Intensity of Perinatal Care for Extremely Preterm Infants: Outcomes at 2.5 Years

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abstract

OBJECTIVE: To examine the association between intensity of perinatal care and outcome at 2.5 years' corrected age (CA) in extremely preterm (EPT) infants (<27 weeks) born in Sweden during 2004–2007.

METHODS: A national prospective study in 844 fetuses who were alive at the mother's admission for delivery: 707 were live born, 137 were stillborn. Infants were assigned a perinatal activity score on the basis of the intensity of care (rates of key perinatal interventions) in the infant's region of birth. Scores were calculated separately for each gestational week (gestational age [GA]–specific scores) and for the aggregated cohort (aggregated activity scores). Primary outcomes were 1-year mortality and death or neurodevelopmental disability (NDI) at 2.5 years' CA in fetuses who were alive at the mother's admission.

RESULTS: Each 5-point increment in GA-specific activity score reduced the stillbirth risk (adjusted odds ratio [aOR]: 0.90; 95% confidence interval [CI]: 0.83–0.97) and the 1-year mortality risk (aOR: 0.84; 95% CI: 0.78–0.91) in the primary population and the 1-year mortality risk in live-born infants (aOR: 0.86; 95% CI: 0.79–0.93). In health care regions with higher aggregated activity scores, the risk of death or NDI at 2.5 years' CA was reduced in the primary population (aOR: 0.69; 95% CI: 0.50–0.96) and in live-born infants (aOR: 0.68; 95% CI: 0.48–0.95). Risk reductions were confined to the 22- to 24-week group. There was no difference in NDI risk between survivors at 2.5 years' CA.

CONCLUSIONS: Proactive perinatal care decreased mortality without increasing the risk of NDI at 2.5 years' CA in EPT infants. A proactive approach based on optimistic expectations of a favorable outcome is justified.

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WHAT'S KNOWN ON THIS SUBJECT: Considerable differences in outcome after extremely preterm birth have been reported between centers and regions providing a comparative level of care, but the reasons for these variations have been poorly examined.

WHAT THIS STUDY ADDS: In extremely preterm fetuses alive at the mother's admission for delivery, and in infants born alive, mortality up to 2.5 years is reduced in regions with a more active use of perinatal interventions without increased neurodevelopmental morbidity.

Perinatal and neonatal mortality due to extremely preterm (EPT) birth has decreased significantly during the past decades.[1,2] This decrease in mortality can be attributed to advances in peri- and neonatal care, such as regionalization, antenatal steroids, monitoring during labor, improved ventilation techniques, surfactant administration, and a positive attitude to intervention by the perinatal team.[2–7] However, large variability in the intensity of perinatal care and outcome of EPT infants is reported between centers, regions, and countries providing comparative levels of care.[6,8–14]

Proactive care, conceptualized as a policy of providing a high intensity of care for all EPT births, including those occurring at the edge of viability,[6,15] may decrease the rate of stillbirth[15–17] and increase survival of infants born alive.[6,12–14] Even so, there are concerns that active life support for vulnerable infants may increase the proportion of disabled survivors.[18,19] The obstetrician's willingness to intervene on fetal behalf was associated with lower stillbirth rates and improved survival in infants weighing <1000 g but was also associated with major neonatal morbidity.[16] Approximately 25% of EPT infants born in the 1990s had a major neurodevelopmental disability at preschool age[20]; since then, decreasing,[21] unchanged,[22,23] or increasing[19,24,25] rates of neurodevelopmental impairment (NDI) have been reported. Few studies, however, have examined outcomes after explicitly proactive care,[6,15,26] and stillbirths are seldom included in outcome studies. There are concerns that intensive care is imposed on infants who ultimately die,[27] and the time to death for these infants has indeed increased.[2,27,28]

The EPT Infants in Sweden Study (EXPRESS study)[29] includes all infants born at a gestational age <27 weeks during 2004–2007 and reported increased 1-year survival compared with other published studies. Despite a generally proactive management strategy, subsequent analysis revealed differences in perinatal activity and in 1-year mortality between Swedish health care regions.[12] This descriptive study only evaluated outcome up to 1 year of age and did not analyze the association between intensity of care and outcome.

