Neonatal Morbidity and 1-Year Survival of Extremely Preterm Infants

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abstract

OBJECTIVE: To determine 1-year survival and major neonatal morbidities (intracranial hemorrhage grade >2, cystic periventricular leukomalacia, retinopathy of prematurity grade >2, necrotizing enterocolitis, severe bronchopulmonary dysplasia) among extremely preterm infants in Norway in 2013–2014, and to compare the results to the first Norwegian Extreme Prematurity Study 1999–2000 and similar contemporary European population-based studies.

METHODS: Population-based study of all infants born at 22 through 26 weeks' gestation in Norway in 2013–2014. Prospectively collected data were obtained by linking data in the Norwegian Neonatal Network to the Medical Birth Registry of Norway.

RESULTS: Of 420 infants (incidence 3.5 per 1000 births), 145 were stillborn (34.5%), 275 were live-born (82.3% of the 334 fetuses alive at admission for obstetrical care), and 251 (91.3% of live-born infants) were admitted to a neonatal unit. The survival among live-born infants was 18% at 22 weeks, 29% at 23 weeks, 56% at 24 weeks, 84% at 25 weeks and 90% at 26 weeks (for each week increment in gestational age: odds ratio 3.3; 95% confidence interval, 2.4–4.4). Among infants surviving to 1 year of age, major neonatal morbidity was diagnosed in 55%. Decreasing gestational age was moderately associated with rates of major morbidity (odds ratio 1.6; 95% confidence interval, 1.2–2.2).

CONCLUSIONS: Compared to the previous 1999–2000 cohort, the rate of stillbirth before admission to an obstetrical unit increased, whereas the survival rate among live born infants was similar in our 2013–2014 cohort. Neonatal morbidity rates remain high among extremely preterm infants.

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WHAT'S KNOWN ON THIS SUBJECT: Extremely preterm infants have high rates of morbidity and mortality.

WHAT THIS STUDY ADDS: Survival after extremely preterm birth has not improved from 1999–2000 to 2013–2014 in Norway. Decreasing gestational age was strongly associated with mortality and moderately associated with major neonatal morbidity. Among survivors, neonatal morbidity rates remain high.

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The decision to initiate or withhold active care for infants at the border of viability is challenging and ethically complex. A recent systematic review of national guidelines for the management of extremely premature deliveries reported a general agreement for comfort care at 22 weeks' gestational age (GA) and active care at 25 weeks' GA. However, recommendations at 23 and 24 weeks varied substantially.[1] Attitudes and tradition in the intensity of perinatal care differ among centers, regions, and countries and influence the rates of stillbirths, NICU admissions, and outcomes. Recently, a more active pre- and postnatal approach has been reported to increase survival without an increase in severe impairment.[2–4]

The first Norwegian Extreme Prematurity Study (NEPS1) investigated all infants with a GA of 22 to 27 weeks or a birth weight <1000 g born in 1999 and 2000 and reported high survival rates and low rates of neonatal morbidities compared with previous reports.[5–9] Among the 306 children investigated at 5 years, 84% had mild or no disability. However, 15 of 18 infants with severe neurodevelopmental disability were below 26 weeks' GA.[10] Pre- and postnatal care change over time, and there is a continuous need for population-based studies to provide current data to guide caregivers and parents in decision-making. The aims of this study were to describe perinatal care, neonatal morbidity, causes of death, and 1-year survival among infants born at 22 through 26 weeks' gestation in Norway in 2013 and 2014 (NEPS2). We also aimed to compare current results with NEPS1 and recent population-based studies from other countries.

METHODS

The study population included all live-born and stillborn infants born at 22 through 26 weeks in Norway between January 1, 2013, and December 31, 2014.

Data Collection

Data from the Norwegian Neonatal Network (NNN) and the Medical Birth Registry of Norway (MBRN) were linked for analyses. The MBRN receives compulsory reported data on all births and terminations after 12 weeks' gestation, including information about pregnancy, labor interventions, birth complications, whether the infant is born alive, and evidence of congenital anomalies.[11] Practically all pregnant women in Norway attend standardized antenatal care free of charge. Fetal age and estimated date of delivery is calculated at routine fetal ultrasound screening between 17 and 19 gestational weeks or based on last menstrual period (LMP) if no fetal ultrasound before 20 weeks' gestation is available.

