One-year survival and outcomes of infants born at 22 and 23 weeks of gestation in Sweden 2004–2007, 2014–2016 and 2017–2019

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ABSTRACT

Objective To explore associations between perinatal activity and survival in infants born at 22 and 23 weeks of gestation in Sweden.

Design/Setting Data on all births at 22 and 23 weeks' gestational age (GA) were prospectively collected in 2004–2007 (T1) or obtained from national registers in 2014–2016 (T2) and 2017–2019 (T3). Infants were assigned perinatal activity scores based on 3 key obstetric and 4 neonatal interventions.

Main outcome One-year survival and survival without major neonatal morbidities (MNM): intraventricular haemorrhage grade 3–4, cystic periventricular leucomalacia, surgical necrotising enterocolitis, retinopathy of prematurity stage 3–5 or severe bronchopulmonary dysplasia. The association of GA-specific perinatal activity score and 1-year survival was also determined.

Results 977 infants (567 live births and 410 stillbirths) were included: 323 born in T1, 347 in T2 and 307 in T3. Among live-born infants, survival at 22 weeks was 5/49 (10%) in T1 and rose significantly to 29/74 (39%) in T2 and 31/80 (39%) in T3. Survival was not significantly different between epochs at 23 weeks (53%, 61% and 67%). Among survivors, the proportions without MNM in T1, T2 and T3 were 20%, 17% and 19% for 22 weeks and 17%, 25% and 25% for 23 weeks' infants (p>0.05 for all comparisons). Each 5-point increment in GA-specific perinatal activity score increased the odds for survival in first 12 hours of life (adjusted OR (aOR) 1.4; 95% CI 1.3 to 1.6) in addition to 1-year survival (aOR 1.2; 95% CI 1.1 to 1.3), and among live-born infants it was associated with increased survival without MNM (aOR 1.3; 95% CI 1.1 to 1.4).

Conclusion Increased perinatal activity was associated with reduced mortality and increased chances of survival without MNM in infants born at 22 and 23 weeks of GA.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Mortality and neonatal morbidity are high in extremely preterm births at 22 and 23 weeks' gestation.

⇒ Because of anticipated poor prognosis, active life-support of these infants at birth has been questioned.

WHAT THIS STUDY ADDS

⇒ Active obstetric and neonatal care of births at 22–23 weeks' gestation has been associated with decreased stillbirths, decreased delivery room deaths, increased admission rates for neonatal intensive care and increased 1-year survival.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Increased perinatal activity in births at 22–23 weeks' gestation was associated with increased survival without increase in major neonatal morbidity.

INTRODUCTION

More extremely preterm (EPT) infants have survived the past two decades. However, there has been substantial variations in practices for infants born at 22 and at 23 weeks of gestation within and between countries,[1–4] despite that these infants nowadays can achieve survival rates of 25%–50%.[3–8]

The first national consensus guidelines on perinatal management of EPT infants in Sweden were published in 2016 by the Swedish Society of Perinatal Medicine. These provided recommendations on centralisation,[9] antenatal corticosteroid treatment, mode of delivery, neonatologists attendance and cardiopulmonary resuscitation (CPR) of infants born at 22–24 weeks of gestational age (GA).[9] They suggested centralisation for all deliveries at 22–24 weeks, that a neonatologist should be present at births from $22^{0\ days}$ weeks and that antenatal corticosteroids and neonatal CPR could be considered from $22^{0\ days}$ weeks. At $23^{0\ days}$ weeks of GA, antenatal corticosteroids and CPR were recommended, and caesarean section for fetal distress could be considered. It is unclear if these guidelines changed perinatal care or if they only served as confirmation of changes in attitudes and practices that had already taken place.

We hypothesised that perinatal practice in Sweden has changed to a more uniform provision of active care for babies born at 22 and 23 weeks of

GA, and that this would be associated with an increased overall 1-year survival and survival without major neonatal morbidities (MNM). The primary aim of this study was to evaluate survival rates without MNM of infants born at 22 and 23 weeks' GA in relation to obstetric and early neonatal care intensity before, during the development of guidelines and after implementing the national guidelines.

METHODS

Participants and data collection

Data were collected on all births at 22 or 23 weeks of GA during 2004–2007 (T1), 2014–2016 (T2) and 2017–2019 (T3). Infants born in T1 were part of the Extremely Preterm Infants in Sweden Study (EXPRESS) that included all infants born from $22^{0\ days}$ to $26^{6\ days}$ weeks between April 2004 and March 2007.[10] During T2 and T3, all data were collected from national registers. In T2, the infants were part of a national investigation of infants born at 22–26 weeks of GA from January 2014 to December 2016.[11] In T2 and T3, the same inclusion and exclusion criteria as in the EXPRESS study were used.[10] Infants with congenital malformation including chromosomal anomalies were not excluded. Dislocation of the hip (Q65.0–Q65.5), preauricular tags (Q17.0), undescended testes (Q53.0–Q53.9), and patent ductus arteriosus coded as a malformation (Q25.0) were not classified as anomalies.

