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Proactive Management Promotes Outcome in Extremely Preterm Infants: A Population-Based Comparison of Two Perinatal Management Strategies

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ABSTRACT. *Objective.* **There is a need for evidence-based knowledge regarding perinatal management in extreme prematurity. The benefit of a proactive attitude versus a more selective one is controversial. The objective of the present study was to analyze perinatal practices and infant outcome in extreme prematurity in relation to different management policies in the North (proactive) and South of Sweden.**

Methods. **A population-based, retrospective, cohort study design was used. Data in the Swedish Medical Birth Register (MBR) from 1985 to 1999 were analyzed according to region of birth and gestational age (22 weeks + 0 days to 27 weeks + 6 days). A total of 3 602 live-born infants were included (North = 1040, South = 2562). Survival was defined as being alive at 1 year. Morbidity in survivors, based on discharge diagnoses of major morbidity during the first year of life, was described by linking the MBR to the Hospital Discharge Register.**

Results. **In infants with a gestational age of 22 to 25 weeks, the proactive policy was significantly associated with 1) increased incidence of live births, 2) higher degree of centralized management, 3) higher frequency of caesarean section, 4) fewer infants with low Apgar score (<4) at 1 and 5 minutes, 5) fewer infants dead within 24 hours, and 6) increased number of infants alive at 1 year. There were no indications of increased morbidity in survivors of the proactive management during the first year of life, and the proportion of survivors without denoted morbidity was larger.**

Conclusion. **In infants with a gestational age of 22 to 25 weeks, a proactive perinatal strategy increases the number of live births and improves the infant's postnatal condition and survival without evidence of increasing morbidity in survivors up to 1 year of age.** ***Pediatrics*** **2004;114:58–64;** ***perinatal, prematurity, infant, outcome, management.***

ABBREVIATIONS. 25WG, 25-week guideline; GA, gestational age; MBR, Medical Birth Register; CLD, chronic lung disease; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity; OR, odds ratio; CI, confidence interval.

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Survival of premature infants at the verge of viability has improved dramatically during recent years, involving the joint efforts of the obstetric and neonatal professions to optimize perinatal management and neonatal care.[1–3] However, this development has raised concern about the fact that improved viability is accompanied by an increasing number of survivors with disabling morbidity, although the proportion of disabled survivors seems to be constant.[4] Lorenz et al[5] compared the proactive perinatal management in the United States with the selective approach practiced in the Netherlands. In infants of 23 to 26 weeks' gestation, the provision of a proactive strategy seemed to do more good than harm: for every 100 live births, the proactive management added 24 lives and 7 cases of disabling cerebral palsy at a cost of almost 1400 ventilator days.

Controlled trials to evaluate effects of different perinatal practices at extremely preterm birth are not feasible. Instead, population-based, uncontrolled experiments may be a second-best alternative to gain acceptable evidence.[6] In Sweden, 2 different regional strategies for perinatal management of extreme prematurity have emerged during the recent decades. This situation offers a unique possibility to appraise and compare the outcome of each strategy in a common national setting. In the northern region of the country, the policy can be described as "proactive," indicating that the Swedish so-called "25-week guideline" (25WG) of 1990 was never endorsed. In the southern region, where the adherence to this recommendation has been more prevalent, the policy could be designated as "selective and active." In summary, the 25WG advises a restrictive attitude toward active obstetric intervention on fetal indication at ≤25 weeks of gestation and an individualized approach to the resuscitation of infants with "very low birth weight or very short gestational length."[7]

The purpose of the present study was to investigate whether outcome data could favor the advocacy of either of these purportedly altruistic strategies. We therefore conducted a population-based study to assess perinatal practices, survival, and discharge diagnoses of major neonatal morbidity in infants of very short gestational age, in relation to the different exposures of perinatal management.