The NNN was established in 2004 as a governmental funded national medical quality registry for infants admitted to a neonatal unit. All 21 Norwegian neonatal units enter clinical data into a Web-based electronic database on a daily basis. The database includes anthropometric and demographic data, detailed data on resuscitation, treatment modalities, invasive procedures, diagnoses, outcome parameters, and status at discharge. Dedicated members of the NNN at each study site participate in quality control and supplementation of missing data.

Both MBRN and NNN collect personal identifiable data without consent according to the MBRN Regulation and the Personal Health Data Filing Systems Act of Norway. The current study was approved by the Regional Committees for Medical and Health Research Ethics in Norway.

Outcome and Treatment Definitions

Data on stillborn infants, defined as no clinical signs of life at birth, were retrieved from the MBRN, and data on live-born infants were obtained from MBRN and NNN. All live-born infants were followed until death or discharge home. One-year survival was recorded in the MBRN. Congenital anomalies were defined in accordance with the *International Classification of Diseases, 10th Revision*. Patent ductus arteriosus (Q25.5), luxation of the hip (Q65.0–65.5), and aplasia of the umbilical artery (Q27.0) were not classified as anomalies. Antenatal steroids were defined as a full course when given at least 24 hours before birth. Small for GA was defined as birth weight below the 10th centile according to Norwegian growth charts.[12] Sepsis was diagnosed as growth of bacteria or fungi in blood culture and antibiotic treatment of at least 5 days or death before 5 days during the episode. When coagulase-negative staphylococci were identified, a C-reactive protein value exceeding 95 nmol/L (10 mg/L) was required. Severe bronchopulmonary dysplasia (BPD) was defined as need for at least 30% oxygen or respiratory support at postmenstrual age 36 weeks.[13] Verified necrotizing enterocolitis (NEC) was diagnosed according to Bell stage 2 or 3.[14] Intracranial hemorrhage (ICH) and cystic periventricular leukomalacia (cPVL stage ≥2)[15] were determined by the most severe cranial ultrasonogram (CUS) before hospital discharge or death. Grade 3 or 4 ICH and/or cPVL was considered severe CUS abnormality. Severe retinopathy of prematurity (ROP) was defined as stage 3 to 5.[16] Major neonatal morbidity was defined as any of the following morbidities: severe BPD, verified NEC, severe CUS abnormality, or severe ROP. Deaths in the NICU were categorized according to the primary causes and whether death occurred after a decision to withdraw intensive care.

Comparisons With Other Population-Based National Cohorts

For comparison with the NEPS1 study and with recent population-based national cohorts, numbers

of live-born and stillborn infants, and the different outcomes for each completed gestational week were extracted from the original publications. The Swedish Express study from 2004 to 2007,[17] the Epicure 2 cohort from England in 2006,[18] and the French Epipage 2 cohort born in 2011[19] were included for graphical illustration of variations in perinatal care and outcomes at 22 to 26 weeks.

Statistical Analyses

Statistical analyses were performed with SPSS 23.0 (SPSS, Armonk, NY) and Stata 14.1 (Stata, College Station, TX). Results are presented as median with interquartile range, numbers with proportion (%), proportion with exact 95% binomial confidence interval (CI), or as odds ratios (OR) with 95% CI. Group differences were examined using the χ^2 test and Fisher exact test for dichotomous variables and Mann-Whitney *U* test for continuous variables. *P* values <.05 were defined as statistically significant.

Associations between GA and the risk for not being admitted to NICU were analyzed by using logistic regression for each gestational week, with infants born at 26 weeks set as reference. Assessing the effect of GA on mortality and neonatal morbidity, linear logistic regression was applied, and infants <24 weeks' gestation were categorized into 1 group because of the small number of surviving infants. Differences between NEPS1 and NEPS2 were analyzed with logistic regression by using NEPS1 as reference, adjusted for GA.

RESULTS

Study Population and Interventions

Of a total birth population of 120 007 in Norway in 2013 and 2014, 423 were born at 22 to 26 weeks' gestation. Three pregnancies were terminated due to lethal malformations and were excluded from the analyses. Among the 420 infants included, 145 were stillborn (1.2 per 1000 total births), and 275 were live-born (2.3 per 1000 total births). In total, 251 infants (91% of live-births) were admitted to a NICU, and most of them (237 of 251; 94%) were born at 1 of 9 hospitals designated to care for infants <27 weeks during the study period.

