0031-3998/01/4903-0388
PEDIATRIC RESEARCH
Vol. 49, No. 3, 2001
Printed in U.S.A.

Hypocarbia during the First 24 Postnatal Hours and White Matter Echolucencies in Newborns ≤28 Weeks Gestation

OLAF DAMMANN, ELIZABETH N. ALLRED, KARL C.K. KUBAN, LINDA J. VAN MARTER, JANE E. STEWART, MARCELLO PAGANO, AND ALAN LEVITON
FOR THE DEVELOPMENTAL EPIDEMIOLOGY NETWORK INVESTIGATORS

Neuroepidemiology Unit, CA 505, Children's Hospital, Boston, Massachusetts 02115, U.S.A. [O.D., E.N.A., A.L.]; Pediatric Neurology, New England Medical Center, Boston, Massachusetts 02111, U.S.A. [K.C.K.K.]; Hunnewell 438, Children's Hospital, Boston, Massachusetts 02115, U.S.A. [L.J.V.M.]; Neonatal-Perinatal Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts 02215, U.S.A. [J.E.S.]; and Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts 02115, U.S.A. [M.P.]

ABSTRACT

The purpose of the present study was to test the hypothesis that newborns ≤28 wk gestation who have a Pco_2 measurement in the lowest gestational age-specific quartile (hypocarbia) on the first day of life are not at increased risk for ultrasonographic white matter echolucency (EL) after adjustment for confounders. The sample consisted of 799 infants ≤28 wk gestation born during 1991–1993. Forty-eight infants with EL were classified as cases and compared with 751 controls, *i.e.* those without EL. We performed univariable comparisons, stratified analyses, and multivariable logistic regression. In the univariable analyses, hypocarbia on the first day of life was associated with an increased EL risk. The odds ratios for the hypocarbia-EL relationship were prominently elevated in the strata of infants who did not have other major risk factors for EL (*e.g.* gestational age 26–28 wk, normothyroxinemia, no characteristics of antenatal infection). In the multivariable analyses, the association diminished after adjustment with a hypocarbia propensity score (odds ratio = 1.7; 95% confidence interval, 0.8–3.2) or with potential confounders. **(*Pediatr Res* 49: 388–393, 2001)**

Abbreviations

$Paco_2$, partial pressure of arterial carbon dioxide
MAP, mean arterial pressure
OR, odds ratio
EL, echolucency
PVL, periventricular leukomalacia
WMD, white matter damage

White matter EL predicts spastic cerebral palsy among preterm very-low-birth-weight infants (1–3). Among the risk factors we previously found for EL are subnormal neonatal thyroid hormone levels (4), absence of antenatal exposure to corticosteroid (5), and inflammation of the fetal vessels in the chorionic plate or umbilical cord (fetal vasculitis) (6). Although hypoxia-ischemia is a causative factor in controlled experimental settings (7, 8), its role as a risk factor for EL in preterm infants is less clear (9).

Extremely low carbon dioxide levels appear to be associated with an increased risk for ultrasound-defined WMD (10–15) and cerebral palsy (16, 17). Many of these studies, however, suffer from small numbers and/or the lack of adjustment for potential confounders in multivariable analyses. In the present study, we compared the occurrence of hypocarbia among 48 infants with ultrasonographic EL to that among 751 infants who did not have EL. Our study has the advantages of large size (n = 799), detailed high-quality data about outcome and many antecedents, and the use of a propensity score to adjust for antecedents of hypocarbia.

METHODS

Permission. The present study was approved by the Institutional Review Boards of all participating centers. Written informed consent was obtained before enrollment of an infant was initiated.

Sample. The multicenter cohort that provided the study population for these analyses enrolled 1607 very-low-birth-weight infants (500–1500 g) born January 1, 1991 through December 31, 1993 at five medical centers in the cities of

Received May 3, 2000; accepted July 19, 2000.
Correspondence: Olaf Dammann, M.D., Neuroepidemiology Unit, CA 505, Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, U.S.A.
Supported by United Cerebral Palsy Research and Educational Foundation (R-712-96, EH-003-98) and NIH (NS 27306).