METHODS

A population-based, retrospective, cohort study design was used, with data collected from national medical and epidemiologic service registers. Eligible subjects were live-born infants with gestational age (GA) from 22 weeks + 0 days to 27 weeks + 6 days during the years 1985–1999. Information was obtained from the Medical Birth Register (MBR) kept by the Epidemiologic Centre of the Swedish National Board of Health and Welfare (www.sos.se/epc). The register data in the MBR are collected prospectively, starting at the first antenatal visit, usually at 10 weeks' GA, and subsequently include data on pregnancy surveillance, complications, delivery (for all hospital births), and events pertaining to the infant during the neonatal period (days 0–27). The MBR is validated annually against the National Population Register, using the unique personal identification number of mother and infant, and contains >99% of all births in Sweden.[8] It does not record stillbirths before 28 weeks of gestation. The register is updated continuously with the Cause of Death Register regarding death and cause of death during and after the neonatal period. Survival was defined as being alive at 1 year of age. Morbidity in survivors was assessed by linking the MBR with the Hospital Discharge Register and based on selected diagnoses at discharge from all episodes of hospital care occurring within the first year of life. The time period investigated, 1985–1999, was divided further into three 5-year periods (period 1: 1985–1989; period 2: 1990–1994; period 3: 1995–1999) for assessment of trends over time.

The northern region was defined as the regional catchment areas of the level III neonatal intensive care units of the university hospitals in the cities of Umeå and Uppsala (Fig 1). Within this region, there are also 7 county hospitals and 14 district hospitals. The southern region comprises 5 level III neonatal intensive care units at the university hospitals in Stockholm, Örebro, Linköping, Gothenburg, and Lund; 12 county hospitals; and 23 district hospitals (Fig 1). The northern region covers 60% of the area of the country with a population of 2.5 million. The southern region has ~6.5 million inhabitants. In all, there were there 1 577 030 live births with an average annual birth rate of North/South of 27 005/78 130 (ratio: 1/2.89). During the three 5-year periods, there were 525 669, 595 073, and 456 288 live births, respectively. There was a notable accretion of live births during period 2, followed by a sharp decline during period 3. Birth rates in the North and South, however, were not concordant during the 3 time periods with a changing ratio of 1 to 2.76, 2.85, and 3.11.

The exposure categories, North and South, were defined by region of birth or, when explicitly stated, region of maternal domicile. The cohort comprised 3952 infants. From the total group, 350 infants were excluded. Of these, 174 (North/South = 51[4.6%]/123 [4.3%]) had a registered birth weight of >+2 standard deviations according to intrauterine growth curves[9] or a

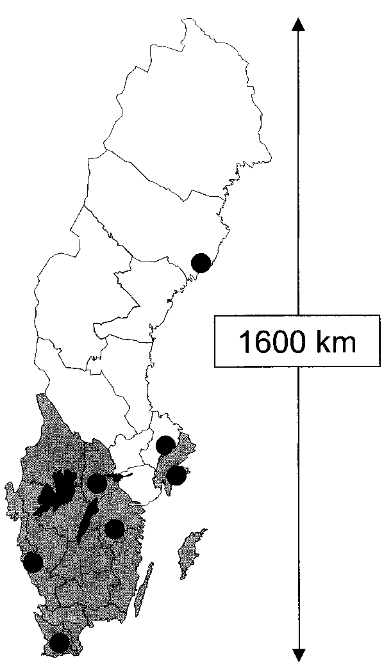

Fig 1. Map of Sweden with the 2 regions North (white) and South (gray) defined. Level III perinatal units depicted.

TABLE 1. GA in Relation to Birth Weight, 1985–1999*

GA Weeks	Mean Birth Weight/SD (g)	
	North (n = 1040)	South (n = 2562)
22	479/70	504/70
23	605/84	594/100
24	671/106	688/103
25	765/135	786/129
26	878/165	883/163
27	1017/203	1000/187

SD indicates standard deviation
* No significant differences between North and South

record of birth weight missing (n = 176; North/South = 25 [2.2%]/151 [5.3%]). Thus, a total of 3602 live-born infants (North/South = 1040/2562) were included in the study.