GA was calculated based on ultrasound dating for 405 (96.4%) infants, on LMP for 14 infants, and not specified for 1 infant. Among 275 live-born infants, 234 (85.1%) had both ultrasound dating and LMP registered. The median GA was 25.2 for ultrasound dating and 25.3 for LMP. Infants were classified within the same gestational week with LMP and ultrasound dating in only 49%. In 17% of the infants, LMP classified GA at least 1 week higher than ultrasound dating, and in 34% at least 1 week lower.

The characteristics and interventions among live-born infants are presented in Table 1. Congenital anomalies were preset in 12.4%. Birth weight ranged from 300 to 1180 g, with a median of 685 g. Antenatal steroids were given to 87%, and 61% of the infants received a full course. There was no association between GA and proportions receiving antenatal steroids for infants >22 weeks. Surfactant was administered in the delivery room to 211 of 275 (77%) infants, and 29 infants received surfactant by a less invasive technique without intubation.[20] Among infants admitted to NICU, 227 of 251 (90%) received surfactant, and 228 of 251 (91%) received mechanical ventilation.

NICU Admission, Survival, and Morbidities Among Surviving Infants

Among fetuses alive at maternal admission to an obstetrical unit, the risk of not being admitted to NICU was higher for infants born at 22 weeks (OR 174.3, 95% CI 44.5–683.3), 23 weeks (OR 12.8, 95% CI 4.1–40.1), and 24 weeks (OR 3.8, 95% CI 1.2–12.5) compared with those born at 26 weeks. Adjusted for GA, cesarean delivery was associated with a higher NICU admission rate (OR 3.1, 95% CI 1.2–8.2).

The 1-year survival rate was 44% for all births, 67% for all live-born infants, and 74% for infants admitted to NICU (Table 1). The survival rate among live-born infants was 18% at 22 weeks, 29% at 23 weeks, 56% at 24 weeks, 84% at 25 weeks, and 90% at 26 weeks (for each week increment in GA: OR 3.3, 95% CI 2.4–4.4). Antenatal steroid use was associated with increased survival (OR 3.5, 95% CI 1.4–8.8), whereas no significant association was found between survival and cesarean delivery, small for GA, sex, or multiple birth, adjusted for GA.

The morbidity rates among the 185 surviving infants are shown in Table 2 and in Supplemental Table 5. ICH grade 3 or 4 and/or cPVL were diagnosed in 14 (13%) infants, but not among the 15 surviving infants with GA <24 weeks. Verified NEC was diagnosed in 10 infants, and 8 had laparotomy, including 2 with ileostomy at discharge. Major neonatal morbidities were found in 102 of 185 (55%) surviving infants. Decreasing GA was associated with major neonatal morbidities (OR 1.6, 95% CI 1.2–2.2), severe BPD (OR 1.4; 95% CI 1.02–1.9), and severe ROP (OR 1.9, 95% CI 1.3–2.8) but not with the risk of NEC or severe CUS abnormality.

The main causes of death are presented in Table 3. In 34 of 66 (52%) NICU deaths, an explicit decision to withhold active care was made. Among these infants, severe CUS abnormality was the main reason for withholding active care in 17 of 34 (50%). Of all infants diagnosed with ICH grade 4 or cPVL, death due to withholding intensive care ranged from 74% for infants <25 weeks to 15% at 25 to 26 weeks.

TABLE 1 Number of Births, Admissions, and Characteristics of Live-Born and Admitted Infants, Born in 2013–2014, GA 22 to 26 Weeks