Boston, MA, New York City, NY, and New Brunswick, NJ, who had at least one of three cranial ultrasound scans at times established by the study design (4–6, 18–21). Infants with major malformations were excluded.

Defining preterm populations by birth weight rather than gestational age results in an overrepresentation of growth-restricted infants at older gestational ages (22). To minimize this bias, we limited these analyses to infants whose gestational age was ≤ 28 completed wk (n = 799).

Data collection. We used standardized data collection forms for the documentation of pre- and postnatal exposures and ultrasound (*i.e.* outcome) findings. The infant's sociodemographic characteristics, mother's characteristics and exposures during pregnancy, events leading to preterm delivery, and labor and delivery characteristics were collected by interview of the mother and from detailed review of medical records.

Ultrasound data. Manuals were created to standardize the ultrasound-scanning procedure and the interpretation of scans. The six standard coronal views were those recommended by Teele and Share (23). The five sagittal views include the midline, each lateral ventricle, and lateral to each lateral ventricle. Protocol scans were obtained once during the first 4 postnatal d (median = d 1), once between postnatal d 5–15 (median = d 7), and once between d 15 and 60 (median = d 21). The first protocol cranial ultrasound set of scans was available for 766 infants, the second set for 688, and the third set for 637.

Each set of scans was read independently by two sonologists. Scans were brought to a consensus committee if either reader identified an EL anywhere in the cerebral white matter. The definite diagnosis of EL required consensus among a minimum of three sonologists reading together about the presence, size, and location of all hypoechoic white matter abnormalities.

Hypocarbia. The lowest Pco_2 on postnatal d 1 in an arterial or capillary serum sample was the basis for our definition of hypocarbia. Because Pco_2 on d 1 increases with increasing gestational age (Fig. 1), we created a Z score for the lowest Pco_2 that adjusts for completed weeks of gestation. This was achieved by subtracting the gestational age-specific median from each child's Pco_2 and dividing the resulting number by the gestational age-specific SD of Pco_2. We then defined those infants in the lowest Z-score quartile as hypocarbic. Thereby, an infant needed to be below the solid line in the Figure to be classified as having been exposed to hypocarbia. Infants above the solid line were classified as not exposed, including infants between the two lines who would have been classified as exposed had we used a fixed cutoff value of Pco_2 for exposure definition, for example, 30 mm Hg (dashed line, Fig. 1).

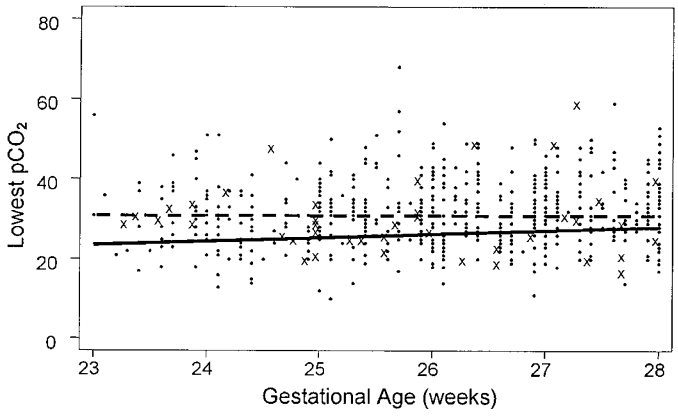

Figure 1. The lowest carbon dioxide measurement on postnatal d 1 in 799 preterm infants plotted against gestational age. The *solid line* indicates the Pco_2 level separating the lowest from the three upper Pco_2 quartiles. The *dashed line* defines Pco_2 <30 mm Hg. The symbol *x* indicates infants with white matter EL on neonatal cranial ultrasound. *Dots* represent individual control infants or control infants sharing the same gestational age and Pco_2