In T1, all data were prospectively collected.[10] Information on stillbirths in T2 and T3 were extracted from the Swedish Medical Birth Register.[12] There was no information on when the stillbirths had occurred. Data on live births in T2 and T3 were collected from the Swedish Neonatal Quality Register (SNQ).[13] SNQ data for MNM in T2 were retrospectively validated against the infants' medical records.[11] In T3, SNQ data were collected

Table 1 Mother-infant characteristics and obstetric and neonatal care management among live-born infants delivered at 22 and 23 weeks of gestational age in Sweden during 2004–2007, 2014–2016 and 2017–2019

	22 weeks			23 weeks		
	T1 2004–2007*	T2 2014–2016	T3 2017–2019	T1 2004–2007*	T2 2014–2016	T3 2017–2019
Pregnancy complications						
Placental abruption/vaginal bleeding	3/49 (6)	16/74 (22)	19/80 (24)†	11/101 (11)	30/148 (20)	30/115 (26)†
Chorioamnionitis	9/49 (20)	11/74 (15)	10/80 (13)	11/101 (11)	23/148 (16)	12/103 (12)
Pre-eclampsia	2/47 (4)	0	2/80 (3)	4/100 (4)	6/147 (4)	6/114 (5)
PPROM	9/49 (20)	15/74 (20)	12/80 (15)	22/101 (22)	31/148 (26)	22/115 (19)
Multiple birth	10/49 (20)	20/74 (27)	16/80 (20)	8/101 (8)	33/148 (22)	23/115 (20)
Infant characteristics						
Male	27/49 (55)	39/74 (53)	41/80 (51)	55/101 (55)	82/148 (55)	59/115 (51)
Female	22/49 (45)	35/74 (47)	39/80 (49)	46/101 (46)	66/148 (45)	56/115 (49)
Birth weight, median (min–max), g	498 (280–730)	489 (345–670)	485 (322–648)	590 (320–808)	592 (300–1615)	565 (366–777)
Birth weight, median (min–max), Z-score	−0.26 (−3,2, 3.9)	−0.51 (−4.0, 3.0)	−0.48 (−3.0, 2.0)	−0.42 (−3.8, 3.1)	−0.44 (−4.7, 15.77)	−0.67 (−3.4, 2.15)
SGA	4/49 (8)	8/74 (11)	6/80 (8)	7/100 (7)	16/148 (11)	10/115 (9)
Apgar score						
1 min Apgar score ≤3	35/49 (71)	49/73 (67)	47/73 (64)	53/101 (53)	77/145 (53)	57/108 (53)
5 min Apgar score ≤3	36/49 (74)	31/74 (42)†	31/80 (39)†	31/101 (31)	40/148 (27)	32/115 (28)
10 min Apgar score ≤3	na	24/71 (34)	23/73 (32)	na	24/146 (16)	13/107 (12)
Apgar score in survivors						
1 min Apgar score ≤3	1/5 (20)	18/29 (62)	14/31 (45)	13/53 (25)	44/91 (48)†	30/77 (40)
5 min Apgar score ≤3	0	8/29 (28)	7/31 (23)	2/53 (4)	20/91 (22)†	13/77 (17)†
10 min Apgar score ≤3	na	2/28 (7)	4/29 (14)	na	8/90 (9)	4/71 (6)
Obstetric care management						
Any antenatal corticosteroids‡	20/49 (41)	47/74 (64) †	56/80 (70) †	85/101 (84)	132/148 (89)	103/115 (90)
Received two doses of ANCS	5/49 (10)	22/74 (30)	28/80 (35)	54/99 (55)	89/148 (60)	62/115 (54)
Caesarean delivery	3/49 (6)	4/74 (5)	9/80 (11)	17/101 (17)	50/148 (34)†	25/115 (22)
Born at level III hospital	22/49 (45)	66/74 (89)†	68/80 (85)†	79/101 (78)	127/148 (86)	99/115 (86)
Born at level I–II hospital	27/49 (53)	8/74 (11)†	12/80 (15)†	22/101 (22)	20/148 (14)	16/115 (14)
Neonatal care management						
Admitted to NICU (all live-born infants)	19/49 (39)	50/74 (68)†	67/80 (84)†	81/101 (80)	138/148 (93)†	110/115 (96)†
Transport of infant to level III NICU from level I–II	6/27 (22)	7/8 (88)†	9/12 (75)†	13/22 (59)	16/21 (76)	15/16 (94)†
Neonatologist present a birth	24/49 (47)	66/74 (89)†	65/80 (81)†	82/101 (81)	132/148 (89)	94/115 (82)
Intubated at birth	13/49 (27)	52/74 (70)†	58/80 (73)†	68/101 (67)	129/148 (87)†	95/115 (83)†
Surfactant <2 hours	11/49 (22)	44/74 (59)†	50/80 (63)†	62/93 (67)	121/148 (82)†	79/115 (69)
Congenital malformations	0	2/74 (3)	6/80 (8)	9/101 (9)	20/148 (14)	18/115 (16)

Data are presented as numbers (%) unless stated otherwise.
*Data are from Fellman *et al*.[10]
†P<0.01 for pairwise adjusted comparisons with the T1 (2004–2007).
‡Any receipt of antenatal glucocorticoids was defined as one or two doses of betamethasone (12 or 24 hours apart).
ANCS, antenatal corticosteroids; na, not available; NICU, neonatal intensive care unit; PPROM, preterm prelabour rupture of membranes; SGA, small for gestational age.

