ARTICLE

5-Year Morbidity Among Very Preterm Infants in Relation to Level of Hospital Care

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Objective: To determine whether birth and care in the highest-level hospitals (level III) compared with birth in or postnatal transfer to lower-level hospitals (level II) are associated with 5-year morbidity in very preterm children.

Design: A cohort study.

Setting: Finland.

Participants: All surviving 5-year-old children born very preterm (gestational age <32 weeks or birth weight ≤1500 g) born in level II or level III hospitals (n=2168) and full-term (gestational age, 37-42 weeks) children (n=238 857) born from January 1, 2000, through December 31, 2004.

Main Outcome Measures: Diagnoses issued after the first discharge home and overrepresented in very preterm compared with full-term children. Diagnoses were analyzed between very preterm children (1) born and treated in level III hospitals (group III), (2) born in level III and transferred to lower-level hospitals (group III/II), and (3) born and treated in level II hospitals (group II).

Results: Group III/II children had an increased incidence of retinal disorders (odds ratio, 2.43 [95% CI, 1.66-3.56]) and asthma (1.41 [1.09-1.81]) but fewer viral infections (0.75 [0.59-0.95]) compared with group III infants. The risks for epilepsy (odds ratio, 2.71 [95% CI, 1.29-5.70]) and hyperkinetic disorders (2.19 [1.13-4.25]) were higher among group II than among group III children. No statistically significant differences between the groups for the 14 other diagnoses were found.

Conclusions: The increased incidence of retinopathy and asthma among infants transferred from level III to lower-level hospitals calls for analysis of the differences in treatment practices between hospital levels.

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A HIGHER-LEVEL BIRTH HOSpital (level III) has been shown to be associated with decreased mortality in infants born at very low gestational ages or very low birth weights in several countries,[1-3] including Finland.[4] Birth in a higher-level hospital has also been associated with a reduced risk for severe intraventricular hemorrhage.[5] In Finland, however, we did not previously detect differences according to the birth hospital level in morbidity and the use of health care services,[6] development or behavior,[7] or the quality-adjusted life-years at 5 years of age.[8]

Although the days after birth are crucial to the survival of very preterm infants, care during the entire initial hospitalization likely affects their later outcome. Birth outside of or transfer to a level III hospital has been shown to be associated with increased mortality and short-term morbidity compared with infants born and treated in a level III hospital.[9-14] During the initial hospitalization, stable infants are often transferred from a level III hospital to a level II or a level I hospital closer to home because very preterm infants require a long initial hospitalization with a median duration of 53 days.[15] However, researchers have not studied whether transferring very preterm infants from level III to lower-level hospitals after birth is associated with long-term morbidity.

The aim of this study was to determine whether birth and care in level III hospitals compared with birth in or postnatal transfer to lower-level hospitals are associated with 5-year morbidity in very preterm children. We hypothesized that birth and treatment in a level III hospital are associated with fewer long-term morbidities than birth in a level III hospital and transfer to a level II or level I hospital during the first care episode or birth and treatment in a level II hospital.

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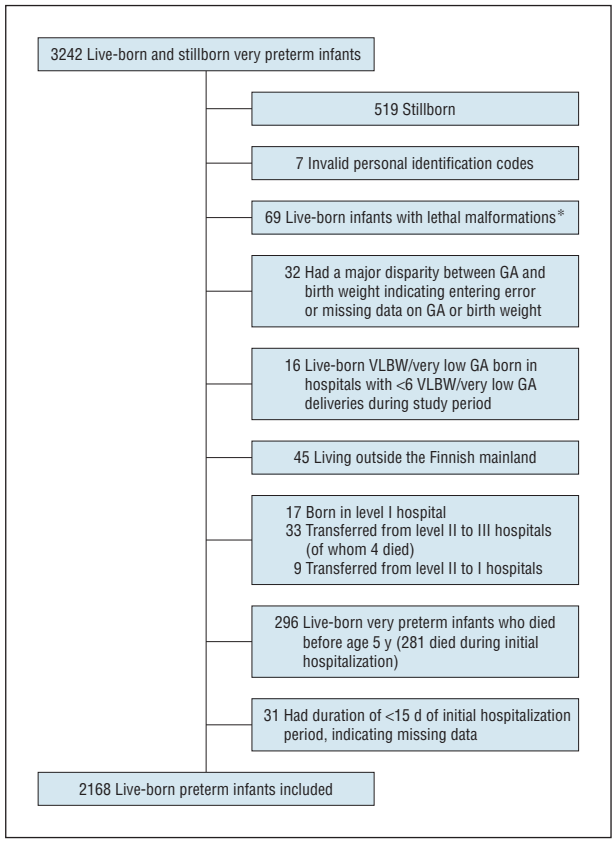