Potential confounders. Gestational age was defined by antenatal ultrasound (33%), dates (64%), or examination in the delivery suite (3%). The birth weight distribution within each gestational age week was normalized using a Z score. A birth weight Z score of < -1 indicates a birth weight more than 1 SD below the gestational age-specific median. Antenatal magnesium sulfate, corticosteroid, and antibiotic therapy were recorded as present or absent. Chorioamnionitis was defined as the presence of polymorphonuclear leukocytes in the chorion or chorioamnion. Fetal vasculitis is a morphologic characteristic of a fetal inflammatory response we define as polymorphonuclear leukocytes in the wall of a blood vessel in the umbilical cord or chorionic plate (6).

We calculated the lowest MAP using the following formula: lowest MAP = lowest diastolic blood pressure + (pulse pressure/3), where the pulse pressure = lowest systolic pressure − lowest diastolic pressure. We created a Z score for the lowest MAP among infants classified by their completed weeks of gestation. This was achieved by subtracting the gestational age-specific median from each child's MAP and dividing the resulting number by the gestational age-specific SD of MAP. We finally defined those infants in the lowest epoch-specific MAP Z-score quartile as hypotensive. The administration of vasopressors and volume expanders was included as either present or absent. A neonatal white blood cell count <6000 was defined as leukopenia. Hypothyroxinemia of prematurity was defined as a neonatal total thyroxine serum value <5.3 μg/dL, the cutoff between the lowest quartile and the remainder of our entire sample (4).

Hypothesis. The main null hypothesis of this study is that infants with EL are no more likely than those without EL to be exposed to hypocarbia during the first 24 h of life.

Specific analytic issues. All 47 infants with EL (cases) were compared with 751 without EL (controls). Infants who had an echodensity were excluded if they had no EL and no later ultrasound scan to establish that the echodensity either disappeared (so they could be considered controls) or became an EL (so they could be considered cases).

In our exploratory analyses, exposure to hypocarbia was more frequent among infants with EL only on the first day of life but not later (Table 1). We, therefore, did not include exposure information from later time points.

We compared the prevalence of potential confounders among cases and controls. We considered confounders to be those variables that were unequally distributed ($p \leq 0.3$) (24) among infants classified by exposure (hypocarbia) and by

Table 1. *Prevalence (column percent) of hypocarbia among infants with and without white matter EL on d 1, d 2–4, and d 5–7*

	White matter EL		
Hypocarbia on d	Yes (max. $n = 48$)	No (max. $n = 751$)	p
1	36	23	0.02
2–4	25	25	0.56
5–7	21	26	0.29

outcome (EL) and unlikely to be situated on the presumed causal pathway from hypocarbia to EL.

Hypocarbia may be a marker of an antecedent (*e.g.* mechanical ventilation leading to hypocarbia; see Table 2). To avoid attributing to hypocarbia what may more appropriately be attributed to its antecedents, which include medical care decisions, we created a propensity score (25) for hypocarbia. In brief, we fit a logistic regression model that predicted hypocarbia, including the antecedent variables associated with hypocarbia on the univariable level with a p value ≤ 0.3 (24). These were gestational age <26 wk, birth-weight Z score < -1, male sex, maternal receipt of antenatal magnesium sulfate, initiator of preterm delivery, labor >12 h, rupture of membrane >24 h, maternal leukocytosis, antenatal antibiotic treatment, mechanical ventilation, systemic hypotension on d 1, neonatal leukopenia on d 1, neonatal hypothyroxinemia, and administration of volume expanders and/or vasopressors on d 1 (see Tables 3–5). The propensity score is the predicted probability of hypocarbia based on the model. We used this score as a covariable with hypocarbia in multivariable logistic regression models predicting EL. We also created logistic regression models using different sets of individual confounders instead of the propensity score.