Table 2 One-year survival of infants delivered at 22 and at 23 weeks of gestation during 2004–2007, 2014–2016 and 2017–2019

	22 weeks			23 weeks		
	T1 2004–2007*	T2 2014–2016	T3 2017–2019	T1 2004–2007*	T2 2014–2016	T3 2017–2019
Total number	140	134	125	183	213	182
Stillbirths†	91 (65)	60 (45)‡	45 (36)‡	82 (45)	65 (31)‡	67 (37)
Live-born infants	49 (35)	74 (55)‡	80 (64)‡	101 (55)	148 (69)‡	115 (63)
Died before 1 year, total	44/49 (90)	45/74 (61)‡	49/80 (61)‡	48/101 (48)	57/148 (39)	38/115 (33)
≤12 hours§	37/49 (76)	27/74 (37)¶	23/80 (29)¶	27/101 (27)	15/148 (10)‡	10/115 (9)‡
13 hours to 7 days	2/49 (4)	5/74 (7)	11 (14)	12/101 (12)	12/148 (8)	7/115 (6)
8–27 days	4/49 (8)	11/74 (15)	9 (11)	7/101 (7)	16/148 (11)	12/115 (10)
28 days to 1 year	1/49 (2)	2/74 (4)	6 (8)	2/101 (2)	14/148 (9)	9/115 (8)
One-year survival						
All births**	5/140 (4)	29/134 (22)‡	31/125 (25)‡	53/183 (29)	91/213 (43)‡	77/182 (42)‡
Live-born infants	5/49 (10)	29/74 (39)‡	31/80 (39)‡	53/101 (53)	91/148 (61)	77/115 (67)
NICU admissions	5/19 (26)	29/50 (58)	31/67 (46)	53/81 (65)	91/138 (66)	77/110 (70)
One-year survival without major neonatal morbidity††						
Live-born infants	1/49 (2)	5/74 (7)	6/74 (8)	9/101 (9)	23/148 (16)	19/115 (17)
Infants admitted to NICU	1/19 (5)	5/50 (10)	6/67 (9)	9/81 (11)	23/138 (17)	19//110 (17)
Of survivors at 1 year	1/5 (20)	5/29 (17)	6/31 (19)	9/53 (17)	23/91 (25)	19/76 (25)

Data are presented as n (%) unless otherwise indicated.

*Data are from Fellman *et al*.[10]
†Stillbirths in T2 and T3 were identified from the Swedish Medical Birth Registry.[12]
‡P<0.01 for pairwise adjusted comparisons with the T1 (2004–2007).
§Difference in time categories of mortality were examined with adjusted multiple comparisons by χ^2 test with post hoc analysis (Bonferroni correction).
¶P<0.001 for pairwise adjusted comparisons with the T1 (2004–2007).
**Includes stillbirths.
††Major neonatal morbidity defined as intraventricular haemorrhage grade 3 or 4, cystic periventricular leucomalacia, surgically treated necrotising enterocolitis, retinopathy of prematurity stage 3, 4 or 5 or severe bronchopulmonary dysplasia (treatment with ≥30% oxygen at 36 weeks+0 days of postmenstrual age).
NICU, neonatal intensive care unit.

electronically on a daily basis after validation against medical records. The overall completeness of the SNQ has been judged to be excellent for preterm infants.[13]

Perinatal definitions

GA was determined by early ultrasound examinations during the second trimester in >95% of the subjects. Maternal characteristics included pre-eclampsia, preterm prelabour rupture of membranes (PPROM), abruptio placentae, chorioamnionitis, multiple pregnancies, type 1 and gestational diabetes. There was no available information on type 2 diabetes in pregnancy in the data sources. Information on the infants comprised Apgar scores <4 at 1 and 5 min after birth, birth weight, sex and being small for GA (SGA; defined as a birth weight <−2 SD below the expected weight according to normal fetal growth)[14] (online supplemental etable 1).

Table 3 Neonatal morbidities among 1-year infant survivors delivered at 22 and 23 weeks of gestation in 2004–2007, 2014–2016 and 2017–2019

	22 weeks			23 weeks		
	T1 2004–2007*	T2 2014–2016	T3 2017–2019	T1 2004–2007*	T2 2014–2016	T3 2017–2019
Intraventricular haemorrhage, grade 3 or 4	1/5 (20)	4/29 (14)	3/31 (10)	10/52 (19)	11/89 (12)	14/77 (18)
ROP, stage 3–5	4/5 (80)	21/29 (72)	17/31 (55)	34/53 (64)	53/91 (58)	44/77 (58)
ROP, laser-treated	4/5 (80)	13/28 (46)	15/31 (48)	23/53 (43)	30/91 (33)	26/77 (34)
Cystic periventricular leucomalacia	0	0	0	5/53 (9.4)	1/91 (1)	3/77 (4)
Late-onset sepsis	3/5 (60)	16/29 (55)	19/31 (61)	41/53 (72)	39/91 (43)	41/77 (54)
Surgical NEC	0	2/29 (7)	1/31 (7)	1/52 (2)	8/91 (9)	7/77 (5)
Bronchopulmonary dysplasia (severe)†	2/5 (40)	10/29 (35)	9/31 (29)	12/53 (23)	21/91 (23)	17/77 (22)
Postnatal steroids for lung disease	3/5 (60)	17/29 (59)	20/31 (65)	31/52 (60)	52/91 (57)	47/77 (61)
Days of mechanical ventilation, median (range), days	42 (17–96)	45 (16–126)	46 (22–202)	24 (1–134)	32 (6–378)	34 (0–295)
Length of stay in neonatal care, median (min–max), days‡§	138 (136–186)	154 (92–302)	129 (82–423)	133 (98–258)	135 (78–378)	113 (58–378)¶