	22 Weeks	23 Weeks	24 Weeks	25 Weeks	26 Weeks	22–26 Weeks
Births, live-births, and admissions to NICU						
Total births, *n*	66	72	85	91	106	420
Fetuses alive by admission to an obstetrical unit, *n* (% of all births)	47 (71.2)	55 (76.4)	71 (83.5)	74 (81.3)	87 (82.1)	334 (79.5)
Live-births, *n* (% of all births)	17 (25.8)	42 (58.3)	62 (72.9)	70 (76.9)	84 (79.2)	275 (65.5)
Admitted to NICU, *n* (% of live-births)	5 (29.4)	34 (81.0)	60 (96.8)	69 (98.6)	83 (98.8)	251 (91.3)
Characteristics/perinatal interventions of live-born infants						
Birth wt, median (IQR)	500 (438–532)	562 (504–611)	665 (611–711)	781 (667–835)	860 (734–964)	685 (575–830)
Female, *n* (%)	8 (47.1)	21 (50.0)	29 (46.8)	33 (47.1)	38 (45.2)	129 (46.9)
Singleton, *n* (%)	14 (82.4)	33 (78.6)	45 (72.6)	56 (80.0)	68 (81.0)	216 (78.5)
Small for GA, <10th percentile, *n* (%)	3 (17.6)	9 (21.4)	10 (16.1)	15 (21.4)	22 (26.2)	59 (21.5)
5 min Apgar score below 4	11 (68.8)	14 (33.3)	9 (15.0)	3 (4.3)	11 (13.4)	48 (17.8)
Born outside a regional designated NICU hospital,[a] *n* (%)	8 (47.1)	1 (2.4)	4 (6.5)	8 (11.4)	2 (2.4)	23 (8.4)
Cesarean delivery, *n* (%)	2 (11.8)	5 (11.9)	20 (32.3)	35 (50.0)	52 (61.9)	114 (41.5)
Antenatal steroids, *n* (%)	6 (35.3)	36 (85.7)	58 (93.5)	63 (90.0)	76 (90.5)	239 (86.9)
Antenatal steroids given >24 h before birth, *n* (%)	0 (0)	25 (59.5)	38 (61.3)	43 (61.4)	61 (72.6)	167 (60.7)
Surfactant in delivery room, *n* (%)	4 (23.5)	35 (83.3)	54 (87.1)	55 (78.6)	63 (75.0)	211 (76.7)
Intubation in delivery room, *n* (%)	5 (29.4)	37 (88.1)	58 (93.5)	52 (74.3)	47 (56.0)	199 (72.4)
Unsuccessful resuscitation, *n* (%)	0 (0)	6 (14.3)	2 (3.2)	1 (1.4)	1 (1.4)	10 (3.6)
Characteristics/treatment of infants admitted to NICU						
Clinical Risk Index for Babies, median (IQR)	17 (16–17)	16 (15–17)	14 (13–15)	12 (12–13)	10 (10–12)	13 (11–15)
Mechanical ventilation, any, *n* (%)	5 (100)	34 (100)	60 (100)	66 (95.7)	63 (75.9)	228 (90.8)
Mechanical ventilation before 3 d of age, *n* (%)	5 (100)	34 (100)	57 (95.0)	61 (88.4)	52 (62.7)	209 (83.3)
Indomethacin or ibuprofen for PDA, *n* (%)	0 (0)	18 (52.9)	27 (45.0)	20 (29.0)	17 (20.5)	82 (32.7)
Surgical ligation of PDA, *n* (%)	0 (0)	1 (2.9)	7 (11.7)	2 (2.9)	2 (2.4)	12 (4.8)
Postnatal corticosteroids for BPD, *n* (%)	3 (60.0)	14 (41.2)	35 (58.3)	32 (46.4)	29 (34.9)	113 (45.0)

IQR, interquartile range; PDA, patent ductus arteriosus.

[a] Born outside of the 9 hospitals designated to treat infants <27 wk during the study period.

TABLE 2 One-Year Survival and Neonatal Morbidities Among Infants Born in 2013–2014, GA 22 to 26 Weeks

	22 Weeks	23 Weeks	24 Weeks	25 Weeks	26 Weeks	22–26 Weeks
One-year survival						
Survival, *n*	3	12	35	59	76	185
% survival of all births (95% CI)	5 (1–13)	17 (9–27)	41(31–52)	65 (54–75)	72 (62–80)	44 (39–49)
% survival of fetuses alive by admission to an obstetrical unit (95% CI)	6 (1–18)	22 (12–35)	49 (37–61)	80 (69–88)	87 (79–94)	55 (50–61)
% survival of live-births (95% CI)	18 (4–43)	29 (16–45)	56 (43–69)	84 (74–92)	90 (82–96)	67 (61–73)
% survival of infants admitted to NICU (95% CI)	60 (15–95)	35 (20–54)	58 (45–71)	86 (75–93)	92 (83–97)	74 (68–79)
Morbidities						
Early-onset sepsis,[a] *n* (% admitted to NICU)	0 (0)	1 (2.9)	4 (6.7)	3 (4.3)	2 (2.4)	10 (4.0)
Late-onset sepsis,[b] *n* (% admitted to NICU)	1 (20.0)	8 (23.5)	13 (21.7)	27 (39.1)	18 (21.7)	67 (26.7)
ICH, Papile grade 3–4, *n* (% of survivors)	0 (0)	0 (0)	5 (14.3)	6 (10.2)	3 (3.9)	14 (7.6)
cPVL, *n* (% of survivors)	0 (0)	0 (0)	0 (0)	3 (5.1)	7 (9.2)	10 (5.4)
ROP, stage 3–5, *n* (% of survivors)	0 (0)	4 (33.3)	12 (34.3)	11 (18.6)	5 (6.6)	32 (17.3)
NEC, Bell stage 2–3, *n* (% of survivors)	0 (0)	2 (16.7)	2 (5.7)	5 (8.5)	1 (1.3)	10 (5.4)
Severe BPD,[c] *n* (% of survivors)	2 (66.7)	7 (58.3)	20 (57.1)	20 (33.9)	29 (38.2)	78 (42.2)
Major neonatal morbidity,[d] *n* (% of survivors)	2 (66.7)	9 (75.0)	25 (71.4)	32 (54.2)	34 (44.7)	102 (55.1)