With a sample size of 799 infants, an estimated exposure prevalence of 25% among controls (*e.g.* the lowest quartile of Pco_2), and 48 infants with EL, our analyses have a statistical power of 93% to detect a doubling in EL risk with hypocarbia.

Terminology. Some investigators use terms such as IVH grade IV, cystic PVL, or even ischemic lesions for ultrasound findings. We prefer the umbrella term EL to avoid any *a priori* attribution of pathologic diagnoses or etiologic inferences to sonographic findings (9, 26).

We use the term Pco_2 for carbon dioxide values from our study. When referring to the work of others, we use either Pco_2 or $Paco_2$ in accordance with the other authors' terminology.

RESULTS

On the first day of life, 36% of infants with EL had hypocarbia compared with 23% of those without (Table 1). The finding that later hypocarbia was not associated with EL prompted us to focus on the first day of life in all further analyses.

Table 2. *Percent of infants with white matter EL on d 1 among 799 infants ≤28 wk gestation in groups of infants defined by the presence/absence of hypocarbia and mechanical ventilation*

		Hypocarbia on d 1	
		Yes	No
Ventilation	Yes	10 (167)	6 (427)
	No	0 (15)	2 (190)

No. in parentheses are the no. of infants in each of the four groups.

Of the 182 infants with hypocarbia, only 15 (8%) were not ventilated, and none of these infants had EL (Table 2). Among infants who were ventilated, hypocarbia appeared to increase the EL risk from 6 to 10%, whereas the EL risk was appreciably lower among nonventilated infants.

Gestational age and male sex were the only infant characteristics related to both hypocarbia and EL with a p value ≤ 0.3 (Table 3). The only obstetric, maternal, and placental variables identified as potential confounders were duration of labor >12 h and maternal antenatal antibiotic therapy (Table 4). The major postnatal characteristics associated with both hypocarbia and EL were mechanical ventilation, hypotension, hypothyroxinemia, and volume expander/vasopressor treatment (Table 5).

In the total sample of infants ≤28 wk, hypocarbia was associated with a 90% EL risk increase in the univariable analysis and with a 70% risk increase when we adjusted with the propensity score (Table 6). Adjustment for individual confounders and the propensity score or for sets of confounders without the score did not reduce the OR appreciably below 1.7 (data not shown). In high-risk strata (*i.e.* among infants who were <26 wk or hypothyroxinemic or exposed to antenatal antibiotic treatment), the risk for EL after hypocarbia was not increased. On the other hand, it was tripled in the corresponding low-risk strata. It was also increased approximately 2-fold in one high-risk stratum of infants who received volume expanders or vasopressors.

DISCUSSION

In univariable analyses and in strata of infants at otherwise low risk for EL, hypocarbia appeared to be a significant risk factor for EL. Because unadjusted prevalences of EL led to the impression that some antecedents of hypocarbia (*e.g.* ventilation) are more important than hypocarbia in distinguishing who develops white matter EL (Table 2), we adjusted for a propensity score derived from variables that predict hypocarbia.

Propensity scores are used in observational studies to adjust for nonrandom treatment allocations (25). We adjusted for nonrandomly occurring differences in background variables associated with hypocarbia because hypocarbia is closely related to a nonrandomly allocated treatment, *i.e.* ventilation. By reducing 14 antecedents of hypocarbia to one summary score, we also reduced the degrees of freedom in our logistic regression model.

The resulting multivariable risk estimate is relatively small (OR = 1.7) and not statistically significant (95% confidence interval, 0.8–3.2). However, our finding of an OR of 1.7 may be real whether statistically significant or not. Thus, there could be a 60 to 70% risk increase we cannot explain away using the antecedent variables we have at hand. This would leave us with the challenge of explaining how hypocarbia may be associated with EL.