The mothers of North and South did not differ significantly by age, parity, or smoking in early pregnancy. Estimation of GA was based on ultrasonography or last menstrual period as performed in normal clinical practice. When data were available from both methods, GA was based on ultrasound. This method was used more extensively in the northern region, and the percentage of second trimester ultrasound was increasing both in North and South during the study period (North = 39%, 68%, and 79%; South = 33%, 59%, and 72% per respective time periods 1, 2, and 3). The differences between North and South were significant during time periods 2 (P > .001) and 3 (P > .01). The infants of North and South did not differ by birth weight in relation to GA (Table 1). The proportion of multiple births was equal in both regions. Some mothers gave birth in a region different from their region of domicile. The proportion of parturients from the southern region who gave birth in a hospital of the northern region per time period was 3.6%, 5.6%, and 10.6%. In contrast, the proportion of parturients from the northern region who gave birth in a hospital of the southern region was 1.4%, 0.9%, and 0.4%.

Of 2225 survivors, a total of 2114 (North/South = 665/1449) were retrieved from the Hospital Discharge Register. Of these, 1903 subjects had complete records of diagnoses (North/South = 629/1274). Only 1 of the few survivors of 22 weeks' GA had complete diagnoses; therefore, the analysis of morbidity was restricted to infants of 23 to 27 weeks' GA (North/South = 628/1274). The frequencies of infants with the following diagnoses were determined: chronic lung disease (CLD), intraventricular hemorrhage (IVH; all grades), and retinopathy of prematurity (ROP; all stages) as coded in the *International Classification of Diseases*, 9th and 10th revisions during respective time periods. Many infants were initially cared for in a level III unit after in utero transfer and later transferred to a local hospital for continued care before diagnoses of ROP or CLD could be confirmed. For this reason, discharge diagnoses from all hospitalization episodes during the first year of life were retrieved from the central register to which all hospitals report.

Statistical analyses when appropriate were performed by χ^2 test for proportions and linear trends, t test, or odds ratio (OR) with 95% confidence interval (CI). The Ethical Board of the Epidemiologic Centre as well as the Research Ethical Committee of Umeå University approved of the study.

RESULTS

Incidence of Premature Live Birth and Infant Survival

The cohort of premature infants was initially analyzed for putative regional differences regarding GA, number of live births, incidence per 1000 live births, and survival to age 1 year. These analyses were performed with reference to completed weeks of gestation or birth weight in classes of 100-g increments over the whole period 1985–1999. A sharp division between North and South was found between 25 and 26 weeks' GA regarding incidence and survival. Both variables were significantly increased in the North in infants of a GA ≤25 weeks. When the data were analyzed in relation to birth weight, a similar division occurred between the 700- and 800-g strata. In infants with GA >25 weeks or birth weight >799 g, survival but not incidence was increased in the North (Tables 2 and 3).

The analysis of incidence was based on region of maternal domicile. Because a considerably larger number of mothers from the South gave birth in the North than vice versa, the figures would become falsely high for the North and falsely low for the South had calculations been based on region of delivery. Over the whole study period, there was a higher incidence of live births at or below 25 weeks' GA in the North (1.08 vs 0.85 per 1000 live births; $P < .001$). In both regions, there were increasing trends of incidence, and during time period 3, the figures were 1.41% and 0.99%, respectively ($P < .001$). For infants of 26 to 27 weeks' GA, there were no significant differences in incidence between North and South during any of the 3 time periods.

Survival was analyzed in detail per week of GA and time period. During time period 1, there were no regional differences in survival in infants of ≤25 weeks' GA. From 1990, survival increased in both regions but was significantly and increasingly higher in the North. The OR with 95% CI for survival to age 1 year in the North was 1.7 (1.2–2.5) in period 2 and 2.5 (1.7–3.6) in period 3. In infants with a GA >25 weeks, the OR for survival in the North during period 1 was 1.8 (1.2–2.6). This difference disappeared during periods 2 and 3, with close or equal survival rates in the 2 regions (Table 3, Fig 2).

