Antenatal Antecedents of Cognitive Impairment at 24 Months In Extremely Low Gestational Age Newborns

WHAT'S KNOWN ON THIS SUBJECT: Among extremely premature infants, survival has improved, but the rate of cognitive impairment has not. Impaired cognition is the most frequent developmental problem identified in survivors. Several antenatal factors have been associated with cognitive impairment, mostly related to social disadvantage.

WHAT THIS STUDY ADDS: In addition to social disadvantage, antenatal characteristics associated with cognitive impairment include maternal obesity and thrombosis of fetal stem vessels. Prenatal infection and inflammation were not associated with impaired early cognitive function among extremely preterm infants.

AUTHORS: Jennifer B. Helderma, MD, MS,^a Thomas M. O'Shea, MD, MPH,^a Karl C. K. Kuban, MD, SMEpi,^b Elizabeth N. Allred, MS,^c Jonathan L. Hecht, MD, PhD,^d Olaf Dammann, MD,^e Nigel Paneth, MD, MPH,^f T. F. McElrath, MD, PhD,^g Andrew Onderdonk, PhD,^h and Alan Leviton, MD,^c for the ELGAN study Investigators

^aDepartment of Pediatrics (Neonatology), Wake Forest University Health Sciences, Winston-Salem, North Carolina; ^bDepartment of Pediatrics (Pediatric Neurology), Boston Medical Center, Boston, Massachusetts; ^cNeuroepidemiology Unit, Children's Hospital of Boston, Boston, Massachusetts; ^dDepartment of Pathology, Beth Israel Deaconess Medical Center, Boston, Massachusetts; ^eDepartment of Public Health and Community Medicine, Tufts University School of Medicine, Boston, Massachusetts; ^fDepartments of Epidemiology and Pediatrics and Human Development, Michigan State University, East Lansing, Michigan; and ^gDivision of Maternal-Fetal Medicine, and ^hChanning Laboratory, Brigham and Women's Hospital, Boston, Massachusetts

KEY WORDS

prematurity, placenta, chorioamnionitis, fetal growth restriction, mental development

ABBREVIATIONS

BSID-II—Bayley Scales of Infant Development, second edition
CI—confidence interval
ELGAN—extremely low gestational age newborn
GMFCS—Gross Motor Function Classification System
MDI—Mental Development Index
OR—odds ratio

www.pediatrics.org/cgi/doi/10.1542/peds.2011-1796

doi:10.1542/peds.2011-1796

Accepted for publication Nov 9, 2011

Address correspondence to Jennifer B. Helderma, MD, MS, Department of Pediatrics, Wake Forest University Health Sciences, Medical Center Blvd, Winston-Salem, NC 27157. E-mail: jhelderm@wfubmc.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2012 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by a cooperative agreement with The National Institute of Neurologic Disorders and Stroke (NINDS) (5U01NS040069-05). Funded by the National Institutes of Health (NIH).

abstract

BACKGROUND AND OBJECTIVES: Extremely low gestational age neonates are more likely than term infants to develop cognitive impairment. Few studies have addressed antenatal risk factors of this condition. We identified antenatal antecedents of cognitive impairment determined by the Mental Development Index (MDI) portion of the Bayley Scales of Infant Development, Second Edition (BSID-II), at 24 months corrected age.

METHODS: We studied a multicenter cohort of 921 infants born before 28 weeks of gestation during 2002 to 2004 and assessed their placentas for histologic characteristics and microorganisms. The mother was interviewed and her medical record was reviewed. At 24 months adjusted age, children were assessed with BSID-II. Multinomial logistic models were used to estimate odds ratios.

RESULTS: A total of 103 infants (11%) had an MDI <55, and 99 infants (11%) had an MDI between 55 and 69. No associations were identified between organisms recovered from the placenta and developmental delay. Factors most strongly associated with MDI <55 were thrombosis of fetal vessels (OR 3.1; 95% confidence interval [CI] 1.2, 7.7), maternal BMI >30 (OR 2.0; 95% CI 1.1, 3.5), maternal education ≤12 years (OR 3.4; 95% CI 1.9, 6.2), nonwhite race (OR 2.2; 95% CI 1.3, 3.8), birth weight z score < -2 (OR 2.8; 95% CI 1.1, 6.9), and male gender (OR 2.7; 95% CI 1.6, 4.5).