The primary aims of the current study were to evaluate whether the intensity of perinatal care is associated with 1-year mortality and whether regional variations in intensity of care are associated with death before follow-up assessment or NDI at 2.5 years' corrected age (CA) in EPT fetuses alive at the mother's admission for delivery. We hypothesized that (1) the intensity of perinatal care would be associated with a reduced risk of death up to 1 year and (2) that death or NDI at 2.5 years' CA would be reduced in health care regions with a higher intensity of perinatal care (high-activity regions) when compared with regions with lower intensity of care (low-activity regions). Secondary aims were to determine the associations between regional variations in perinatal care and outcomes in infants born alive.

METHODS

Participants

Between April 1, 2004, and March 31, 2007, research coordinators from each health care region collected perinatal and neonatal data on all 1011 infants born at 22+0 to 26+6 weeks' gestation, including stillbirths (the EXPRESS study[29]). Data on mothers and stillborn infants were collected at the time of delivery, and information on live-born infants was prospectively collected during the first 180 days of hospitalization, until discharge, or death. The follow-up evaluation at 2.5 years' CA included neurologic, hearing, vision, and developmental assessments.[23] The 844 fetuses alive at the mother's admission for delivery constituted the primary study population. Further details on the EXPRESS study design, survival, and neonatal morbidity rates up to 1 year[29,30] and outcome at 2.5 years[23] are published elsewhere. With the exception of minor variations in maternal age and fetal gender, there were no significant differences in maternal and fetal background characteristics between the 7 health care regions.[12]

Regional Activity Scores

The intervention rates vary widely across Swedish health care regions[12]; the rates for selected interventions are shown in Supplemental Fig 2. Obstetric and neonatal activity scores reflecting the intensity of care in each region were calculated on the basis of the rates of 4 key obstetric indicators (delivery at level III hospitals, complete course of antenatal steroids, cesarean delivery, tocolytic treatment) and 4 key neonatal indicators (surfactant within 2 hours after birth, delivery attended by a neonatologist, intubation immediately after birth, infants admitted for intensive care [out of infants alive at 30 minutes after birth]). The mean obstetric and neonatal activity scores comprised the perinatal activity score (henceforth, activity score). Each step included normalization by assigning the region with the highest rate for each indicator a score of 100; the remaining regions were assigned proportional scores. Region-specific activity scores were calculated for each gestational week (gestational age [GA]–specific activity scores), and each infant was assigned the GA- and region-specific activity score of the region of birth. These scores were used to evaluate the association between intensity of perinatal care and outcome. Region-specific activity scores were also calculated for the total 22- to 26-week cohort (aggregated activity scores), and these scores were used to contrast outcomes

in high-activity regions (combined) with low-activity regions (combined).

Definitions

The primary outcome was measured among fetuses alive at the mother's admission for delivery. This outcome included the association between (1) the intensity of perinatal care and death up to 1 year (as measured by the GA-specific activity scores) and (2) the composite outcome death before follow-up assessment or NDI at 2.5 years' CA in 3 high-activity regions (combined) compared with 4 low-activity regions (combined; as measured with the aggregated activity scores). Prespecified secondary outcomes included outcomes among infants born alive and survivors assessed at 2.5 years' CA. All outcomes included prespecified comparisons between higher and lower GA strata.

Obstetric definitions are listed in Supplemental Table 5. GA was estimated by using ultrasound before 20 postmenstrual weeks in 95% of the pregnancies: there were no differences between regions in the use of ultrasound dating; systematic regional differences in GA estimation are unlikely.[12] Intraventricular hemorrhage, cystic periventricular leucomalacia, and retinopathy of prematurity were defined according to international criteria.[33–35] Severe bronchopulmonary dysplasia was defined as the need for ≥30% oxygen at 36 weeks' GA. Major neonatal disability was defined as ≥1 intraventricular hemorrhage of grade 3 or higher, cystic periventricular leucomalacia, retinopathy of prematurity of stage 3 or higher, or severe bronchopulmonary dysplasia.

Neurodevelopmental outcome was assessed with the cognitive, language, and motor subscales of the *Bayley Scales of Infant and Toddler Development, Third Edition* (Bayley-III).[36] Because comparisons of normative scores (mean: 100; SD: 15) tend to underestimate disability rates,[37] the tests scores for the EPT group were related to the mean (SD) of a matched control group born at term. Cerebral palsy was defined according to Bax et al[38]; children who walked with an aid or were unable to walk were classified as being disabled. NDI was defined by ≥1 of disabling cerebral palsy; Bayley-III, cognitive, language, or motor score less than the mean – 2 SDs of controls; visual impairment (attending low-vision centers or bilateral blindness, as assessed by ophthalmologists); or deafness (need for amplification in both ears).