Perinatal Practices

A significantly larger number of deliveries in the North were centralized to level III units. During period 3, 85% of all live births of ≤ 25 weeks' GA in the North occurred in such units as compared with 56% in the South. Also for pregnancies of >25 weeks, a significantly larger proportion of births were centralized in the North during the whole study period. A considerable proportion of parturients from the South were actively referred to the southernmost center of the North (Uppsala) for delivery. Therefore frequencies of centralized management were based on maternal domicile to give a true assessment of the ambition in either region to centralize management of women with threatening preterm labor (Fig 2B–F).

Delivery by cesarean section was more frequently performed in infants who were ≤25 weeks' GA in the North during periods 2 and 3. In both regions, there were increasing trends over time. Perinatal management in the North yielded a reduced number of infants who were ≤25 weeks' GA and had Apgar scores <4 at 1 and 5 minutes, and there was a lower number of infants who died within 24 hours of life (Fig 3). When these early deaths were excluded from analyses of survival, there remained no significant differences between North and South for infants with a GA of ≤25 weeks (data not shown).

Morbidity

The graph illustrating morbidity presents data for the period 1990–1999, ie, after the promulgation of the 25WG. The cohort was divided into 2 groups with a GA of 23 to 25 or 26 to 27 weeks. In the group with lower GA, the proportion of 23- to 24-week infants was significantly higher in the North (79 of 182 [43%] vs 63 of 232 [27%]; $P < .001$). Despite this, there was no indication that exposure to the proactive management in the North increased morbidity. The number of cases of ROP was lower in the North in both groups of infants, and the proportion of infants without any of the diagnoses of CLD, ROP, or IVH was larger in the North (Fig 4).

During the first time period, the pattern of morbidity was similar with a lower number of cases with ROP in all infants in the North. There were no significant differences regarding the number of infants without the investigated diagnoses (data not shown).

DISCUSSION

The management of extreme prematurity raises an array of concerns that involve medical, socioeconomic, and ethical issues. The relative lack of evidence to define which management strategy is in the best interest of the premature infant and the difficulty to obtain such evidence from controlled trials allow the emergence of different opinions. Professional attitudes to these questions may vary greatly among nations[10]—and even within nations[11,12]—in a way that would not be expected in other categories of patients who face comparable perils and prospects of a propitious outcome.

The 25WG from 1990 has originated from the Swedish medical professions concerned[7] and is based on the belief that a more active management would put the pregnant woman at undue risk and increase disabling morbidity in surviving infants. Although it was not accepted unanimously, the im-

TABLE 2. Incidence of Premature Birth Per 1000 Live Births, Number of Live Births, and Survival in Relation to GA or Birth Weight, 1985–1999

GA (Weeks) or Birth Weight (g)	Incidence/1000 Live Births		No. of Live Births		No. of Survivors (%)	
	North	South	North	South	North	South
22–25 wk	1.08	0.85	468	964	241 (51)‡	356 (37)
26–27 wk	1.37	1.38	572	1598	448 (78)*	1180 (74)
<800 g	1.13	0.88	491	1001	254 (52)‡	406 (41)
≥800 g	1.32	1.34	549	1561	435 (79)†	1130 (72)

* $P < .05$.
† $P < .01$.
‡ $P < .001$.

TABLE 3. Survival per GA, Time Period, and Region of Delivery (Live Births/Survivors [%]).