Data are presented as n (%) unless otherwise indicated.
*Data are from Fellman *et al*.[10]
†Severe bronchopulmonary dysplasia, defined as treatment with ≥30% oxygen at 36 weeks+0 days of postmenstrual age.
‡Length of stay in neonatal care before discharge home.
§Data for full length of stay are missing on few infants (22 weeks, T2, n=2; 23 weeks, T3, n=1). These infants were transferred to other units for long-term intensive care (infants with long-term need of invasive respiratory care-tracheotomised infants). SNQ register lacked information on length of stay until discharge home on these infants.
¶P<0.001 for pairwise adjusted comparisons with the T2 (2014–2016).
NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; ROP, retinopathy of prematurity; SNQ, Swedish Neonatal Quality Register.

Table 4 Intensity of perinatal care, measured with GA-specific perinatal activity scores in Swedish healthcare regions for live-born infants

	Perinatal activity scores* (normalised mean scores) Healthcare regions					
	A	B	C	D	E	F
22 weeks of gestation						
T1 (2004–2007)/n=49	40	42	18	61	62	32
T2 (2014–2016)/n=74	51	66	44	93	85	53
T3 (2017–2019)/n=80	58	60	56	91	81	59
All time periods (22 weeks), PA scores, mean national average (min–max)/ n=203	61 (18–93)					
23 weeks of gestation						
T1 (2004–2007)/n=101	67	85	66	79	92	53
T2 (2014–2016)/n=148	77	94	92	96	95	82
T3 (2017–2019)/n=115	85	90	82	92	82	69
All time periods (23 weeks), PA scores, mean national average (min–max)/ n=364	84 (53–96)					

Among the live-born infants at 22 weeks of gestation, regions with scores above national average had a mean score of 81 (range 61–93) and regions with scores below the national average had a mean score of 45 (range 18–60). With regard to live-born infants at 23 weeks, regions with scores above the national average had a mean score of 91 (range 84–96) and regions with scores below national average had a mean score of 73 (range 53–82).
*The perinatal activity score is a regional measure of intensity of perinatal care in the six healthcare regions. See 'Methods' section for definitions. Actual regional intervention rates in T1, T2 and T3 are shown in online supplemental efigure 1.
GA, gestational age.

Outcomes

The primary outcome was survival until 1 year of age without MNM. MNM were defined as intraventricular haemorrhage grade 3–4 (IVH 3–4),[15] cystic periventricular leucomalacia,[16] surgical necrotising enterocolitis (NEC),[17] retinopathy of prematurity stage ≥3 (ROP)[18] or severe bronchopulmonary dysplasia (BPD) with ≥30% inspired oxygen at $36^{0\ days}$ weeks of postmenstrual age.

Perinatal activity scores for Swedish healthcare regions

There are six greater healthcare regions in Sweden, each typically served by one- or two-level III–IV perinatal centres. We calculated each region's obstetric and neonatal activity scores to demonstrate the intensity of care provided at 22 and 23 weeks' GA during each study period. The scores were based on three key indicators of active obstetric care (delivery at level III–IV hospitals, any antenatal corticosteroids and caesarean delivery), and four key indicators of active neonatal care (intubation at birth, surfactant administration <2 hours of birth, delivery attended by a neonatologist and admission to a neonatal intensive care unit (NICU) of infants alive at 30 min of life). The perinatal activity scores comprised the mean obstetric and neonatal activity scores and were determined as previously described[19] and are explained in online supplemental efigure 1).

Statistical analyses

Descriptive statistics, such as percentages, means, medians and range values, were stratified by GA in weeks and time periods. Maternal and neonatal characteristics and 1-year outcomes between the three periods were compared using the χ^2 and Kruskal-Wallis tests. Pairwise comparisons between T1, T2 and T3 were performed using post hoc subgroup analyses for χ^2 test or analysis of variance. Pairwise comparisons over time relate to T1 versus T2 or T3, and GA comparisons relate to 22 vs 23 weeks. Adjusted p values indicate pairwise comparisons across three time periods. In the post hoc analyses, Bonferroni-adjusted p values <0.017 were considered significant, and p<0.05 was significant for all other analyses. Multivariable logistic regression analyses examined associations between GA-specific perinatal activity scores using 5-point increments and mortality at different time points, overall 1-year survival and survival without MNM. We also examined the associations between the individual key obstetric and neonatal interventions included in the perinatal activity score and 1-year survival. All the logistic regression models were adjusted for potential effect modifiers such as GA, birth weight, SGA, sex and multiple gestations. The Kaplan-Meier method compared survival for regions and the three periods (T1, T2, T3) with perinatal activity scores above or below the national mean in live-born infants at 22 and 23 weeks' GA. The data were analysed with SPSS V.27.0 (IBM, New York, New York, USA).