Figure 1. Exclusion graph for very preterm infants (gestational age [GA], <32 weeks, or birth weight, ≤1500 g) born in Finland from January 1, 2000, through December 31, 2004. *Malformations considered lethal included trisomy 13 or 18, triploidy, severe cardiac defects (eg, acardia, univentricular heart, transposition of great arteries, interrupted aorta), severe cerebral malformations (eg, anencephaly, holoprosencephaly), and other clearly defined lethal conditions. VLBW indicates very low birth weight.

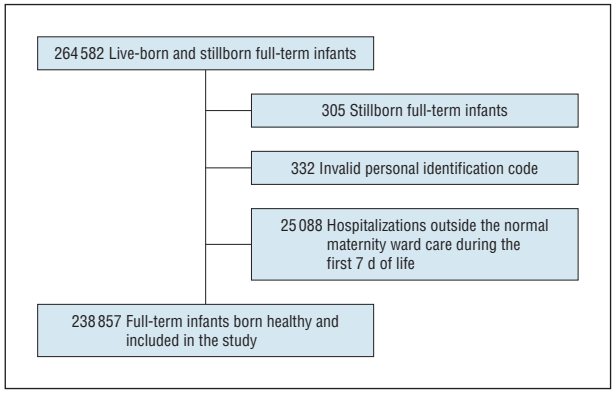

Figure 2. Exclusion graph for full-term (gestational age, 37-42 weeks) children born in Finland from January 1, 2000, through December 31, 2004.

METHODS

STUDY PATIENTS

This population-based study included all surviving very preterm infants (defined as having a gestational age of <32 weeks or a birth weight of ≤1500 g) born in Finland from January 1, 2000, through December 31, 2004. In addition, data from full-term infants (gestational age, 37-42 weeks) born during the same period were analyzed. The exclusions are reported in **Figure 1** and **Figure 2**. The final sample size after all exclusions was 2168 very preterm infants and 238 857 full-term infants.

DATA COLLECTION AND STATISTICAL ANALYSIS

Data from the Birth Register were linked to data from the Hospital Discharge Register, the Cause of Death Register, and the Register of Congenital Malformations. All visits to special health care facilities in Finland and the related diagnoses according to the *International Statistical Classification of Diseases, 10th Revision (ICD-10)*[16] are reported to the National Hospital Discharge Register. The Ethics Committee of the National Research and Development Centre for Welfare and Health approved the study protocol.

The criteria for categorizing hospital levels followed those proposed by the American Academy of Pediatrics Committee on Fetus and Newborn[17] for neonatal intensive care units. Accordingly, all 14 Finnish central hospitals with very preterm deliveries during the study period had at least level IIB neonatal care (ie, a "special care nursery where preterm and ill infants can be resuscitated and stabilized, and . . . [which]provide care for infants who are convalescing after intensive care, and have the capability to provide mechanical ventilation for brief durations or continuous positive airway pressure"). All 5 university hospitals had at least level IIIB neonatal intensive care units (ie, "the capabilities to provide comprehensive care for extremely low-birth-weight infants, advanced respiratory support such as high-frequency ventilation and inhaled nitric oxide for as long as required, access to a full range of pediatric medical subspecialists, advanced imaging with interpretation, pediatric surgical specialists and pediatric anesthesiologists available to perform major surgery"). These hospitals are referred to hereinafter as levels II and III hospitals, respectively.