GA (Weeks)	1985–1989		1990–1994		1995–1999		1990–1999	
	North	South	North	South	North	South	North	South
22	7/1 (14)	12/0 (0)	10/1 (10)	16/2 (13)	8/1 (13)	18/1 (6)	18/2 (11)	34/3 (9)
23	30/7 (23)	38/3 (8)	30/7 (23)	49/7 (14)	34/14 (41)*	44/7 (16)	64/21 (33)†	93/14 (15)
24	28/8 (29)	72/20 (28)	62/30 (48)‡	131/29 (22)	46/32 (70)*	77/38 (49)	108/62 (57)‡	208/67 (32)
25	54/22 (41)	127/47 (37)	70/42 (60)	199/94 (47)	89/76 (85)‡	181/108 (60)	159/118 (74)‡	380/202 (53)
26	65/48 (74)†	218/121 (56)	116/84 (72)	291/202 (69)	65/52 (80)	217/179 (82)	181/136 (75)	508/381 (75)
27	97/74 (76)	264/185 (70)	141/114 (81)	346/272 (79)	88/76 (86)	262/221 (84)	229/190 (83)	608/493 (81)
22–25	119/38 (32)	249/70 (28)	172/80 (47)†	395/132 (33)	177/123 (69)‡	320/154 (48)	349/203 (58)‡	715/286 (40)
26–27	162/122 (75)†	482/306 (63)	257/198 (77)	637/474 (74)	153/128 (84)	479/400 (84)	410/326 (80)	1116/874 (78)

* $P < .05$.
† $P < .01$.
‡ $P < .001$.

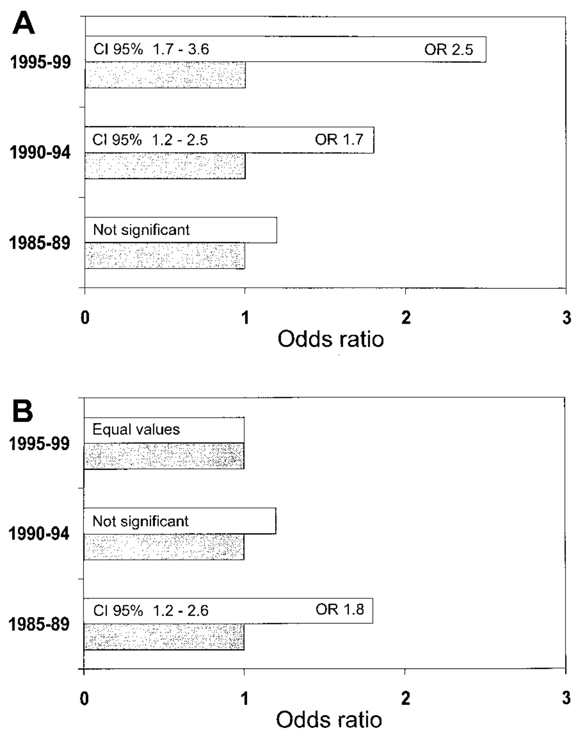

Fig 2. Graph illustrating OR for survival at 1 year of age per time period, GA, and region of birth. White bars, North; gray bars; South (reference). Upper panel, 22 to 25 weeks; lower panel, 26 to 27 weeks.

pact of this guideline on perinatal management in Sweden is clear. In a national study conducted in 1990–1992, 79% of all live births at 23 to 24 weeks of gestation died and the majority of these infants died in the delivery room without active measures of resuscitation.[12] It is probably this practice that motivated the description of Sweden as a country with a "statistical" approach to the management of extreme prematurity.[13,14] In the North of Sweden, the 25WG was declined in favor of the proactive management already established during the 1980s. In contrast, this policy was based on the belief that it can increase the number of surviving infants without putting mothers at undue risk or increasing disabling morbidity in survivors. After >10 years of practicing these divergent regimens, it may be appropriate to present data from which it could be decided whether either is preferable.

For the regional comparison of outcome data on premature birth, it is crucial that the estimation of gestational age be comparable in the 2 geographic areas. The information on GA is a solid variable in the MBR with <0.5% of parturient protocols missing. Although there is no gold standard,[15] early ultrasound is more accurate than judgments made from dates of the last menstrual period.[16] Because the proportion of women in which ultrasound had been performed was significantly greater in the North, we also compared the birth weight of infants per gestational week without finding any differences. Infants with a registered birth weight of >+2 standard deviations were not included in the analyses to avoid outliers where the recorded weight in relation to GA seemed implausible or unreasonable. The proportion of infants so excluded was small (<5%) and similar in North and South. The analysis of survival rate and incidence in relation to birth weight showed very good coherence with the results obtained from the data based on GA. Therefore, we have no reason to believe that there are any systematic regional differences in the determination of gestational length.