First, there may be a causal relationship. In experimental models, decreases in systemic Pco_2 levels are associated with decreased cerebral blood flow, which in turn has been sug-

Table 3. *Infant characteristics (column percents) among infants ≤28 wk (n = 799) classified by hypocarbia and by white matter EL*

Characteristic	maximum *n*	Hypocarbia Yes (182)	Hypocarbia No (617)	*p*	White matter EL Yes (48)	White matter EL No (751)	*p*
White matter EL		9	5	0.03			
Pco2 in lowest gestational age-specific quartile					35	22	0.03
Pco2 <30 mm Hg					60	37	0.001
Gestational age <26 wk		31	35	0.15	52	33	0.007
Birth weight *Z* score <−1		25	17	0.01	19	19	0.58
Male		49	53	0.16	46	53	0.21
Singleton		72	74	0.37	83	73	0.07

Table 4. *Obstetric, maternal, and placenta characteristics (column percents) among infants <28 wk (n = 799) classified by hypocarbia and by white matter EL*

Characteristic	maximum *n*	Hypocarbia Yes (182)	Hypocarbia No (617)	*p*	White matter EL Yes (48)	White matter EL No (751)	*p*
Antenatal magnesium sulfate		49	46	0.24	44	46	0.42
Any antenatal corticosteroids		53	50	0.37	29	52	0.001
Initiator of delivery							
Preterm labor		49	45	0.06	46	46	0.99
Premature rupture of membranes		31	31		33	31	
Toxemia / PIH*		14	11		10	11	
Other		7	14		10	12	
Duration of labor >12 h		36	29	0.06	38	30	0.16
Duration of membrane rupture > 24 h		32	27	0.14	31	28	0.39
Cesarean section delivery		56	57	0.41	42	58	0.02
Maternal fever > 100.4°F		28	30	0.31	40	29	0.09
Maternal white blood cell count > 20 k		25	23	0.28	27	23	0.32
Maternal antibiotic therapy		42	46	0.23	52	45	0.19
Any chorioamnionitis		61	59	0.40	70	59	0.16
Fetal vasculitis		42	43	0.53	60	42	0.04

* PIH, pregnancy-induced hypertension

Table 5. *Postnatal characteristics (column percents) among infants ≤28 wk (n = 799) classified by hypocarbia and by white matter EL*

Characteristic	maximum *n*	Hypocarbia Yes (182)	Hypocarbia No (617)	*p*	White matter EL Yes (48)	White matter EL No (751)	*p*
Mechanical ventilation		92	69	<.001	90	73	0.007
Lowest MAP <23 mm Hg		36	36	0.51	47	35	0.08
Lowest MAP in lowest gestational age-specific quartile		28	25	0.28	32	26	0.22
Leukopenia (WBC < 6 K)		27	24	.17	26	24	.49
Highest Pco2 > 60 mm Hg		15	26	.001	21	24	.38
Highest Pco2 in highest gestational age-specific quartile		14	28	<.001	21	25	.32
Hypothyroxinemia		32	36	.21	55	33	.005
Volume expander or vasopressor		75	52	<.001	73	56	.01

gested as a risk factor for brain abnormalities (27). Second, hypocarbia may be a marker for a risk factor we did not measure. The strong association of hypocarbia with variables of intervention (mechanical ventilation, vasopressor or volume expander treatment) suggests that hypocarbia may be a measure of illness severity, which in turn may be either a cause or a marker of WMD.

As always, some stratified analyses suffer from small numbers more than others. However, in some strata, the association between hypocarbia and EL was statistically significant. Some of these were in strata of infants who may be considered at lower overall risk than their peers in the counterstratum (>26 wk gestational age, normothyroxinemic, and infants not exposed to antenatal antibiotic treatment). Here, the concept of competing risks may apply. In short, only if an infant is not at risk for some other reason may he be at increased risk for EL due to hypocarbia.