[a] Microbiologically verified sepsis at <3 d of life.

[b] Microbiologically verified sepsis at 3 d of life or older.

[c] Need for positive pressure ventilation or at least 30% oxygen at 36 wk postmenstrual age.

[d] ICH Papile grade 3–4 or cystic.

Trends in Norway Between 1999–2000 and 2013–2014

Table 4 and Supplemental Table 5 compare birth rates, NICU admissions, and outcomes in Norway between the NEPS1 and NEPS2 studies. The total birth population and the number of live-born infants at 22 to 26 weeks' gestation were similar in the 2 periods. However, the proportion of intrauterine death outside hospital increased by 117% (P = .001) over the 15 years, and the total incidence of infants born at 22 to 24 weeks' gestation increased by 29% (P = .014). Among infants <26 weeks admitted to the NICU, the proportion delivered by cesarean delivery increased from 25% in NEPS1 to

TABLE 3 Main Causes of Death Among Infants Admitted to a NICU, Born at 22 to 26 Weeks?(tm) Gestation

Main Cause of Death	Respiratory Failure	Severe Neurologic Morbidity[a]	NEC or Bowel Perforation	Sepsis	Other[b]	Total
Death despite ongoing intensive care treatment, *n* (%)	11 (34.4)	2 (6.3)	8 (25.0)	5 (15.6)	6 (18.8)	32
Death after a decision to withdraw intensive care treatment, *n* (%)	11 (32.4)	17 (50.0)	5 (14.7)	0 (0)	1 (2.9)	34
Total, *n* (%)	22 (33.3)	19 (28.8)	13 (19.7)	5 (7.6)	7 (10.6)	66

[a] ICH Papile grade 3?″4, cPVL, or clinical signs of severe neurologic damage.

[b] Other causes were congenital malformation ($n = 1$), perinatal asphyxia ($n = 1$), accidental extubation ($n = 1$), and refractory hypotension ($n = 4$).

TABLE 4 Total Births and ORs for Stillbirth, NICU Admission, and Survival in NEPS2 Compared With NEPS1