The incidence of premature live birth at 22 to 25 weeks but not at 26 to 27 weeks was higher in the North. It is not probable that this is attributable to regional biological differences in the populations of fertile women or more successful treatment for postponing preterm delivery in the South. It seems more likely that the regional differences in the incidence of preterm live births are related to reciprocal differences in the number of preterm stillbirths. The MBR suffers from a serious imperfection in that it does not include stillbirths at 22 to 27 weeks of gestation. Therefore, this question cannot be resolved from register data. It has also been described that in cases in which it is decided to forego resuscitation, notwithstanding that signs of life are present, the infant incorrectly may not be registered as a statutory live birth.[17] This phenomenon was also encountered by 1 of the authors (F.S.) when participating in the previously mentioned Swedish national study.[12]

Survival of the premature infant increased in both regions during the study period. Before implementation of the 25WG (period 1), there was a better chance for survival in the North for infants with a gestational age of 26 to 27 weeks. At 25 weeks or below, chances of survival were similar. After the introduction of the guideline in 1990, the regional differences of survival in infants of 26 to 27 weeks'

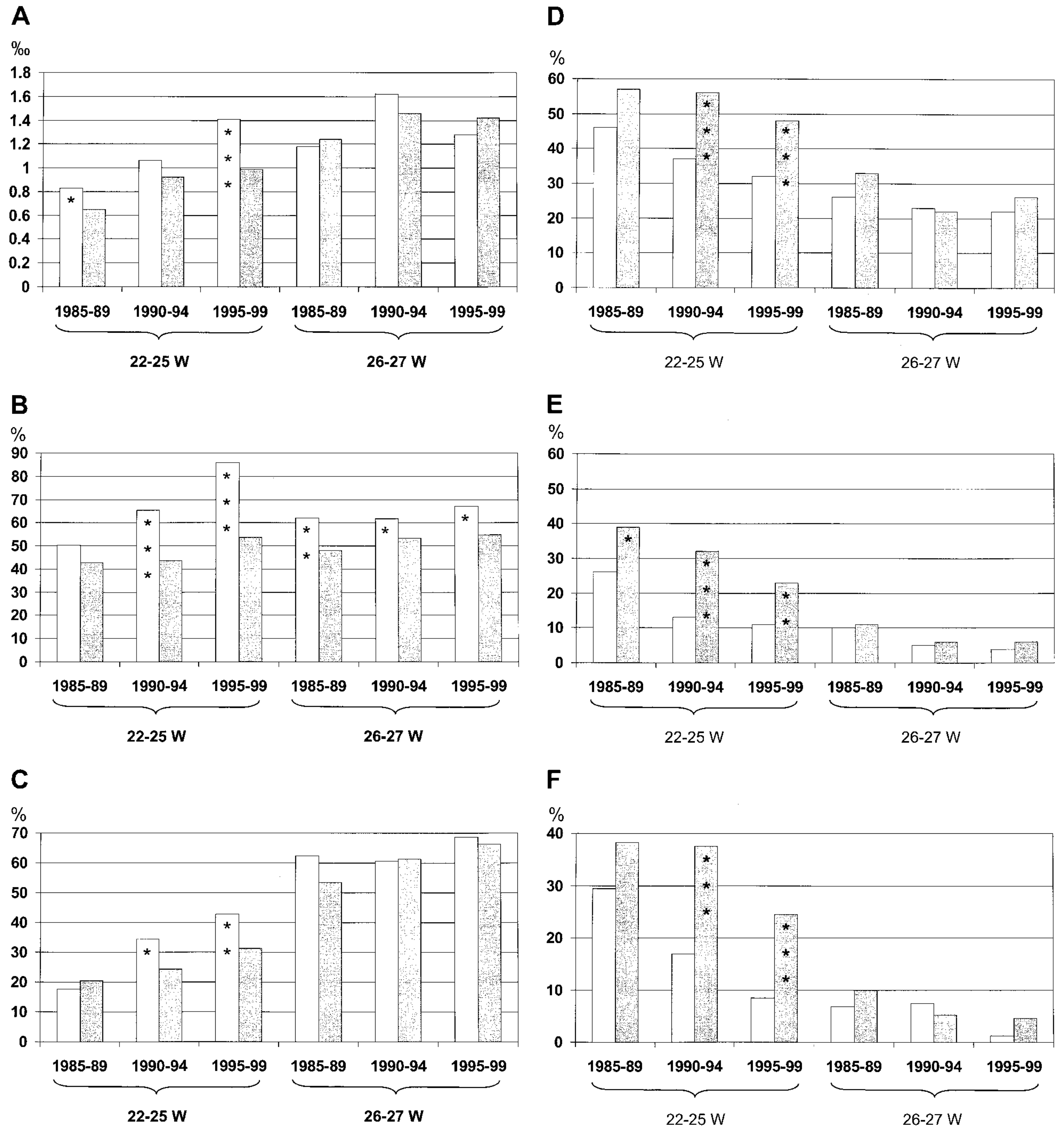

Fig 3. Incidence of preterm live birth and perinatal practices. Proportions of infants in respective region per time period depicted by bars (white, North; gray, South). A, Incidence per 1000 live births. B, Centralized management of premature birth. C, Delivery by cesarean section. D, Apgar score at 1 minute <4. E, Apgar score at 5 minutes <4. F, Deaths within 24 hours after birth (*P < .05, **P < .01, ***P < .001).