Statistical Analysis

Univariate and multivariate logistic regression was performed with activity score as a continuous variable. To improve readability, the activity score was rescaled so that 1 step represented a 5-point increase in activity score. Where specified, the aggregated activity score was used to create a binary variable where "1" represents the 3 regions with the highest activity scores (scores >90) for the aggregated 22- to 26- week GA cohort and "0" represents the remaining 4 regions (scores ≤90). Where specified, adjustments were made for GA (entered as a second-degree polynomial in analyses on the basis of ≥3 GA groups; otherwise entered as a continuous, linear variable), multiple birth (yes or no), infant gender (male or female), and birth weight SD score (entered as a continuous linear variable). Statistical analyses were performed by using Gauss (Aptech Systems, Maple Valley, WA). Age at death in high- and low-activity regions was compared with the Mann-Whitney test.

The Regional Research Ethics Board at Lund University, Sweden, approved the study. Parents were informed of the purposes of the study and consented to data acquisition.

RESULTS

Participants

The primary study population consisted of 844 fetuses who were alive at the mother's admission for delivery. Of those, 707 (84%) infants were born alive and 137 (16%) were stillborn. Four hundred ninety-seven infants (70%) survived to 1 year; and of these, 6 infants died between 1 year and the assessment at 2.5 years' CA. Parents of 5 children declined participation and 30 were not eligible for follow-up[23]; thus, 456 children including 41 children assessed by chart review were assessed at 2.5 years' CA (91% of children alive at 1 year).

Outcomes

GA-Specific Activity Score and Short-term Outcome

Regional variations in the GA-specific activity scores are shown in Table 1, and the effect on mortality risk for

TABLE 1 Intensity of Perinatal Care as Measured With GA-Specific and Aggregated Activity Scores in Swedish Health Care Regions

	Health Care Region						
	A	B	C	D	E	F	G
GA-specific activity scores							
At 22 weeks	40	97	52	56	62	39	100
At 23 weeks	72	100	58	88	85	95	82
At 24 weeks	71	95	86	100	77	83	100
At 25 weeks	78	87	86	100	83	81	97
At 26 weeks	84	94	81	99	80	90	100
Aggregated scores (22–26 weeks)							
Obstetric	74	93	87	100	88	82	99
Neonatal	72	98	69	96	75	78	100
Perinatal	74	96	78	98	82	80	100

The activity score is a regional measure of intensity of perinatal care. See Methods for definitions. Actual regional intervention rates are shown in Supplemental Fig 2.

each 5-point increment in the activity score is shown in Table 2. Among fetuses alive at the mother's admission for delivery, higher activity scores were associated with a reduced risk of stillbirth (adjusted odds ratio [aOR]: 0.90; 95% confidence interval [CI]: 0.83–0.97) and death before 1 year (aOR: 0.84; 95% CI: 0.78–0.91). Among infants born alive, higher scores were associated with a reduced risk of death within 12 hours (aOR: 0.79; 95% CI: 0.71–0.88) and 1 year (aOR: 0.86; 95% CI: 0.79–0.93). When analyzed by GA groups, the risk reductions were confined to the 22- to 24-week group. After exclusion of infants who died before 12 hours, no significant effect remained.

Aggregated Perinatal Activity Score and Outcome in High- and Low-Activity Regions

The aggregated activity scores were distinctly higher in 3 regions (range: 96–100; high-activity regions) than in the remaining 4 regions (range: 74–80; low-activity regions) (Table 1). Except for the rate of small for GA birth, baseline maternal and infant characteristics were similar in high- and low-activity regions (Table 3).

Outcome for Fetuses Alive at Mother's Admission for Delivery

Information on the primary composite outcome (death before 2.5 years' CA [stillbirth or postnatal death] or survival with NDI among fetuses alive at the mother's admission for delivery) was available for 358 of 376 (95%) children born in high-activity regions and for 451 of 468 (96%) children born in low-activity regions (Table 4). For the entire cohort, death or NDI was lower in high-activity regions (54%) than in low-activity regions (64%; aOR: 0.69; 95% CI: 0.50–0.96). Similarly, death before follow-up (stillbirth or postnatal death) was lower (35%) in high-activity regions than in low-activity regions (47%; aOR: 0.67; 95% CI: 0.48–0.93). When analyzed by GA groups, the risk reductions were confined to the 22- to 24-week group. Unadjusted stillbirth risk was reduced for fetuses delivered at 22 to 24 weeks (OR: 0.62; 95% CI: 0.39–0.99), but the adjusted risk was not significant.