Ethical approval

During T1, informed consent was obtained from the caregivers. In T2 and T3, all caregivers were informed that perinatal data would be recorded in SNQ with the possibility of withdrawing their participation.

RESULTS

Maternal and infant characteristics

This study comprised 977 infants (567 live births and 410 stillbirths): 323 born in T1, 347 in T2 and 307 in T3. The birth rates at 22 and 23 weeks were 0.46 and 0.60 per 1000 births in T1, 0.38 and 0.60 in T2 and 0.36 and 0.52 in T3, respectively (p>0.05 for all comparisons). The mothers of live-born infants in T1–T3 had no significantly different rates of chorioamnionitis, PPROM and pre-eclampsia. However, higher rates of vaginal bleeding were seen in T3 than T1 (adjusted p<0.01). The distribution of birth weight, SGA and sex did not differ significantly over time. Congenital anomalies affected 9/150 (6%) live-born infants at 22 and 23 weeks during T1, 22/222 (9.9%) in T2 and 24/195 (12%) during T3 (table 1).

Perinatal practices

Use of antenatal corticosteroids among live births at 22 weeks' GA increased significantly from T1 to T2 and T3 (41%, 64%, 70%, p<0.01). The corresponding values at 23 weeks were not significantly different. The number of infants intubated at birth and given surfactant before 2 hours of age increased significantly from T1 to T2 and T3. Admissions to NICU from the delivery room increased over time in infants born at 22 (39%, 68%, 84% in T1, T2 and T3, adjusted p<0.001) and 23 weeks (80%, 93%, 96%, respectively, adjusted p<0.01). There were significantly fewer infants born at 22 weeks at level II hospitals in T2 and T3 than in T1 (adjusted p<0.001) and significantly more infants born at 22 and 23 weeks were transferred after birth to level III–IV NICUs in T2 and T3 (adjusted p<0.001) (table 1).

Stillbirths and live births

Among infants born at 22 weeks' GA, significant reductions in stillbirth rates were found from T1 (65%) to T2 (45%) and T3 (36%) (p<0.001). Conversely, live births accounted for 35%, 55% and 64% of all births at 22 weeks during T1, T2 and T3 (adjusted p<0.01). The corresponding proportions of live births at 23 weeks were 55%, 69% and 63%, respectively (adjusted p, T1 vs T2=0.012) (table 2).

