stages III through V (open circles), and obvious or suspected neurological abnormalities (crosses) in surviving ELBW infants at the age corresponding with 36 GWs.

most common cause of ELBW infant neonatal deaths in our study was RDS, in agreement with other investigations.[25,26] In a recent study, 50% of the neonatal deaths of ELBW infants were ascribed to infections,[27] considerably more than the 9% ($n = 12$) in our study, but we cannot exclude that some infections were masked under the immaturity diagnosis.

The survival rate and the neurological outcome of infants born at the limit of viability, at 22 to 24 GWs, remain unsatisfactory and have not improved significantly during the last decade.[9,21,23,28–30] More active treatment, ie, cesarean section and active resuscitation, of these infants does not always improve the outcome,[30] although surfactant treatment has been found beneficial.[31] The study by Emsley et al[9] showed improved survival of infants born at 23 to 25 GWs between 1984 and 1994 but showed a significant rise in disability rates. The deteriorated outcome was primarily caused by visual impairments, whereas the incidence of cerebral palsy remained constant. In studies from the 1990s, neonatal survival rates of infants born at 22 to 23 GWs varied from 0% to 25%[21,23,28] and was 9% in our study, which was significantly lower than that of the infants born at 24 to 25 GWs (60%). However, statistically significant differences in neonatal survival among GW groups

at 25 to 29 GWs were not found. Besides of low survival rate, the infants born at 22 to 23 GWs also have poor outcome: long-term disability rates varied in previously mentioned studies from 67% to 100%.[21,23,28] In our study, no infant born at 22 to 23 GWs had completely normal short-term follow-up results.

The incidence of RDS of those ELBW infants who were alive at the age of 12 hours did not decrease significantly with increasing gestational age from 24 to 29 GWs. The oxygen dependency rate at the age corresponding to 36 GWs also did not differ significantly between 24 and 29 GWs, which reflects the constant incidence of RDS of these infants. The lower rates of NEC in infants born at 22 to 23 GWs (Fig 4) may be ascribed to a greater proportion of these infants dying before getting the disease.

In Sweden, a recent study showed increased activity in intensive care of infants born at 24 GWs but relatively conservative attitudes toward intensive treatment of infants born at 22 to 23 GWs.[32] Based on survival and outcome results, some countries, such as Sweden, Norway, and Canada have given recommendations about the treatment of the extremely immature infants born at 22 to 25 GWs.[21,33,34] The national advice usually justifies active antenatal and

TABLE 4. Significant Risk Factors for Death and Disabilities*

Risk Factors for Death in Live-Born Infants (n = 351)†

	OR	95% CI for OR	P Value
5-min Apgar score <4	4.2	2.1–8.7	<.001
No antenatal steroid treatment	2.5	1.4–4.7	.003
Birth weight <600 g	4.4	2.0–9.8	<.001
Gestational age <25 GWs	3.4	1.7–6.6	<.001
University hospital area A	4.0	2.0–7.7	<.001
Intraventricular hemorrhage	2.7	1.3–5.5	.008

Risk Factors for IVH (Grades II–IV) in Live-Born Infants (n = 351)

	OR	95% CI for OR	P Value
Vaginal delivery	3.5	1.8–6.9	<.001
5-min Apgar score <4	2.5	1.1–5.5	.025
RDS	33.9	9.0–127.0	<.001
No antenatal steroid treatment	2.2	1.2–5.0	.020

Risk Factors for Oxygen Dependency at the Age of 36 GWs in Surviving Infants (n = 211)

	OR	95% CI for OR	P Value
IVH	3.6	1.1–11.7	.035
Male sex	3.6	1.8–7.0	<.001
RDS	4.1	1.9–8.9	<.001
Birth weight <600 g	3.7	1.01–13.5	.049
University hospital area B	.1	.02–.4	.001
University hospital area D	2.7	1.1–6.7	.030

Risk Factors for ROP (Stages III–V) in Surviving Infants (n = 211)

	OR	95% CI for OR	P Value
Gestational age <25 GW	26.1	7.8–87.2	<.001
University hospital area D	6.1	1.7–22.0	.006