Outcome for Infants Born Alive

Among infants born alive, the risk of death or NDI at 2.5 years' CA (aOR: 0.68; 95% CI: 0.48–0.95) was reduced in high- compared with low-activity regions (Table 4). When analyzed by GA groups, the risk reduction was confined to the 22- to 24-week GA group. Although the risk reduction for death within 12 hours in high-activity regions was marked, there were no intensity score–related differences in mortality in infants alive at 12 hours (Table 4). The risk of obtaining a 1- or 5-minute Apgar score ≤3 was reduced, and the risk of major neonatal morbidity in surviving infants was marginally lower in high-activity regions. Survival curves from birth to 2.5 years for live-born infants are presented in Fig 1. Among infants born at 22 to 24 weeks, the survival advantage in high-activity regions was established early and persisted to 2.5 years' CA.

Postnatal age at death was higher ($P < .001$) in high-activity regions (median: 64 hours) than in low-activity regions (median: 4 hours). There was no difference in age at death between high- and low-activity regions (median: 188 vs 181 hours) for infants who were alive at 12 hours and who died before 1 year.

Survivors Assessed at 2.5 Years' CA

Among children assessed at 2.5 years' CA, the rates of NDI were similar in both high-activity (27%) and low-activity (30%) regions, and after adjustment there were no intensity-related differences in NDI risk between high- and low-activity regions (Table 4).

TABLE 2 Change in Mortality Risk for Each 5-Point Step Increment in GA-Specific Activity Score

	n/N	Unadjusted		Adjusted[a]	
		OR	95% CI	OR	95% CI
Live fetus at mother's admission for delivery					
Stillbirth[b]					
22–26 weeks	137/844	0.79*	0.75–0.84*	0.90*	0.83–0.97*
22–24 weeks	108/404	0.86*	0.81–0.91*	0.90*	0.83–0.97*
25–26 weeks	29/440	0.78*	0.62–1.00*	0.84	0.65–1.10
Death before 1 year					
22–26 weeks	347/844	0.74*	0.69–0.78*	0.84*	0.78–0.91*
22–24 weeks	250/404	0.75*	0.70–0.81*	0.80*	0.73–0.88*
25–26 weeks	97/440	0.97	0.84–1.12	1.00	0.83–1.13
Infant born alive					
Death before 12 hours					
22–26 weeks	99/707	0.63*	0.58–0.69*	0.79*	0.71–0.88*
22–24 weeks	84/296	0.69*	0.63–0.76*	0.76*	0.68–0.86*
25–26 weeks	15/411	1.00	0.72–1.40	0.93	0.71–1.38
Death before 1 year					
22–26 weeks	210/707	0.76*	0.71–0.82*	0.86*	0.79–0.93*
22–24 weeks	142/296	0.78*	0.72–0.84*	0.83*	0.75–0.91*
25–26 weeks	68/411	0.98	0.83–1.16	0.97	0.82–1.16
Alive at 12 hours					
Death before 1 year					
22–26 weeks	117/608	0.92	0.83–1.02	0.93	0.83–1.03
22–24 weeks	60/212	0.93	0.83–1.04	0.93	0.82–1.05
25–26 weeks	57/396	0.98	0.81–1.17	0.96	0.79–1.16

The activity score is a regional measure of intensity of perinatal care. Each infant was assigned the GA-specific activity score valid for the infant's region of birth (see Methods). *Significant ($P < .05$). *n/N*, number of events/total number in group.

[a] Adjustments were made for multiple birth, infant gender, birth weight *z* score,[32] and GA (quadratic model for 22–24 weeks, linear model for 25–26 weeks).

[b] ORs based only on GA-specific obstetric activity scores.