We identified in several steps the most common diagnoses in very preterm children after the first discharge home compared with children born full-term. First, all congenital and neonatal diagnoses were excluded (*ICD-10* codes Q00-Q99 [ie, congenital malformations, deformations, and chromosomal abnormalities] and P00-P96 [ie, certain conditions originating in the perinatal period]). Second, symptomatic diagnoses were not included in comparisons (*ICD-10* codes R00-R99 [ie, symptoms, signs, and abnormal clinical and laboratory findings not classified elsewhere] and Z00-Z99 [ie, factors influencing health status and contact with health care services]). Third, *ICD-10* codes with a cumulative incidence of 2% or more by the age of 5 years in the very preterm children were defined as "common" and were included in further analyses as clustered in *ICD-10* groups without decimals. In addition, we decided to include epilepsy (*ICD-10* code G40) in the analyses owing to its nature as a marker of brain injury despite the cumulative incidence of only 1.2% for the most common *ICD-10* code for epilepsy (G40.9 [unspecified epilepsy]). The *ICD-10* code for urinary tract infection of unspecified site (N39.0) was also included because it is likely to have been used in some cases of pyelonephritis. We then compared the risk for the remaining *ICD-10* diagnoses by the age of 5 years between the very preterm children and the children born full-term without adjustments using the χ^2 test. A more conservative α level of .01 was used herein to protect against type I error given the large number of diagnoses that were compared. Those diagnoses overrepresented in the very preterm children compared with full-term children ($P < .01$) were arranged into groups of diagnostic entities for further analyses. These diagnoses were divided into those that might be influenced by the level of neonatal care and those that are not influenced, according to current knowledge, by neonatal care. In all other analyses performed in the study, $\alpha = .05$ was used.

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Table 1. Assignment of Study Groups by Hospital Level[a]

Birth Hospital	Place of Treatment During the Initial Hospitalization	Study Group
Level III (n = 1771)	Level III hospital (n = 686)	Group III
	Transferred from level III to level II hospitals (n = 761)	Group III/II
	Transferred from level III to level I hospitals (n = 324)	
Level II (n = 397)	Level II hospitals (n = 397)	Group II

[a]The 3 study groups were formed according to the first and second hospital of treatment during the initial hospitalization period. Hospital levels are described in the "Data Collection and Statistical Analysis" subsection of the "Methods" section. Study patients include preterm infants born in Finland from January 1, 2000, through December 31, 2004.

Table 2. Baseline Characteristics of the Very Preterm Infants[a]

Characteristic	All (N = 2168)	Group III (n = 686)	Group III/II (n = 1085)	Group II (n = 397)
Perinatal data, % of infants				
Maternal hospitalization during pregnancy owing to maternal hypertension	17.8	16.9	17.2	20.9
Maternal smoking during pregnancy				
Smoking	16.2	15.7	15.1	20.0
Nonsmoking	78.6	76.5	81.7	74.1
No data	5.1	7.7	3.2	5.8
Birth weight in relation to gestational age				
<2 SDs below mean	27.8	28.1	27.3	28.5
Within 2 SDs of mean	69.8	69.7	70.5	68.3
>2 SDs above mean	2.4	2.2	2.2	3.3
No. of fetuses in a pregnancy				
1	71.5	71.9	67.6	81.9
2	25.5	27.3	27.2	17.9
3	3.0	0.9	5.3	0.3
Mode of delivery, cesarean sections[b]	32.6	30.3	35.4	28.7
Neonatal data				
Gestational age at birth, median (range), wk	30.3 (23.0-38.0)	30.1 (23.0-37.6)	30.0 (23.3-38.0)	31.1 (24.6-36.7)
Male sex, %	55.0	55.1	55.9	52.4
Birth weight, mean (SD),g	1278 (369)	1258 (367)	1234 (375)	1431 (312)
Nonlethal malformations, %	10.1	14.3	8.7	6.6
Data on the initial hospitalization period				
Median length, d	53	54	58	44
Gestational age at discharge, median (range), wk	38.0 (26.9-103.1)	38.0 (28.4-100.3)	38.1 (26.9-103.1)	37.6 (32.3-45.3)