The only other stratum in which hypocarbia was associated with a significantly increased EL risk was the one characterized by the receipt of volume expanders or vasopressors. This finding is not consistent with a competing-risks hypothesis because infants with white matter EL were more likely than controls to be exposed to volume expanders or vasopressors (Table 5). Unfortunately, we lack information about the hypo-

Table 6. *Unstratified and stratified analyses among infants ≤28 wk (n = 799)*

		OR (95%, CI)	
		Crude	Adjusted*
UNSTRATIFIED		1.9 (1.05–3.6)	1.7(0.8–3.2)
STRATIFIED			
Gestational age <26 wk	yes	1.3 (0.5–3.3)	1.0 (0.3–2.8)
	no	3.1 (1.3–7.2)	2.6 (1.0–6.7)
Any antenatal corticosteroid	yes	1.8 (0.6–5.6)	1.5 (0.4–5.0)
	no	2.1 (.98–4.4)	1.6 (0.7–3.6)
Fetal vasculitis	yes	1.5 (0.5–4.5)	1.0 (0.3–3.6)
	no	2.0 (0.6–6.8)	3.2 (0.8–13)
Hypothyroxinemia	yes	1.2 (0.4–3.8)	1.6 (0.6–4.4)
	no	3.8 (1.7–8.6)	3.1 (1.1–8.9)
Volume expanders or vasopressors	yes	2.4 (1.2–4.8)	2.3 (1.1–4.7)
	no	‡	‡
MAP in lowest gestational age-specific quartile	yes	2.1 (0.7–6.2)	3.0 (0.9–10)
	no	1.8 (0.9–3.9)	1.3 (0.6–3.0)
Female	yes	2.0 (0.9–4.7)	2.1 (0.9–5.3)
	no	1.8 (0.7–4.5)	1.0 (0.4–2.9)
Any antenatal antibiotic	yes	1.2 (0.4–3.0)	0.9 (0.3–2.9)
	no	3.1 (1.3–7.3)	2.7 (1.1–6.6)
Mechanical ventilaton	yes	1.7 (0.9–3.3)	1.7 (0.9–3.4)
	no	‡	‡

Strata are defined by the presence or absence of the characteristics on the left. All OR and 95% confidence intervals (CI) are for hypocarbia predicting white matter EL.

* Multivariable models adjusting with a propensity score for hypocarbia.

‡ Calculation not possible.

carbia-EL relationship in the counterstratum.

Previous reports on the relationship between hypocarbia and cerebral WMD or its correlates are of considerable heterogeneity regarding sample definition and size, definition of hypocarbia, and analytic methods. Initially, studies were small and did not use multivariable techniques (10, 16). Most subsequent studies were larger (11–13), but still no multivariable data analyses were reported by some (13). Hypocarbia was a risk factor for PVL in some (14) but not all studies of high-frequency jet ventilation (15, 28).

Case reports such as one reporting tachypnea after extubation in a child who later developed PVL (29) do not allow for any causal inference. The interesting question remains, why do infants hyperventilate after extubation? Salokorpi *et al*. (17) recently reported that a $Paco_2$ <3 kPa (25 mm Hg) on two occasions during the first 3 wk of life was associated with a (statistically insignificant) doubling of cerebral palsy risk, but no multivariable analyses were offered.

Strengths and limitations. Among the strengths of our study are the large sample, the data quality, the use of a gestational age-specific definition of hypocarbia, and the use of a hypocarbia propensity score in multivariable models. Among the disadvantages are the use of Pco_2 values from different sources (*i.e.* arterial, venous, and capillary serum samples) and the availability of only one (the lowest) Pco_2 value obtained on the first postnatal day.

CONCLUSION

After adjustment with a propensity score, hypocarbia on the first day of life was not associated with a significant risk increase for EL among preterm infants ≤28 wk gestation. The modestly increased risk (OR 1.7) may indicate either a true causal effect of hypocarbia or that hypocarbia is a marker for other risk factors or even causes of EL.