TABLE 3 Characteristics of Pregnancies With Fetuses Alive at Mother's Admission for Delivery and of Infants Born Alive in 3 Health Care Regions With High Intensity of Perinatal Care (High-Activity Regions) Compared With 4 Health Care Regions With Low Intensity of Perinatal Care (Low-Activity Regions)

	Regional Activity Group					
	Alive at Admission			Live Births		
	High	Low	P^a	High	Low	P^a
Maternal characteristics						
Total number of pregnancies	328	418		283	341	
Non-Nordic origin[b]	—	—	—	53 (18.7)	71 (20.8)	.51
Maternal age, median (range), y	31 (16–46)	31 (14–45)	.30	31 (16–46)	31 (14–45)	.62
<20 years	14 (4.3)	12 (2.9)	.30	14 (5.0)	12 (3.5)	.37
≥35 years	96 (29.4)	120 (28.6)	.87	82 (29.1)	99 (28.9)	.99
Smoking[c]	47 (15.1)	44 (11.6)	.19	40 (14.8)	37 (11.9)	.30
Parity = 0	187 (57.0)	259 (62.0)	.17	164 (58.0)	212 (62.2)	.28
Parity = ≥3	22 (6.7)	22 (5.3)	.41	19 (6.7)	19 (5.6)	.55
Any pregnancy complication[d]	212 (64.6)	242 (57.9)	.06	179 (63.3)	189 (55.4)	.05
Fetal characteristics						
Total number of fetuses	376	468		325	382	
GA, median (range), wk	25.1 (21.9–26.9)	24.9 (21.4–26.9)	.15	25.3 (21.9–26.9)	25.1 (21.4–26.9)	.74
22 weeks	38 (10.1)	65 (13.9)	.10	18 (5.6)	33 (8.6)	.11
23 weeks	55 (14.7)	85 (18.1)	.17	43 (13.3)	58 (15.1)	.46
24 weeks	75 (20.0)	86 (18.3)	.56	71 (21.9)	73 (19.1)	.37
25 weeks	112 (29.9)	112 (23.9)	.06	103 (31.8)	101 (26.4)	.12
26 weeks	96 (25.5)	120 (25.6)	.97	90 (27.7)	117 (30.5)	.39
Birth weight, median (range), g	700 (160–1235)	700 (200–1500)	.74	727 (320–1235)	740 (266–1500)	.50
Male gender	216 (57.4)	246 (52.6)	.16	187 (57.5)	201 (52.6)	.19
Multiple pregnancy	92 (24.5)	97 (20.7)	.19	82 (25.3)	76 (19.8)	.09
Birth defects (weeded)	40 (10.4)	40 (8.7)	.30	38 (11.7)	39 (10.2)	.53
SGA	87 (22.9)	67 (14.5)	.001	67 (20.6)	47 (12.3)	.003

Data are presented as *n* (%) unless otherwise indicated. High-activity regions: aggregated activity scores, median of 98, range of 96–100. Low-activity regions: aggregated activity scores, median of 79, range of 74–82. SGA, small for gestational age.

[a] Differences between proportions were evaluated with χ^2 tests; differences between continuous variables were evaluated with Mann-Whitney *U* tests.

[b] Information available for live births only.

[c] Unknown in mothers of 61 out of 844 fetuses alive at mother's admission (7.2%).

[d] Pregnancy complication includes any of preterm prelabor rupture of membranes, abnormal antenatal cardiotocogram, suspected intrauterine growth retardation, iatrogenic preterm birth indicated by maternal disease, preeclampsia, eclampsia, essential hypertension, chorioamnionitis, placenta previa, placental abruption, polyhydramniosis, oligohydramniosis, diabetes mellitus, gestational diabetes.

DISCUSSION

In a national cohort of EPT births in Sweden, regional variations in the rate of perinatal interventions were reported.[12] In the current study, these differences were further analyzed and activity scores for each infant were calculated on the basis of the intensity of perinatal care in the infant's region of birth. The activity scores thus calculated predicted outcomes: among fetuses alive at the mother's admission, higher scores were associated with a reduced risk of stillbirth and of death before 1 year. When regions were grouped in 2 distinct categories according to intensity of perinatal care, the risk of the composite outcome death or survival with NDI at 2.5 years' CA was reduced in high-activity regions. The magnitude of the mortality difference between high- and low-activity regions was similar to, or larger than, the effect size of proven interventions, such as surfactant administration, antenatal corticosteroids, or centralization of perinatal care.[3–5]

Although most analyses of outcomes are based on individual patient characteristics, the aim of this study was to determine the effect of regional practices on outcome. It is noteworthy that there are no Swedish guidelines regarding the immediate management of EPT infants, but regional guidelines do exist. Perinatal activity scores were calculated for each health care region on the basis of the frequency of obstetric and neonatal interventions. Some interventions included in the scores (antenatal steroids,[3] surfactant replacement,[4] or delivery at a level III center[5]) are known to improve outcome, whereas other interventions (eg, cesarean delivery[39] and tocolysis[40]) may have more questionable effects. The score aimed to reflect overall willingness to intervene actively on behalf of the compromised fetus or infant, not to evaluate the effect of individual interventions. Because the effect of differences in perinatal interventions was studied, outcomes were adjusted only for biological patient characteristics and parental socioeconomic factors. We did not adjust for infant illness severity, because this would have eliminated possible differences in obstetric and early management.