[a]The groups are described in the footnote to Table 1.
[b]Data on the mode of delivery were missing from 1 infant in group III/II and 3 infants in group II.

These diagnostic entities were compared between the very preterm children divided into the following 3 groups: (1) those born and treated in level III hospitals (group III), (2) those born in level III hospitals and transferred during the initial care episode to level II or level I hospitals (group III/II), and (3) those born and treated in level II hospitals (group II) (**Table 1**).

The analyses were performed using multiple logistic regression models. Functional forms of continuous covariates were determined using multivariable model building with fractional polynomials.[18] The comparisons were adjusted for hospitalization during pregnancy due to maternal hypertension (yes or no), maternal smoking during pregnancy, intrauterine growth, multiple pregnancy (continuous; number of fetuses), mode of delivery (vaginal delivery or cesarean section), gestational age (second-degree fractional polynomial), birth weight (second-degree fractional polynomial), sex (male or female), and nonlethal malformations (yes or no). Intrauterine growth was categorized as less than 2 SDs below the mean birth weight for gestational age, within 2 SDs of the mean, and greater than 2 SDs above the mean according to sex-specific reference values from the Finnish population.[19] Because 118 very preterm children had missing data on maternal smoking, we classified the variable to 3 groups (smoking, nonsmoking, or no data) to be able to include these children in the multiple logistic regression analyses. Thus, very few data were missing in the multiple logistic regression; only 4 of the 2168 were excluded owing to missing data on mode of delivery.

If statistically significant associations were found between the level of treatment and the outcome, we extended the analysis to whether the association of the treatment hospital level and risk for morbidity differed between those born at a gestational age of less than 28 weeks and those born at 28 weeks or more. This risk was assessed by adding gestational age classification (<28 weeks or ≥28 weeks) and interaction between the classification and level of the treatment hospital to the previous model. In this analysis, groups II and III/II underwent separate assessment.

RESULTS

The overall mortality of the live-born very preterm infants was 11.9% (296 of 2495), and the median age of

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Table 3. Diagnoses Overrepresented in Very Preterm Children Compared With Full-Term Children Arranged Into 14 Groups of Diagnoses[a]

ICD-10 Code	*ICD-10* Diagnosis	No. (%) of Study Patients			
		All (N = 2168)	Group III (n = 686)	Group III/II (n = 1085)	Group II (n = 397)
Diagnoses likely to be influenced by the level of neonatal care					
F80	Disorders of speech	212 (10.0)	59 (8.6)	125 (11.5)	28 (7.1)
F82	Specific developmental disorder of motor function	207 (9.5)	59 (8.6)	124 (11.4)	24 (6.0)
F83	Mixed specific developmental disorders	155 (7.1)	56 (8.2)	67 (6.2)	32 (8.1)
H35	Retinal disorders (retinopathy of prematurity was diagnosed in 98% of these infants)	220 (10.1)	48 (7.0)	166 (15.3)	6 (1.5)
H50, H52, and H53	Strabismus, disorders of refraction and accommodation, amblyopia ex anopsia	391 (18.0)	142 (20.7)	190 (17.5)	59 (14.9)
G40	Epilepsy	63 (2.9)	15 (2.2)	31 (2.9)	17 (4.3)
G80	Cerebral palsy	109 (5.0)	33 (4.8)	56 (5.2)	20 (5.0)
F90	Hyperkinetic disorders	61 (2.8)	21 (3.1)	20 (1.8)	20 (5.0)
J45	Asthma	449 (20.7)	122 (17.8)	257 (23.7)	70 (17.6)
J15, J18, J20, J21, J22, J35, H65, H66, J03, J04, and J06	Upper and lower respiratory tract infections	1399 (64.5)	447 (65.2)	724 (66.7)	228 (57.4)
Any of the diagnoses likely to be influenced by the level of neonatal care		1631 (75.2)	514 (74.9)	846 (78.0)	271 (68.3)
Diagnoses overrepresented in preterm infants but not likely to be influenced by the level of neonatal care					
A08, A09, and B34	Gastroenteritis, viral infection of unspecified site	463 (21.4)	168 (24.5)	212 (19.5)	83 (20.9)
A10 and N39.0	Pyelonephritis, urinary tract infection of unspecified site	90 (4.2)	35 (5.1)	37 (3.4)	18 (4.5)
K40	Inguinal hernia	337 (15.5)	102 (14.9)	179 (16.5)	56 (14.1)
K59	Other functional intestinal diseases	113 (5.2)	35 (5.1)	59 (5.4)	19 (4.8)
Any of the abovementioned diagnoses		1760 (81.2)	561 (81.8)	889 (81.9)	310 (78.1)