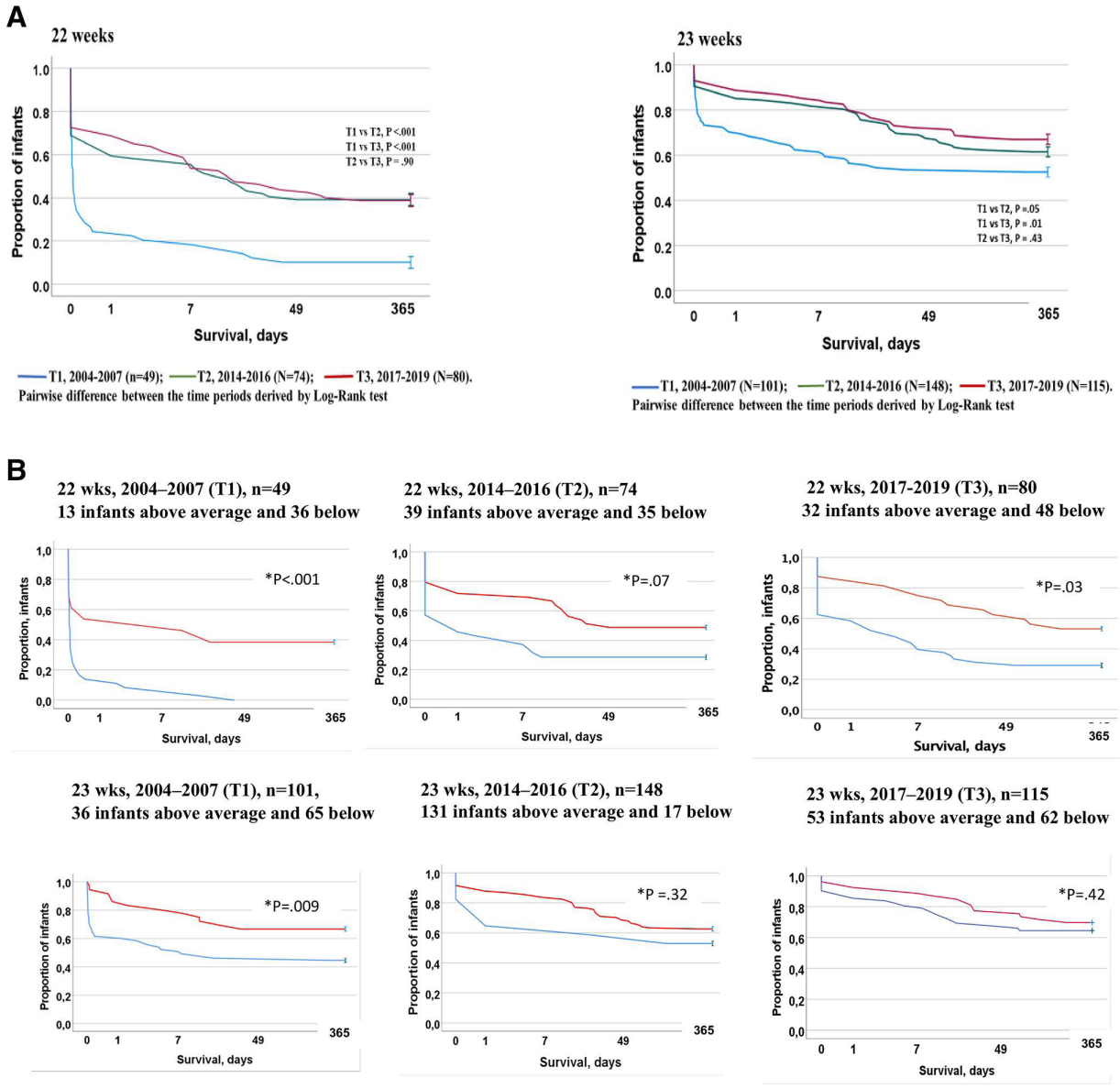

Figure 1 (A) Survival curves from birth to 1 year for infants born alive by GA and time periods. (B) Survival curves from birth to 1 year for infants born alive in regions with above and below average perinatal scores, by GA and time periods. Above average PA scoring regions _____; Below average PA scoring regions _____. *Difference in survival between above and below average PA scoring regions was tested by log-rank test. GA, gestational age; PA, perinatal activity.

Survival

One-year survival among live-born infants at 22 weeks increased significantly from T1 (10%) to T2 (39%) and T3 (39%, p<0.001). The corresponding figures for 23 weeks were 53%, 61% and 67% (p=0.09). Survival rates for infants admitted to NICU at 22 weeks also increased (26%, 58%, 46%, adjusted p<0.01) but were not significantly different at 23 weeks (65%, 66% and 70%, p=0.83). Proportions of live-born infants surviving without MNM did not change significantly across the three epochs at 22 weeks (20%, 17%, 19%, p=0.9) or 23 weeks' GA (17%, 25% and 25%, p=0.5) (table 2).

Neonatal morbidity

The rates of severe BPD, ROP stage 3–5, IVH grade 3–4 and surgically treated NEC among survivors did not differ significantly between T1, T2 and T3 (table 3).

Lumping T1–T3 together, 1 year survivors born at 22 vs 23 weeks' GA, respectively, did not differ significantly in their rates of IVH grade 3–4 (12% vs 16%, p=0.23), severe BPD (32% vs 23%, p=0.11), ROP stage 3–5 (65% vs 59%, p=0.47) and surgically treated NEC (5% vs 8%, p=0.38). Furthermore, survival without MNM (20% vs 23%, p=0.6) as well as proportions of survivors with any one, two or three and more MNM did not differ between infants born at 22 or 23 weeks of GA (online supplemental efigure 2).

Regional GA-specific perinatal activity scores and outcomes

The overall survival rate at 22 weeks was higher in regions with above-average perinatal activity scores than in those with below-average scores (48% vs 20%, p<0.001, adjusted OR (aOR) 3.8, 95% CI 2.0 to 7.2) (table 4, figure 1, online supplemental etable 2).

Table 5 Associations between the perinatal activity scores and mortality, survival, with or without major neonatal morbidity and associations between key neonatal and obstetric interventions, and survival.