TABLE 4 Risk of Adverse Outcome at 2.5 Years' CA in 3 Health Care Regions With High Intensity of Perinatal Care (High-Activity regions) Compared With 4 Health Care Regions With Low Intensity of Perinatal Care (Low-Activity Regions)

Outcome	Regional Activity Group							
	High		Low		Unadjusted		Adjusted[a]	
	n/N	%	*n/N*	%	OR	95% CI	OR	95% CI
Alive at mother's admission for delivery (*n* = 844)								
Primary composite outcome death or NDI[a,b] at 2.5 years' CA								
22–26 weeks	194/358	54.2	289/451	64.1	0.66*	0.50–0.88*	0.69*	0.50–0.96*
22–24 weeks	112/158	70.9	199/232	85.8	0.40*	0.24–0.67*	0.44*	0.25–0.77*
25–26 weeks	82/200	41.0	90/219	41.2	1.00	0.68–1.47	0.91	0.61–1.36
Stillbirth								
22–26 weeks	51/376	13.6	86/468	18.4	0.70	0.48–1.02	0.95	0.62–1.46
22–24 weeks	36/168	21.4	72/236	30.5	0.62*	0.39–0.99*	0.79	0.47–1.33
25–26 weeks	15/208	7.2	14/232	6.0	1.21	0.57–2.57	1.46	0.65–3.26
Death before 2.5 years' CA								
22–26 weeks	133/376	35.4	220/468	47.0	0.62*	0.47–0.82*	0.67*	0.48–0.93*
22–24 weeks	84/168	50.0	168/236	71.2	0.40*	0.27–0.62*	0.41*	0.26–0.66*
25–26 weeks	49/208	23.6	52/232	22.4	1.07	0.69–1.66	1.04	0.66–1.65
Born alive (*n* = 707)								
Composite death or NDI at 2.5 years' CA								
22–26 weeks	143/307	46.6	203/365	55.6	0.70*	0.51–0.94*	0.68*	0.48–0.95*
22–24 weeks	76/122	62.3	127/160	79.3	0.43*	0.25–0.73*	0.48*	0.27–0.84*
25–26 weeks	67/185	36.2	76/205	37.1	0.96	0.64–1.46	0.80	0.52–1.23
Death before 2.5 years' CA								
22–26 weeks	82/325	25.2	134/382	35.0	0.62*	0.45–0.87*	0.63*	0.44–0.91*
22–24 weeks	48/132	36.3	96/164	58.5	0.40*	0.25–0.65*	0.43*	0.26–0.73*
25–26 weeks	34/193	17.6	38 /218	17.4	1.01	0.61–1.69	0.91	0.54–1.54
Death before 365 days								
22–26 weeks	79/325	24.3	131/382	34.3	0.62*	0.44–0.86*	0.62*	0.43–0.91*
22–24 weeks	46/132	34.8	96/164	58.5	0.38*	0.24–0.61*	0.40*	0.24–0.68*
25–26 weeks	33/193	17.2	35/218	16.0	1.08	0.64–1.82	0.99	0.58–1.69
Death before 12 hours								
22–26 weeks	23/325	7.1	76/382	19.9	0.31*	0.19–0.50*	0.27*	0.15–0.49*
22–24 weeks	16/132	12.1	68/164	41.5	0.19*	0.11–0.36*	0.17*	0.08–0.35*
25–26 weeks	7/193	3.6	8/218	3.7	0.99	0.35–2.78	0.86	0.29–2.53
Apgar score ≤3 at 1 minute								
22–26 weeks	84/325	25.8	160/382	41.9	0.48*	0.35–0.67*	0.48*	0.34–0.68*
22–24 weeks	44/132	33.3	107/164	65.2	0.27*	0.16–0.43*	0.29*	0.18–0.47*
25–26 weeks	40/193	20.7	53/218	24.3	0.81	0.51–1.30	0.80	0.50–1.30
Apgar score ≤3 at 5 minutes								
22–26 weeks	42/325	12.9	87/382	22.7	0.50*	0.34–0.75*	0.54*	0.24–0.85*
22–24 weeks	21/132	15.9	76/164	46.3	0.22*	0.13–0.38*	0.23*	0.12–0.42*
25–26 weeks	21/193	10.9	11/218	5.0	2.30*	1.08–4.90*	2.22*	1.03–4.80*
Alive at 12 hours (*n* = 608)								
Death before 2.5 years								
22–26 weeks	59/302	19.5	58/306	19.0	1.04	0.69–1.55	0.84	0.55–1.28
22–24 weeks	32/116	27.6	28/96	29.2	0.92	0.51–1.68	0.82	0.44–1.55
25–26 weeks	27/186	14.5	30/210	14.3	1.02	0.58–1.78	0.90	0.50–1.60
Alive at 365 days (*n* = 497)								
Major neonatal morbidity[c]								
22–26 weeks	132/246	53.7	139/251	55.4	0.93	0.66–1.33	0.70	0.48–1.04
22–24 weeks	60/86	69.8	54/68	79.4	0.60	0.28–1.26	0.57	0.27–1.22
25–26 weeks	72/160	45.0	85/183	46.4	0.94	0.62–1.44	0.74	0.46–1.16
Survivors at 2.5 years' CA (*n* = 456)								
Any NDI								
22–26 weeks	61/225	27.1	69/231	29.9	0.87	0.58–1.31	0.80	0.52–1.22
22–24 weeks	28/74	37.8	31/64	48.4	0.65	0.33–1.28	0.63	0.31–1.28
22–25 weeks	33/151	21.9	38/167	22.8	0.95	0.56–1.61	0.92	0.53–1.57