Abbreviations: *ICD-10*, *International Statistical Classification of Diseases, 10th Revision*.
[a]Groups are described in the first footnote to Table 1. The cumulative 5-year incidence of these diagnoses is presented according to the study group.

death was 2 days. Of the 296 children who died, 281 died during the initial hospitalization, 9 were discharged but died before age 1 year, and 6 died at age 1 to 5 years. The mortality of the infants born in level III hospitals was 12.4% (250 of 2021) and the mortality of those born in level II hospitals was 10.4% (46 of 443). Altogether 1085 very preterm infants (50.0%) were transferred during the initial hospitalization period (Table 1), including 126 who were transferred more than once. The baseline characteristics for the very preterm infants in each study group are shown in **Table 2**. The 31 infants excluded owing to missing data were born at a median gestational age of 30.9 (range, 24.0-36.1) weeks and mean birth weight of 1536 (SD, 523) g.

Twenty-seven *ICD-10* codes were overrepresented in very preterm children compared with the full-term infants. These diagnoses were arranged into diagnostic groups, and the 5-year cumulative incidences of the diagnostic groups are shown in **Table 3**.

In the adjusted comparison with group III, infants in group II had an increased incidence of hyperkinetic disorders (including attention-deficit/hyperactivity disorder) (odds ratio [OR], 2.19 [95% CI, 1.13-4.25]) and epilepsy (2.71 [1.29-5.70]). Compared with group III, infants in group III/II had more retinal disorders (OR, 2.43 [95% CI, 1.66-3.56]) and asthma (1.41 [1.09-1.81]) but less gastroenteritis or unspecified viral infections (0.75 [0.59-0.95]). In addition, group III/II demonstrated a tendency toward decreased incidence of strabismus and other problems of vision (OR, 0.78 [95% CI, 0.60-1.00]) and hyperkinetic disorder (0.53 [0.28-1.00]) compared with group III. When the incidence of all diagnoses or of all diagnoses likely to be influenced by neonatal care were analyzed together, no statistically significant differences were found between the groups (**Table 4**).

The interaction between gestational age and study groups was statistically significant only in the incidence of retinal disorders ($P < .001$). In group III/II compared with group III, the risk for retinal disorders was increased in those born at a gestational age of at least 28 weeks (OR, 6.37 [95% CI, 3.00-13.51], and a tendency toward an increased risk for retinal disorders in those born at a gestational age of less than 28 weeks was seen (1.50

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Table 4. Adjusted ORs for the Comparison of Postdischarge Diagnoses Between the Study Groups[a]