* The ORs are results of multiple regression model controlling other significant risk factors.
† IVH (grades II–IV) associated mortality risk standardized by the risk factors.

perinatal treatment of infants born at 25 GWs. The treatment of infants born at 23 to 24 GWs is recommended to be individualized, and it is usually suggested not to vigorously treat infants born at 22 GWs, although the possible inaccuracies in gestational age estimation should be kept in mind.[21,33,34]

In our study, the administration of antenatal steroids to mothers of infants born at 22 to 23 GWs was uncommon, as was delivery by cesarean section. Few mothers were transported to tertiary care centers, suggesting that the general opinion regarding treatment of these infants was conservative. The attitudes toward active treatment of infants born at 24 GWs seemed to differ among hospitals, but infants born at 25 GWs were actively treated in the whole country.

The survival of ELBW infants born at level III hospitals was better than at level II and I hospitals, in agreement with results of other investigators.[21,35] There are several possible reasons for the outcome differences. Some infants might have been born unexpectedly with no time to transfer the mother to a tertiary care center. Another natural reason is that long distances, especially in the northern parts of Finland, make a safe transport of the mother to high-level center sometimes impossible. The attitudes to-

ward the referral of the mothers and the active treatment of infants born at 22 to 24 GWs could also be different in different hospital levels and in different parts of the country. In all these cases, antenatal treatment is usually not available and, therefore, the infant's primary situation may have been worse. Besides, centers with larger ELBW infant populations get more experience and may develop and evaluate standardized treatment practices. Because there are only ~180 ELBW live births annually in Finland, it seems reasonable, whenever possible, to centralize them to the tertiary care centers.

Some regional differences were found in mortality and short-term outcome among the 5 university hospital areas. Because differences were significant even in multivariate logistic models (Table 4), they are probably not caused by differences in the catchment populations. Besides variation in effectiveness of care, worse outcome may also result from more conservative attitudes toward the intensive care of the most premature infants born at 22 to 24 GWs. In the university hospital area with the highest mortality rate, the patient volume was average and no significant differences were found in the proportion of infants born outside the university hospital compared with the other areas. The notably higher CRIB scores in this hospital area, compared with the other tertiary hospital districts, may reflect the intensity of treatment during the delivery and the first 12 hours, and the differences in study populations.

The need for extra oxygen at the age corresponding to 36 GWs was lower in university hospital area B and higher in area D even after standardization for sex, RDS, and low birth weight (Table 4). Such difference could also reflect variation in treatment practices and not only the disease state of infants. Interestingly, the tertiary center with the highest incidence of oxygen dependency also had the highest incidence of ROP. However, in logistic regression analysis, the duration of oxygen treatment and the highest inhaled oxygen concentration were not risks for ROP. That was in turn contradictory to findings of a previous study.[36]

ELBW (<600 g) and gestational age (<25 GWs) were independent risk factors for death and also for short-term morbidity of surviving infants, a finding supported by other authors.[21,37–40] By antenatal steroid treatment, the risk for death and IVH of the live-born infants could clearly be reduced. Even the survival rate of infants born at 22 to 24 GWs was higher in the group treated prenatally with steroids. Vaginal delivery was significantly associated with IVH. This difference remained even after standardization for low Apgar score, RDS, and lack of antenatal steroid treatment. We did not find increased risks for death associated with male gender or twin pregnancy, described in previous studies.[21,40–42]

Our study confirms that even with modern technology, intrauterine and early deaths of ELBW infants are common. The mortality and morbidity of infants born at 22 to 23 GWs remained high, but with increasing maturity, especially the survival rate improved rapidly. Clear regional and hospital level differences in survival rates and in short-term out-

come were detected. This emphasizes that mortality and morbidity of ELBW infants need to be continuously followed and that the differences need to be evaluated in audit surveys. However, before the overall outcome of ELBW infants can be evaluated, the results of long-term follow-up and the effects of a premature birth on the family should also be taken into consideration.

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Viena Tommiska, Kirsti Heinonen, Sami Ikonen, Pentti Kero, Marja-Leena Pokela, Martin Renlund, Martti Virtanen and Vineta Fellman

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