GA were no longer statistically significant. In contrast, there were dramatic changes in the survival of infants at 25 weeks or less. During period 2, there was a significant OR in favor of survival in the North of 1.7, and during period 3, this ratio increased to 2.5. The greater proportion of 26- to 27-week infants who were delivered at level III units and their higher survival in the North during the first period indicate that a proactive policy existed in the North already during this epoch. These facts also provide a rationale that explains why the more conservative 25WG was never accepted as a precept in the North. The consequent increment of survival in the North of 22- to 25-week infants and the differences in perinatal practices clearly confirm the impact of the 25WG in the southern region.

Centralized management of extremely premature birth is a cornerstone of proactive management.[18] In pregnancies of <26 weeks' duration, the differences between North and South were conspicuous. In the North during period 3, only ~15% of women with extremely preterm birth before 26 weeks' GA were delivered outside a level III unit. It can be surmised that these women for different reasons were not con-

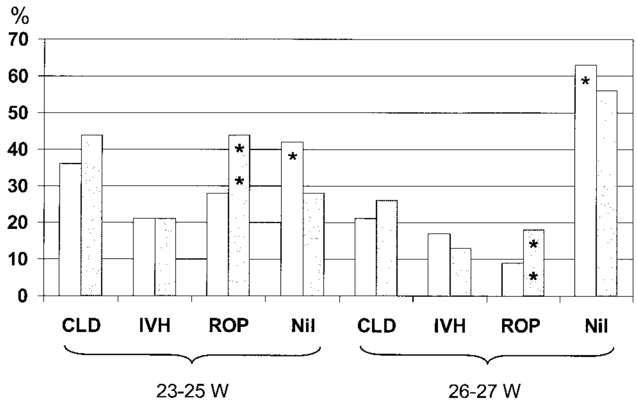

Fig 4. Morbidity in survivors. Proportion of infants with diagnosis of CLD, IVH, or ROP or without these diagnoses (Nil), per GA and region of birth during the period 1990-1999. White bars, North; gray bars, South.

sidered to be in transportable condition, with risk of imminent delivery. It is also noteworthy that the northern region is considerably larger and more sparsely populated than the southern region, showing that successful referral in utero is not dependent primarily on proximity to the level III unit but rather on a foresighted attitude and an expedient transport organization.