APPENDIX

The Developmental Epidemiology Network Investigators Executive Committee: Alan Leviton, Nigel Paneth, M. Lynne Reuss, Mervyn Susser; Neonatology Committee: Thomas Hegyi, Mark Hiatt, Ulana Sanocka, Farrokh Shahrivar, Linda J. Van Marter; Ultrasound Committee: Michael Abiri, Donald DiSalvo, Peter Doubilet, Ram Kairam, Elias Kazam, Madhuri Kirpekar, David Rosenfeld, Steven Schonfeld, Jane Share; Placenta Pathology Committee: Petra Banogan, Margaret Collins, David Genest, Debra Heller, Susan Shen-Schwarz; and Data Analysis Committee: Elizabeth N. Allred, Olaf Dammann, Karl C.K. Kuban, Alan Leviton, Marcello Pagano.

REFERENCES

1. Allan WC, Vohr B, Makuch RW, Katz KH, Ment LR 1997 Antecedents of cerebral palsy in a multicenter trial of indomethacin for intraventricular hemorrhage. Arch Pediatr Adolesc Med 151:580–585
2. Aziz K, Vickar DB, Sauve RS, Etches PC, Pain KS, Robertson CM 1995 Province-based study of neurologic disability of children weighing 500 through 1249 grams at birth in relation to neonatal cerebral ultrasound findings. Pediatrics 95:837–844
3. Pinto-Martin JA, Riolo S, Cnaan A, Holzman C, Susser MW, Paneth N 1995 Cranial ultrasound prediction of disabling and nondisabling cerebral palsy at age two in a low birth weight population. Pediatrics 95:249–254
4. Leviton A, Paneth N, Reuss ML, Susser M, Allred EN, Dammann O, Kuban K, Van Marter LJ, Pagano M 1999 Hypothyroxinemia of prematurity and the risk of cerebral white matter damage. J Pediatr 134:706–711
5. Leviton A, Dammann O, Allred EN, Kuban KCK, Pagano M, Van Marter LJ, Paneth N, Reuss ML, Susser M 1999 Antenatal corticosteroids and cranial ultrasound abnormalities. Am J Obstet Gynecol 181:1007–1017
6. Leviton A, Paneth N, Reuss ML, Susser M, Allred EN, Dammann O, Kuban K, Van Marter LJ, Pagano M, Hegyi T, Hiatt M, Sanocka U, Shahrivar F, Abiri M, DiSalvo D, Doubilet P, Kairam R, Kazam E, Kirpekar M, Rosenfeld D, Schonfeld S, Share J, Collins M, Genest D, Heller D, Shen-Schwarz S 1999 Maternal infection, fetal inflammatory response, and brain damage in very low birth weight infants. Developmental Epidemiology Network Investigators. Pediatr Res 46:566–575