	NEPS1	NEPS2	OR (95% CI)[a]		*P*[b]
	1999–2000	2013–2014	Crude	Adjusted[c]	
Total birth population	119 611	120 007			
All live-births and stillbirths					
22–24 wk, *n* (rate/1000 births)	173 (1.45)	223 (1.86)			.014
25–26 wk, *n* (rate/1000 births)	195 (1.63)	197 (1.64)			.96
22–26 wk, *n* (rate/1000 births)	368 (3.08)	420 (3.50)			.074
Intrauterine death before admission to obstetric unit[d]					
22–24 wk, *n* (% of all births)	24 (14.8)	50 (22.4)	1.66 (0.97–2.84)	1.59 (0.93–2.73)	.090
25–26 wk, *n* (% of all births)	15 (7.7)	35 (17.8)	2.58 (1.36–4.89)	2.57 (1.36–4.89)	.004
22–26 wk, *n* (% of all births)	39 (11.0)	85 (20.2)	2.06 (1.37–3.10)	1.96 (1.30–2.97)	.001
Intrauterine death before admission to obstetric unit[d]					
22–24 wk, *n* (% of all births)	38 (23.5)	52 (23.3)	0.99 (0.62–1.60)	0.80 (0.47–1.34)	.40
25–26 wk, *n* (% of all births)	12 (6.2)	8 (4.1)	0.64 (0.26–1.61)	0.64 (0.25–1.59)	.33
22–26 wk, *n* (% of all births)	50 (14.0)	60 (14.3)	1.02 (0.68–1.53)	0.77 (0.50–1.21)	.26
Live births[d]					
22–24 wk, *n* (% of all births)	100 (61.7)	121 (54.3)	0.74 (0.49–1.11)	0.85 (0.54–1.32)	.46
25–26 wk, *n* (% of all births)	167 (86.1)	154 (78.2)	0.58 (0.34–0.98)	0.58 (0.34–0.99)	.044
22–26 wk, *n* (% of all births)	267 (75.0)	275 (65.5)	0.63 (0.46–0.86)	0.71 (0.51–0.99)	.049
NICU admissions[d]					
22–24 wk, *n* (% of live-births)	83 (83.0)	99 (81.8)	0.92 (0.46–1.85)	1.31 (0.56–3.09)	.53
25–26 wk, *n* (% of live-births)	165 (98.8)	152 (98.7)	0.92 (0.13–6.62)	0.96 (0.13–6.91)	.96
22–26 wk, *n* (% of live-births)	248 (92.9)	251 (91.3)	0.80 (0.43–1.50)	1.21 (0.57–2.58)	.62
Survival to discharge[d]					
22–24 wk, *n* (% of live-births)	44 (44.0)	50 (41.3)	0.90 (0.52–1.53)	1.04 (0.58–1.84)	.90
25–26 wk, *n* (% of live-births)	136 (81.4)	135 (87.7)	1.62 (0.87–3.01)	1.65 (0.89–3.07)	.11
22–26 wk, *n* (% of live-births)	180 (67.4)	185 (67.3)	0.99 (0.69–1.42)	1.27 (0.84–1.93)	.26

[a] NEPS1 set as reference.

[b] *P* values adjusted for GA, except for birth rate/1000 births.

[c] Adjusted for GA.

[d] Twelve infants (11 with GA 22–24 and 1 with GA 26) were excluded from the denominator in NEPS1 due to unknown time of death. In NEPS2, all infants surviving to discharge were also alive at 1 y.

36% in NEPS2 ($P = .04$), and the proportion receiving surfactant in delivery room increased from 69% to 86% ($P = .001$). Among infants who died in the NICU, the median (interquartile range) age of death increased from 2 (8) days in NEPS1, to 8.5 (23) days in NEPS2. The proportion with severe BPD was increased in NEPS2 compared with NEPS1 (42% vs 28%, $P = .007$), but there were no differences in rates of severe CUS abnormalities, ROP, NEC, or mortality between the 2 cohorts.

Comparison Between European Countries in Perinatal Care and Outcomes in Recent Population-Based Studies

Figure 1 illustrates rates of stillbirths, NICU admissions, and survival among live-born infants and the proportion with severe neonatal morbidities among survivors in national cohorts from Norway, Sweden, England, and France.

The proportion of infants classified as stillborn increased with decreasing GA in all countries (Fig 1A). The stillbirth rate in NEPS2 was similar to Sweden and England, whereas France differed significantly with higher stillbirth rates among infants born at 22 to 24 weeks' GA. NICU admission rates among live-born infants were higher in Norway and Sweden compared with England and France, as was the survival of infants at 22 to 26 weeks (Fig 1 B and C). The Express study reported significantly higher survival at 23 weeks compared with Norway, 52% versus 29% ($P = .010$). Among