	Univariate OR (95% CI)	P value	Adjusted OR 95% CI*	P value
Death before 12 hours of life (n=564)				
Perinatal activity scores (GA-specific), 5-point increments	0.72 (0.7 to 0.8)	<0.001	0.70 (0.6 to 0.8)	<0.001
GA (22 vs 23 weeks)	0.21 (0.1 to 0.3)	<0.001	0.92 (0.5 to 1.6)	0.77
Birth weight (1 Z-score)	0.92 (0.8 to 1.1)	0.28	0.76 (0.6 to 1.0)	0.05
SGA (yes vs no)	1.3 (0.8 to 2.2)	0.31	1.2 (0.5 to 2.9)	0.66
Sex (female vs male)	0.84 (0.6 to 1.2)	0.37	0.68 (0.4 to 1.1)	0.10
Multiple birth (single vs multiple)	1.2 (0.8 to 1.9)	0.42	1.0 (0.6 to 1.9)	0.90
Death between 13 hours and 1 year (n=428)				
Perinatal activity sores (GA-specific), 5-point increments	0.92 (0.8 to 0.9)	0.02	1.0 (0.9 to 1.1)	0.25
GA (23 vs 22 weeks)	0.53 (0.3 to 0.8)	0.005	0.6 (0.4 to 1.0)	0.05
Birth weight (1 Z-score)	1.0 (0.9 to 1.2)	0.89	1.0 (0.8 to 1.2)	0.91
SGA (yes vs no)	1.0 (0.6 to 1.8))	1	0.94 (0.4 to 2.1)	0.88
Sex (female vs male)	0.9 (0.6 to 1.3)	0.49	0.8 (0.6 to 1.3)	0.38
Multiple birth (single vs multiple)	1.1 (0.7 to 1.8)	0.72	1.0 (0.6 to 1.7)	0.94
One-year survival (n=564)				
Perinatal activity sores (GA-specific), 5-point increments	1.3 (1.2 to 1.3)	<0.001	1.2 (1.1 to 1.3)	<0.001
GA (23 vs 22 weeks)	3.3 (2.3 to 4.7)	<0.001	1.6 (1.1 to 2.4)	0.05
Birth weight (1 Z-score)	1.0 (0.9 to 1.2)	0.61	1.1 (0.9 to 1.4)	0.31
SGA (yes vs no)	0.9 (0.5 to 1.4)	0.56	0.9 (0.5 to 1.8)	0.77
Sex (female vs male)	1.2 (0.9 to 1.7)	0.28	1.3 (0.9 to 1.9)	0.13
Multiple birth (single vs multiple)	0.9 (0.6 to 1.3)	0.45	0.9 (0.6 to 1.5)	0.72
One-year survival without any major neonatal morbidity in all live births (n=564)				
Perinatal activity sores (GA-specific), 5-point increments	1.3 (1.1 to 1.4)	<0.001	1.3 (1.1 to 1.4)	<0.001
GA (23 vs 22 weeks)	2.4 (1.3 to 4.5)	0.007	1.1 (0.5 to 2.2)	0.82
Birth weight (1 Z-score)	1.1 (0.9 to 1.3)	0.52	1.1 (0.8 to 1.4)	0.72
SGA (yes vs no)	0.7 (0.3 to 1.5)	0.35	0.6 (0.2 to 1.9)	0.41
Sex (female vs male)	1.2 (0.7 to 2.1.)	0.41	1.3 (0.8 to 2.3)	0.27
Multiple birth (single vs multiple)	1.0 (0.5 to 1.9)	0.88	1.0 (0.5 to 2.1)	0.93
One-year survival, key obstetric and neonatal interventions (n=564)†				
Born at the regional centre (level III care)	3.1 (2.0 to 5.0)	<0.001	1.74 (1.01 to 3.0)	0.04
Antenatal corticosteroids given to mother, any‡	5.0 (3.2 to 8.1)	<0.001	2.2 (1.2 to 3.8)	0.008
Caesarean delivery (yes vs no)	1.5 (1.0 to 2.4)	0.04	1.22 (0.8 to 1.9)	0.40
Intubation at birth (within 30 min of life)	4.4 (2.9 to 6.8)	<0.001	1.7 (0.9 to 2.8)	0.06
Surfactant given within 2 hours of life	4.6 (3.2 to 6.8)	<0.001	2.4 (1.6 to 3.6)	<0.001
Neonatologist present at delivery	2.5 (1.6 to 3.9)	<0.001	1.2 (0.7 to 1.9)	0.56
GA (23 vs 22 weeks)	3.3 (2.3 to 4.7)	<0.001	2.4 (1.6 to 3.7)	<0.001
Birth weight (1 Z-score)	1.0 (0.9 to 1.2)	0.61	1.1 (0.9 to 1.3)	0.45
SGA (yes vs no)	0.9 (0.5 to 1.4)	0.56	1.0 (0.4 to 1.9)	0.91
Sex (female vs male)	1.2 (0.9 to 1.7)	0.28	1.2 (0.9 to 1.8)	0.26
Multiple birth (single vs multiple)	1.2 (0.8 to 1.8)	0.45	1.1 (0.7 to 1.8)	0.59

Calculated using multivariable logistic regression models.
SGA (birth weight <−2 SD).[14]
*Adjusted ORs obtained after multiple logistic regression analyses adjusted for GA, birth weight, SGA (yes vs no), multiple births and gender.
†In the logistic model, 1-year survival, key obstetric and neonatal interventions, adjusted ORs were obtained after multiple logistic regression analysis adjusted for all the covariates shown in the univariate analysis.
‡Any receipt of antenatal corticosteroids was defined as one or two doses of betamethasone (12 or 24 hours apart).
GA, gestational age; SGA, small for gestational age.

Among infants born at 22 weeks, the regions with below-average scores showed a significant increase in mean (SD) perinatal activity scores from 26 (17) in T1 to 47 (3.8) in T2 and 59 (0.8) in T3 (adjusted p<0.01), which was associated with an increase in 1-year survival (from 0% in T1 to 29% and 29% in T2 and T3, adjusted p<0.001). Among infants born at 23 weeks, no difference in survival was noted between regions that scored above or below average in T2 and T3.