	OR (95% CI)	
	Group III/II (n = 1084)	Group II (n = 394)
Diagnoses likely to be influenced by the level of neonatal care		
Disorders of speech	1.38 (0.99-1.92)	1.06 (0.66-1.73)
Specific developmental disorder of motor function	1.34 (0.95-1.87)	1.01 (0.60-1.68)
Mixed specific developmental disorders	0.72 (0.49-1.06)	1.60 (0.98-2.60)
Retinopathy of prematurity	2.43 (1.66-3.56)	0.45 (0.18-1.10)
Strabismus, disorders of refraction and accommodation, amblyopia ex anopsia	0.78 (0.60-1.00)	0.90 (0.63-1.27)
Epilepsy	1.44 (0.76-2.72)	2.71 (1.29-5.70)
Cerebral palsy	1.11 (0.71-1.74)	1.52 (0.84-2.76)
Hyperkinetic disorders	0.53 (0.28-1.00)	2.19 (1.13-4.25)
Asthma	1.41 (1.09-1.81)	1.36 (0.97-1.91)
Respiratory infections	1.07 (0.87-1.32)	0.94 (0.72-1.22)
Any of the diagnosis influenced by the level of neonatal care	1.18 (0.93-1.50)	0.97 (0.73-1.30)
Diagnoses overrepresented in preterm infants but not likely to be influenced by the level of neonatal care		
Gastroenteritis or unspecified viral infections	0.75 (0.59-0.95)	0.95 (0.70-1.30)
Pyelonephritis or urinary tract infection	0.73 (0.45-1.19)	0.99 (0.55-1.79)
Inguinal hernia	1.09 (0.82-1.44)	1.14 (0.77-1.67)
Functional intestinal diseases	1.11 (0.71-1.71)	1.16 (0.64-2.10)
Any of the abovementioned diagnoses	1.00 (0.77-1.29)	1.08 (0.78-1.50)

Abbreviation: OR, odds ratio.

[a] Groups are described in the first footnote to Table 1. Odds ratios were adjusted for hospitalization during pregnancy owing to maternal hypertension, maternal smoking during pregnancy, intrauterine growth, multiple pregnancy (number of fetuses), mode of delivery, gestational age, birth weight, sex, and nonlethal malformations. Group III was the reference group.

[0.94-2.39]). No statistically significant evidence of interaction between gestational age classification and study groups was found in any other diagnosis tested (eTable; http://www.jamapeds.com).

COMMENT

The incidence of hyperkinetic disorders and epilepsy were increased in very preterm infants born in level II hospitals compared with those born and treated in level III hospitals. Transfers from level III to level II hospitals after the initial intensive care period were associated with increased incidence of retinal disorders and asthma and with decreased risk for viral infections. However, in most diagnoses, no differences were found in the 5-year cumulative incidence according to the level of the birth and treatment hospitals.

This population-based study included a national cohort of very preterm children and full-term control children with register data, allowing a comprehensive comparison of different ways of organizing the initial care of very preterm infants. The extensive data of the National Birth Register have been shown to be reliable.[20] Linking the Birth Register to the Cause of Death Register and the Register of Congenital Malformations further enhanced the reliability of the data and allowed a more extensive use of background variables in the adjustments. The coverage of the register was excellent, and the amount of missing data was very small. The diagnoses reported to the Hospital Discharge Register have been shown to agree well with diagnoses reported by the parents of 5-year-old very preterm children.[6]

Because the number of infants transferred from level II to level III (n = 29) or to level I (n = 9) hospitals were very small, these groups were not analyzed. Preterm infants transferred from level II to level III hospitals are likely to be sicker than the rest of the preterm infants born in level II hospitals. Excluding them may work in favor of level II hospitals in our study because such transfers of the sickest infants are not an option in level III hospitals. On the other hand, obstetrical data on preeclampsia and the administration of antenatal corticosteroids were not reported reliably in the registers and were not included in the adjustments. Infants born in circumstances in which these data were not reported reliably may have been sicker than others. The lowest gestational age groups born in level II hospitals might be accidental emergency deliveries. Therefore, these very preterm children may lack the benefit of antenatal corticosteroids. This lack may partly explain the increase in the incidence of asthma, cerebral palsy, and epilepsy in those infants born in level II hospitals. However, the same increases were seen in infants born at gestational ages of 28 weeks or more.