7. Yoshioka H, Goma H, Nioka S, Ochi M, Miyake H, Zaman A, Masumura M, Sawada T, Chance B 1994 Bilateral carotid artery occlusion causes periventricular leukomalacia in neonatal dogs. Brain Res Dev Brain Res 78:273–278
8. Uehara H, Yoshioka H, Kawase S, Nagai H, Ohmae T, Hasegawa K, Sawada T 1999 A new model of white matter injury in neonatal rats with bilateral carotid artery occlusion. Brain Res 837:213–220
9. Kuban KC 1998 White-matter disease of prematurity, periventricular leukomalacia, and ischemic lesions. Dev Med Child Neurol 40:571–573
10. Calvert SA, Hoskins EM, Fong KW, Forsyth SC 1987 Etiological factors associated with the development of periventricular leukomalacia. Acta Paediatr Scand 76:254–259
11. Graziani LJ, Spitzer AR, Mitchell DG, Merton DA, Stanley C, Robinson N, McKee L 1992 Mechanical ventilation in preterm infants: neurosonographic and developmental studies. Pediatrics 90:515–522
12. Ikonen RS, Janas MO, Koivikko MJ, Laippala P, Kuusinen EJ 1992 Hyperbilirubinemia, hypocarbia, and periventricular leukomalacia in preterm infants: relationship to cerebral palsy. Acta Paediatr 81:802–807
13. Fujimoto S, Togari H, Yamaguchi N, Mizutani F, Suzuki S, Sobajima H 1994 Hypocarbia and cystic periventricular leukomalacia in premature infants. Arch Dis Child 71:F107–F110
14. Wiswell TE, Graziani LJ, Kornhauser MS, Stanley C, Merton DA, McKee L, Spitzer AR 1996 Effects of hypocarbia on the development of cystic periventricular leukomalacia in premature infants treated with high-frequency jet ventilation. Pediatrics 98:918–924
15. Keszler M, Modanlou HD, Brudno DS, Clark FI, Cohen RS, Ryan RM, Kaneta MK, Davis JM 1997 Multicenter controlled clinical trial of high-frequency jet ventilation in preterm infants with uncomplicated respiratory distress syndrome. Pediatrics 100:593–599
16. Greisen G, Munck H, Lou H 1987 Severe hypocarbia in preterm infants and neurodevelopmental deficit. Acta Paediatr Scand 76:401–404
17. Salokorpi T, Rajantie I, Viitala J, Rita H, von Wendt L 1999 Does perinatal hypocarbia play a role in the pathogenesis of cerebral palsy? Acta Paediatr 88:571–575
18. Leviton A, Paneth N, Susser M, Reuss ML, Allred EN, Kuban K, Sanocka U, Hegyi T, Hiatt M, Shahrivar F, Van Marter LJ 1997 Maternal receipt of magnesium sulfate does not seem to reduce the risk of neonatal white matter damage. Pediatrics 99:E2
19. Kuban K, Sanocka U, Leviton A, Allred EN, Pagano M, Dammann O, Share J, Rosenfeld D, Abiri M, DiSalvo D, Doubilet P, Kairam R, Kazam E, Kirpekar M, Schonfeld S 1999 White matter disorders of prematurity: association with intraventricular hemorrhage and ventriculomegaly. The Developmental Epidemiology Network. J Pediatr 134:539–546
20. Hansen A, Leviton A 1998 The correlation between placental pathology and intraventricular hemorrhage in the preterm infant. Developmental Epidemiology Network Investigators. Pediatr Res 43:15–19
21. Hansen A, Leviton A 1999 Labor and delivery characteristics and risks of cranial ultrasonographic abnormalities among very-low-birth-weight infants. The Developmental Epidemiology Network Investigators. Am J Obstet Gynecol 181:997–1006
22. Arnold CC, Kramer MS, Hobbs CA, McLean FH, Usher RH 1991 Very low birth weight: a problematic cohort for epidemiologic studies of very small or immature neonates. Am J Epidemiol 134:604–613
23. Teele R, Share J 1991 Ultrasonography of Infants and Children. Saunders, Philadelphia, pp 1–5
24. Dales LG, Ury HK 1978 An improper use of statistical significance testing in studying covariables. Int J Epidemiol 7:373–375
25. Rubin DB 1997 Estimating causal effects from large data sets using propensity scores. Ann Intern Med 127:757–763
26. Paneth N 1999 Classifying brain damage in preterms. J Pediatr 134:527–529
27. Greisen G 1997 Cerebral blood flow and energy metabolism in the newborn. Clin Perinatol 24:531–546
28. Wiswell TE, Graziani LJ, Kornhauser MS, Cullen J, Merton DA, McKee L, Spitzer AR 1996 High-frequency jet ventilation in the early management of respiratory distress syndrome is associated with a greater risk for adverse outcomes. Pediatrics 98:1035–1043
29. Kubota M, Matsuda F, Hashizume M, Nakamura T, Nishida A 1996 Periventricular leukomalacia associated with hypocarbia. Acta Paediatr Jpn 38:57–60