Aggregated activity scores, High Activity Regions: median of 98, range of 96–100. Aggregated activity scores:, Low Activity Regions median of 79, range of 74–82. CA, corrected age. *Significant ($P < .05$).

[a] The outcome death or NDI was adjusted for GA (weeks) and (weeks^2), multiple birth (yes/no) gender, SD for birth weight,[32] maternal education, paternal education, and ethnicity (non-Nordic, yes/no). The outcomes stillbirth, death, Apgar scores ≤3 at 1 minute, Apgar scores ≤3 at 5 minutes, and the outcome major neonatal morbidity were adjusted for GA (weeks) and (weeks^2), multiple birth (yes/no) gender, and SD for birth weight. The outcome any NDI was adjusted for GA, maternal education, paternal education, and ethnicity (non-Nordic, yes/no).

[b] NDI was defined as ≥1 of the following: cerebral palsy, deafness, visual impairment, and Bayley-III score[36] < −2 SDs in any scale compared with controls, including children assessed by chart review (*n* = 41) (see Methods).

[c] Only in infants surviving to 1 year. This category includes retinopathy of prematurity stage ≥3, intraventricular hemorrhage grade ≥3, cystic periventricular leucomalacia, and severe bronchopulmonary dysplasia (ie, the need for ≥30% oxygen at 36 weeks' CA).

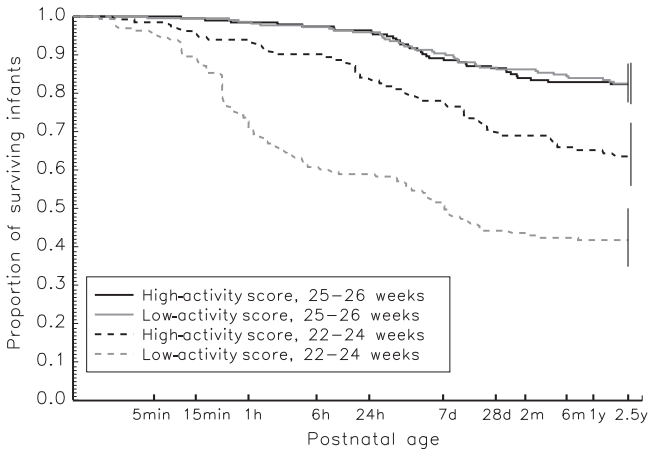

FIGURE 1

Survival curves from birth to 2.5 years' CA for infants born alive in high- and low-activity regions by GA group. Error bars are 95% Kaplan-Meyer estimates.

Neonatal intensive care admissions are often used as the denominator population, ignoring perinatal and delivery room polices and care. Others have proposed that fetuses alive at the onset of labor[41] should be the denominator, but this ignores antepartum deaths that may be related to perinatal practices, such as in utero referral and fetal monitoring.[11] In this study, outcome was considered as a continuum, including both obstetric and neonatal care and the time point "mother's admission with a live fetus" was chosen as the denominator for the primary outcome. To enable comparisons with studies reporting outcomes of infants born alive, outcomes for live births are also presented.