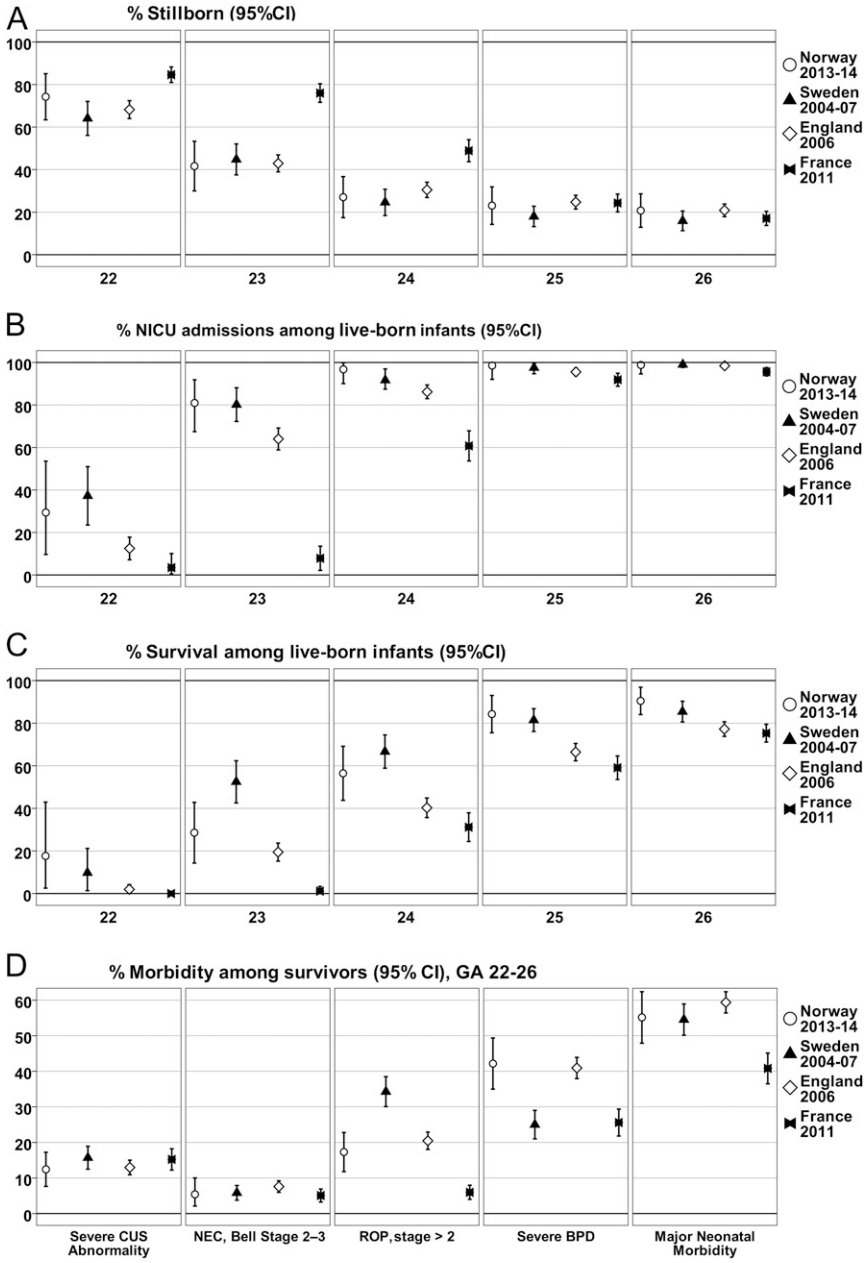

FIGURE 1
Comparison of recent European population-based studies in rates of stillbirth, NICU admissions, survival, and neonatal morbidity among infants born at 22 through 26 gestational weeks.

survivors, the reported rate of major neonatal morbidity was significantly lower in France, and rates of severe BPD were lower in France and Sweden, whereas severe ROP was more frequent in Sweden and less frequent in France compared with Norway. No significant differences were found regarding severe CUS abnormalities or verified NEC among survivors in these studies (Fig 1D).

DISCUSSION

In this study of a complete national cohort of extremely preterm infants born in 2013–2014, 91% of all live-born infants were admitted to the NICU. One-year survival was 67% among live-born infants and 74% among infants admitted to a NICU. Decreasing GA was strongly associated with mortality and moderately associated with major neonatal morbidity. However, no significant association was found between GA and the risk of severe CUS abnormalities among survivors, reflecting a lower threshold for withdrawing intensive care among the most immature infants when severe neurologic morbidity was diagnosed. The survival rate in our 2013–2014 cohort (NEPS2) was similar to the 1999–2000 cohort (NEPS1). In contrast, a recent report from the United States (National Institute of Child Health and Human Development Neonatal Research Network) documented significant increase in survival from 1993 to 2013 for infants born at 23 to 25 weeks.[21] Similarly, the Epicure 2 study reported improved survival compared with Epicure 1.[18] Despite improved survival, none of the mentioned studies reported reduced rates of major morbidity among surviving infants <26 weeks' gestation.