Socioeconomic status was not controlled for in the analyses in our study. Although socioeconomic status in Finland is fairly uniform, it may affect the development of attention-deficit/hyperactivity disorder, for example. In Finland, however, the socioeconomic level does not determine the hospital level in which the preterm infants receive care.

The diagnoses were selected from the extensive register data by comparing very preterm infants with full-term infants born healthy to achieve objective outcome

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selection. Selecting the diagnoses overrepresented in very preterm infants naturally results in including such diagnoses that might be influenced by the level of neonatal care and diagnoses that are not influenced by neonatal care. In addition, some diagnoses influenced by neonatal care may be missing from this list if they are not overrepresented in very preterm infants. Because multiple comparisons were made, a risk for the occurrence of type I error exists. However, to avoid this risk, a more stringent *P* value of less than .01 was used in the comparisons between very preterm and full-term children.

The present study showed an increased incidence of epilepsy and hyperkinetic disorders in very preterm children in group II compared with group III; both conditions are known to be associated with neurologic dysfunction. This difference may be related to several mechanisms in neonatal care, such as nutrition,[21] respiratory support,[22] and infection control.[23] We did not find evidence that the association between treatment at a level II hospital and these outcomes would differ by gestational age. Although a trend of increased incidence of cerebral palsy and developmental disorders was also seen in group II compared with group III, no differences between these groups were found in the rest of the outcomes.

We assume that infants born in level III hospitals receive the most optimal initial care. The increased incidence of retinal disorders in very preterm infants transferred from level III to level II hospitals may reflect differences in the treatment policies in, for example, oxygen use and nutritional practices between level III and level II hospitals in Finland. A recent meta-analysis has shown that the risk for severe retinopathy of prematurity is reduced with treatment targeted to low oxygen saturation levels (76%-96%) during the first weeks of life and high oxygen saturation levels (>94% to 99%) at 32 weeks or more of postmenstrual age.[24] These 2 different oxygen saturation effects may be related to the 2-phased pathogenesis of retinopathy of prematurity. In the first phase, from birth to 30 to 32 weeks of age, hyperoxia suppresses normal vessel growth in the retina; in the second phase, from about 32 to 34 weeks of age, hypoxia causes pathologic neovascularization through increased vascular endothelial growth factor expression.[24-26] Furthermore, hyperglycemia and insulin treatment during the neonatal intensive care unit stay and slow growth rate previously have been shown to increase the incidence of retinopathy of prematurity.[27] Because the median age at transfer was less than 3 weeks in our study, most of the transferred infants were treated in level II or level I hospitals during the second phase of development in retinopathy of prematurity. The increase in the incidence of retinopathy of prematurity even at a gestational age of 28 weeks or more emphasizes the importance of optimizing these treatments also in more mature very preterm infants. The severity of retinopathy of prematurity could not be assessed because stage data were not available in the registers. In addition, some data on retinal disorders may be missing from the registers if follow-up by the ophthalmologist ends before the discharge home. Transfers to lower-level hospitals are needed because of bed shortages in level III hospitals and to provide care closer to home. Therefore, we should evaluate the treatment strategies in lower-level hospitals to achieve levels of retinopathy of prematurity comparable to those of level III hospital care. Altogether, the costs and benefits of transfer to a lower-level hospital should be evaluated.

CONCLUSIONS

Although no differences in most long-term diagnoses were found, transfer from level III to lower-level hospitals seems to be associated with an increased risk for retinal disorders and asthma among very preterm children. In addition, increased incidence of epilepsy and hyperkinetic disorders was seen in very preterm children born in level II compared with those born in level III hospitals. This finding warrants further evaluation of treatment policies, such as oxygen use and nutritional care, in level II hospitals in Finland.

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