According to the "better infant" hypothesis, one third of the observed mortality decline over time in infants who weighed <1500 g at birth could be attributed to improved high-risk obstetric care.[19] Practices such as better ultrasound diagnostics for assessment of fetal well-being, use of antenatal corticosteroids, delay of delivery with tocolytics, and possibly more liberal use of abdominal delivery on fetal indication were significant components of this perinatal management strategy. The higher cesarean section rate in the North could be interpreted in the perspective of a proactive obstetric management. This agrees with the study of Bottoms et al,[20] suggesting that the willingness of the obstetrician to perform cesarean section for fetal indications was associated with increased survival also when controlling for birth weight. Although observational studies indicate a lower mortality in extremely preterm infants who are delivered abdominally,[20–22] no controlled trials have substantiated these findings. Because of selection bias, no evidence-based conclusions can be drawn regarding the influence of mode of delivery on infant survival.[23]

The proportion of infants who were <26 weeks' GA and had an Apgar score <4 at 1 minute was significantly higher in the South during time periods 2 and 3 and at 5 minutes in all periods. The number of infants who died within 24 hours after birth was also significantly higher in this region after 1990. An increased number of infants with a low Apgar score and early death connote a more pronounced level of fetal compromise, shown to be associated with a dismal outcome.[24] The more vigorous postnatal condition of the infants of the North align with the concept of "better infants," presumably achieved by an active obstetric surveillance and intervention, as well as the consistent policy of primary resuscitation. The difference in mortality between North and South was nullified when early deaths (<24 hours) were excluded. This suggests that the quality of neonatal intensive care is similar in North and South and that the different survival rates are accounted for predominantly by different practices regarding delivery and resuscitation.

There were no indications that the proactive management in the North increased morbidity in survivors. The frequencies of the diagnoses investigated are commensurate with other reports[2,11] but still must be interpreted with caution and used primarily for comparison of North and South. The register data did not allow staging of ROP or IVH; therefore, possible regional differences in the severity of these diseases cannot be evaluated. Because of a larger proportion of 23- to 24-week infants in the North, the mean GA in the 23- to 25-week cohort was lower. Still, morbidity was not increased in this group, and, in fact, the number of ROP cases was significantly lower. It should also be noted that the proportion of infants without any of the diagnoses CLD, IVH, or ROP, predicting a more favorable outcome,[25] was larger in the North from 1990 and beyond in all infants. Thus, it seems that management according to the 25WG does not reduce morbidity in survivors, contradicting the conjecture that a selective perinatal management strategy can winnow out infants with a gloomy prognosis in the delivery room. This policy was also associated with an increased number of early deaths. In theory, it can be estimated that for infants with a GA of 23 to 25 weeks, there would have been another 237 survivors added in the South if incidence and survival rates of the North had prevailed in the South during 1990–1999. Hence, the number of survivors of mothers who lived in the South would have increased by 77%, from 307 to 544. Regardless of region of birth, morbidity in survivors was approximately tantamount. Therefore, it is reasonable to infer that the condition of added hypothetical survivors of the South, during their first year of life, probably would not have been different from the condition of those infants who actually survived. The trends of perinatal practices disclose a shift over time toward a more proactive management policy in the South. The data presented here may provide evidence in additional support of this vicissitude.

The major neonatal morbidities such as severe IVH, CLD, and ROP are not the only determinants that herald ulterior outcome and quality of life in prematurely born infants. It has been demonstrated that social factors such as socioeconomic status, level of parental education, and family dysfunction may influence the development of cognitive faculties and behavioral disturbances.[26–28]

Although there is a strong association between severe IVH and cerebral palsy, it is not a mandatory prerequisite.[29] The inflammatory response to infection can contribute substantially to white matter injury and the pathogenesis of disturbed motor function and perception.[30–32] For addressing these complex questions, also in relation to the mode of perinatal management, a case-control follow-up of a national cohort of extremely low birth weight infants is currently accomplished.

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