Multivariable logistic regression analyses

Adjusting for GA, sex, birth weight, SGA and multiple gestations, each 5-point increment in the perinatal activity scores was associated with decreased mortality in the first 12 hours of life (aOR 0.71), increased 1-year survival (aOR 1.2) and increased MNM free 1-year survival (aOR 1.3) among live births at 22–23 weeks of gestation. A separate multivariable logistic regression analysis on the 428 survivors at 13 hours of age revealed that the perinatal activity score was not associated with a further decrease in mortality. Antenatal corticosteroids, delivery at a level III centre and surfactant within 2 hours of life, were independently associated with 1-year survival (table 5).

DISCUSSION

This study showed that there was a fourfold increase in 1-year survival of live-born infants at 22 weeks of GA between 2004–2007 and 2014–2016, but not thereafter. The increased survival

was not accompanied by higher rates of MNM, and MNM did not differ between infants born at 22 and 23 weeks of GA. These improvements were associated with increased perinatal activity around birth and less regional variation in practice which coincided with the issuing of national recommendations on management.

To avoid denominator bias, we provided information on both stillbirths and live births. It was possible to estimate GAs, using ultrasound, in >95% of cases during the total study period. T1 relied on prospective data collection. To reduce bias in T2, register data were cross-referenced to other data sources, including medical records. In T3, we used the SNQ, which has excellent validity and was shown to be robust in T2, as the sole source of the perinatal data.[13]

Limitations of the study include lack of obstetric information on fetal status at the mother's admission to hospital. Hence, we cannot discriminate cases of stillbirth where obstetric interventions possibly could have contributed to a live birth.[20] However, in T1, two out of three fetal deaths at 22–23 weeks of GA had occurred before the pregnant woman was admitted to hospital, and therefore these fetuses were not eligible for perinatal interventions.[10] Some sample sizes, such as the numbers of survivors at 22 weeks in T1, were too small to make valid comparisons with other study data. The time gap between T1 and T2 was 7 years, whereas T2 and T3 ran through consecutive years (2014–16 and 2017–19). Therefore, it was more likely to observe differences in survival between T1 and T2 than between T2 and T3 because more time had passed. Therefore, we may not have seen improved survival between T2 and T3. Implementation of guidelines might also take place gradually over the years. Previous studies have shown that neurodevelopmental impairments are common in the survivors born at 22–23 weeks of gestation, although severe impairments were less prevalent.[4 6–8 21 22] Our study lacks long-term follow-up.

There has been limited consensus about the best way to treat infants born at the lowest GAs. However, hospital practices about initiating active interventions have been reported to increase survival rates up to 50% without increasing rates of impairment.[3–8] Three key initiatives are likely to have contributed to reduce EPT deaths in Sweden. First, well-designed, population-based studies that have demonstrated benefits of active management, including a few Swedish reports,[10 23 24] which have helped to gradually change attitudes. Second, a recommendation of centralisation[25] of EPT deliveries to Sweden's six regional centres has been associated with an increased likelihood of active treatment and reduced the risk of antepartum or neonatal death.[11 23 24 26] Third, national guidelines[9] that suggest that active perinatal care should be considered from 22 weeks have encouraged more obstetricians and neonatologists to promote active care at very low GA. As illustrated by significantly increased perinatal activity scores and less regional variation over time, some Swedish regions had adopted a more proactive approach to managing EPT births already before 2016 guidelines.[1 23 24]

The rates of MNM did not increase among survivors born at 22 weeks, despite a fourfold increase in survival between T1 and T2 or T3. Similar results were seen among 1-year survivors born at 23 weeks. Furthermore, the overall proportion of 1-year survivors without any MNM was not different in infants born at 22 and 23 weeks (20% vs 23%, respectively). A recently published national cohort study of live-born infants at 22–23 weeks' gestation in 2007–2018 and based on data from another source, that is, the Swedish Medical Birth Register, have found similar rates of IVH grade 3–4 and laser-treated ROP as in our study.[27]

Associations between the intensity of care and survival and morbidities have been reported by others.[1 24 28–32] The GA-specific perinatal activity scores used here reflect the willingness by clinicians to actively intervene on behalf of compromised fetuses or infants. Some of the perinatal interventions included in the perinatal activity scores, such as antenatal steroids,[33–35] delivery at a level III–IV centre[20 24] and surfactant replacement,[36] are well known to improve survival. Others, like caesarean delivery[37] and intubation after birth may reflect clinicians' intentions to treat infants, rather than provide evidence-based markers of optimal care. The perinatal activity scores were no longer associated with reduced mortality when early deaths before 12 hours were excluded. This indicates that survival is predominantly due to the perinatal management practised immediately before and after birth.

The current Swedish guidelines[9] for resuscitating babies at 22 weeks' gestation appear similar to the guidelines from the British Association of Perinatal Medicine.[38] The British guidelines underline professional information and counselling parents about the individualised risks for the infant, preferably before delivery. Such counselling may be influenced by the attitudes of medical professionals. Swedish law states that a decision to begin or abstain from life-sustaining treatment should always be based on an individual assessment and include a consideration of the patient's/family's preferences.

CONCLUSION

This study confirmed that all Swedish regions have switched to more active perinatal practices in the management of preterm births at 22–23 weeks' gestation. In association, there was a fourfold increase in the survival of infants born alive at 22 weeks over time, without any increase in major neonatal morbidities.

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