The total incidence of preterm deliveries at 22 through 26 gestational weeks in 2013–2014 in Norway was 3.5 per 1000 total births, similar to the Express study (3.3 per 1000 births), but lower than the Epipage 2 study (4.4 per 1000 births). Although the total preterm birth rate in Norway is low,[22] we observed a 14% increase in the incidence of extremely preterm births between 1999–2000 and 2013–2014. This finding was explained mainly by an increased rate of intrauterine death outside a hospital, whereas the rate of intrauterine death after admission to an obstetrical unit and the total number of live-born infants remained stable over the 15-year period. This study was not designed to investigate risk factors for fetal death outside a hospital, and unfortunately we do not have data to explore this in detail. Despite improvements in antenatal care, the rate of extremely preterm birth in Norway and in most comparable countries is not declining,[22] and preterm birth complications are the most common cause of childhood death in high income countries.[23]

This underlines the need for more studies addressing the epidemiology and causes of prematurity, to identify ways to prevent preterm birth, and disability and death related to prematurity.

The strengths of this study are the prospective collection of data on a daily basis with a standardized, electronic registration tool, and the inclusion of a complete national birth cohort of live births and stillbirths with a very high compliance to prenatal ultrasound dating of the pregnancy at 17 to 19 weeks. This allows us to explore the national practice in initiating or withholding care. It also makes it possible to compare our data with other population-based studies without risk of selection bias due to different denominators.[24] However, there is a risk of bias due to different protocols for ROP and CUS examinations and due to different pregnancy dating formulae in different countries.[25] One important limitation with our study is that the absolute numbers in each gestational week are small, increasing the risk of incidental fluctuations. Given the 2-year sample size, our study was underpowered to detect differences in survival <17% compared with the previous NEPS1 study.

The lower stillbirth rates and the higher rates of NICU admissions in the Nordic countries compared with England and France probably reflect a more proactive attitude toward offering care to the most immature infants. Furthermore, survival rates among live-born infants were significantly higher in Norway and Sweden, without higher rates of NEC or severe CUS abnormalities among survivors, compared with the other countries. The higher rates of severe BPD and major neonatal morbidity in the current study compared with Epipage 2 may partly be explained by the higher survival for the most immature infants.

Several recent publications have focused on how active care influences outcomes. The Express study reported reduced mortality with a more active use of perinatal intervention without increasing the risk of neurodevelopmental impairment at 2.5 years of age.[3,4] Similarly, a recent publication from the US National Institute of Child Health and Human Development Neonatal Research Network reported that the variation in hospital rates of active treatment at 22 and 23 weeks accounted for 78% of the between hospital variation in survival and 75% of the variation in survival without severe impairment.[2] The results from these studies need to be taken into account in prenatal parental counseling and decision-making. However, advances in the care of extremely preterm infants possibly increase the risk for prolonged exposure of potentially burdensome intensive treatment to the infants who eventually die in the NICU. In Norway, the median age of death among admitted infants increased from 2 days in NEPS1 to 8.5 days in NEPS2. Similar trends have been reported by others.[18,21] This is a fact that needs to be addressed when debating whether the best time for decision-making is before birth, in the delivery room, or later in the NICU. Certainly, there is a need for further observational studies because shift in care and outcomes over time will change the premises for what is in the best interest of each individual infant.

CONCLUSIONS

In this population-based Norwegian study of extremely preterm infants below 27 weeks' GA, the rate of stillbirth before admission to an obstetrical unit increased, whereas no significant improvement in survival among live-born infants was found in the 2013–2014 cohort compared with the 1999–2000 cohort. Only a few infants born at 22 weeks are offered active care in Norway, and decreasing GA was strongly associated with mortality. Among survivors, there was a moderate association between GA and the rate of major neonatal morbidity, but not with the rate of severe CUS abnormalities. This probably reflects a lower threshold for withdrawing intensive care among the most immature infants in the presence of severe neurologic complications.

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ABBREVIATIONS

BPD: bronchopulmonary dysplasia
CI: confidence interval
cPVL: cystic periventricular leukomalacia
CUS: cranial ultrasonogram
GA: gestational age
ICH: intracranial hemorrhage
LMP: last menstrual period
MBRN: Medical Birth Registry of Norway
NEC: necrotizing enterocolitis
NEPS: Norwegian Extreme Prematurity Study
NNN: Norwegian Neonatal Network
OR: odds ratio
ROP: retinopathy of prematurity

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