In the unadjusted, but not in the adjusted, risk analysis, the risk of stillbirth at 22 to 24 weeks was lower in high-activity regions than in low-activity regions. However, active obstetric care may improve neonatal survival: according to the "better infant concept," one-third of the decline in neonatal mortality over time in infants with birth weights <1500 g can be attributed to improved obstetric care.[42] In our study, birth in high-activity regions was associated with a reduced risk of being born in poor condition, as measured by the Apgar scores; low Apgar scores indicate a more pronounced fetal compromise and are associated with poor outcome.[29,43]

When analyzed by GA groups, all risk reductions were confined to the 22- to 24-week GA group. Among infants born alive at 22 to 24 weeks, the 1-year mortality rate was 35% in high-activity regions and 59% in low-activity regions. Both rates were lower than the rate reported in comparable studies.[2,14] The differences in mortality risks between high- and low-activity regions were nullified when early deaths (<12 hours) were excluded, indicating that differences in mortality rates are predominantly due to different practices for delivery and management immediately after birth. Despite the increased survival in high-activity regions, the rate of major neonatal morbidity did not increase. As reported in a previous publication,[23] the rate of NDI at 2.5 years' CA was similar or better than in studies reporting lower survival rates.

As reported in other studies,[2,27,28] better survival was associated with increased age at death. Although some infants died later in high-activity regions, in most cases the increased age at death (median: 2.5 days) allowed for a trial of life. In contrast, the early age of death in low-activity regions (median: 4 hours) did not allow for further assessments beyond the delivery room assessment for most infants.

Associations between intensity of care and survival have been reported by others.[6,7,10,11,14–17] Håkansson et al[6] found higher survival for infants born at 22 to 25 weeks in health care regions with proactive care than for infants in regions with a restrictive attitude. The Models of Organizing Access to Intensive Care for Very Preterm Babies in Europe (MOSAIC) study[11] calculated a composite obstetric score on the basis of antenatal corticosteroids, antenatal transfer, and cesarean delivery: this composite score varied between European regions and a higher score was associated with lower stillbirth rate and in-hospital mortality of live-born infants delivered at 24 to 25 weeks. A recent National Institute of Child Health and Human Development study[14] examined associations of center-specific neonatal intervention scores on the basis of selected neonatal interventions with mortality before discharge: the intervention score predicted overall mortality and early mortality (<12 hours), especially for infants born at <25 weeks' GA.

Compared with other studies relating intensity of care to outcome, the scope of this study was wider because all births before 27 gestational weeks in Sweden were enrolled prospectively, including intrapartum stillbirths, and the outcome was examined at several time points, including follow-up at 2.5 years' CA. In contrast to most studies, the focus was on region-specific differences in management rather than on outcome based on individual patient characteristics. The follow-up rate at 2.5 years' CA was high and included region-specific controls born at term. Finally, the rather homogenous characteristics of the Swedish population reduce the influence of nonmedical factors on outcomes and facilitate interpretation of results. A potential weakness of this study was that the proxy used (ie, the frequency of selected perinatal

interventions) may miss some aspects of perinatal care. Whereas intubation and surfactant administration at birth may not always be necessary, most infants born at 22 to 24 weeks need these interventions.[44] Another potential limitation is the early age at follow-up, because more subtle dysfunctions are likely to appear later in life.[45]

The EXPRESS study did not explore parents' opinions regarding management at birth. According to Swedish law, obstetric intervention (eg, operative delivery) can be performed only after oral consent. For the treatment of neonates, no formal consent is required. Decisions regarding care are discussed with parents, and disagreements between parents and the professional staff are extremely rare. It is likely, however, that the parents' ultimate wishes are greatly influenced by the attitudes of the caregivers

In conclusion, in infants born at 22 to 26 weeks of gestation, increased intensity of perinatal care reduced 1-year mortality in fetuses alive at the mother's admission for delivery, and death or survival with NDI at 2.5 years' CA. was reduced in health care regions with higher intensity compared with regions with lower intensity of perinatal care. Increased survival was not associated with increased neonatal morbidity or rate of NDI. These findings, combined with the knowledge that survival cannot be predicted by initial appearance at birth,[46] support a proactive approach to perinatal management of the EPT infant.

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