CONCLUSIONS: Antenatal factors, including thrombosis of fetal vessels in the placenta, severe fetal growth restriction, and maternal obesity, convey information about the risk of cognitive impairment among extremely premature newborns. *Pediatrics* 2012;129:494–502

Among extremely low gestational age newborns (ELGANs), the survival rate improved during the 1990s, but the rate of low scores on assessments of cognition did not.^{1,2} Cognitive impairment is the most frequent developmental problem identified in extremely premature survivors.^{3–5} Impaired early cognitive function, assessed with the Bayley Scales of Infant Development (BSID), is moderately predictive of cognitive function at school age.⁶

Antenatal factors associated with cognitive limitations in ELGANs include unmarried mother,⁷ minority race,⁵ fewer years of education,⁵ lack of antenatal steroid exposure,^{5,8} maternal smoking during pregnancy,⁸ and pre-eclampsia.⁹ Most previous studies relied on samples defined by birth weight,^{10–15} which distorts associations with factors that influence birth weight,¹⁶ whereas some relied on small samples,^{9,11,17} and none focused on detailed data about prenatal factors.

METHODS

The ELGAN Study

The ELGAN study was designed to identify characteristics and exposures that increase the risk of structural and functional neurologic disorders in ELGANs.¹⁸ During 2002 to 2004, women delivering before 28 weeks of gestation at 1 of 14 participating institutions in 11 cities in 5 states were asked to enroll in the study. The enrollment and consent processes were approved by the individual institutional review boards.

Mothers were approached for consent either on antenatal admission or shortly after delivery, depending on clinical circumstance and institutional preference. A total of 1249 mothers of 1506 infants consented. Approximately 260 women were either missed or did not consent to participate.

Demographic and Pregnancy Variables

After delivery, a trained research nurse interviewed each mother in her native

language by using a structured data collection and following procedures contained in a manual. The mother's report of her own characteristics and

FIGURE 1

Study participants who contributed data to the present analysis among the 1506 newborns enrolled in the Extremely Low Gestational Age Newborn Study.

TABLE 1 Risks of MDI Scores Associated With Social and Demographic Characteristics of the Mother

Maternal Characteristics		<55	55–69	≥70	Row <i>N</i>
Racial identity	White	7	8	85	545
	Black	20	15	65	242
	Other	13	16	71	119
Hispanic	Yes	17	13	70	108
	No	11	10	79	808
Age	<21	14	12	74	125
	21–35	11	11	78	618
	>35	10	10	80	178
Years of education	<12	28	12	60	142
	12 (high school)	11	15	75	232
	>12 to <16	8	10	80	201
	16 (college)	7	6	86	176
	>16	4	8	88	138
Marital status	Single	16	14	70	379
	Married	8	9	83	542
Self and/or partner support	Yes	10	11	79	800
	No	20	11	69	101
Public insurance	Yes	17	15	69	336
	No	8	9	86	566
Pregpregnancy BMI	<18.5	9	6	85	66
	18.5 to <25	9	11	80	452
	25 to <30	11	9	80	183
	>30	16	14	70	184
Maximum number of infants		103	99	719	921
Percent		11	11	78	

These are row percents.

TABLE 2 Risks of MDI Scores Associated With Pregnancy Characteristics and Exposures During Pregnancy

Pregnancy Characteristics		<55	55–69	≥70	Row <i>N</i>
Smoking prepregnancy	Yes	14	12	75	212
	No	11	11	79	685
Smoking during pregnancy	Yes	12	15	73	117
	No	11	10	79	781
Passive smoking	Yes	14	9	77	212
	No	11	11	78	683
Years since last pregnancy	<1	8	15	77	107
	1–2	14	15	71	144
	2+	15	12	73	267
Conception assistance	Yes	6	8	87	197
	No	13	12	75	698
No. of prenatal visits	10+	9	14	77	619
	< 10	12	10	78	273
Vaginal bleeding during 1st 12 wk	Yes	9	11	80	361
	No	13	11	76	534
Vaginal bleeding after 12 wk	Yes	8	11	81	261
	No	13	11	77	634
Fever during pregnancy	Yes	9	12	79	58
	No	11	11	78	837
Vaginal/cervical infection	Yes	14	14	72	113
	No	11	10	79	782
Urinary tract infections	Yes	8	13	79	134
	No	12	10	75	761
Highest white blood cell count ^a	>20 K	9	4	88	187
	≤20 K	12	13	75	715
Any medication	Yes	12	11	78	786
	No	9	13	78	108
Aspirin	Yes	15	11	71	46
	No	11	11	78	846
Nonsteroidal anti-inflammatory drugs	Yes	9	12	79	57
	No	12	11	78	834
Acetaminophen	Yes	9	9	82	453
	No	14	12	74	438
Antibiotic	Yes	11	13	77	265
	No	12	10	78	627
Maximum no. of infants		103	99	719	921
Percent		11	11	78	

These are row percents.

^a Within the interval from before delivery to 48 h after delivery.

exposures, as well as the sequence of events leading to preterm delivery was taken as truth, even when her medical record provided discrepant information.

Shortly after discharge, the research nurse reviewed the maternal chart by using a second structured data collection form to collect information about events after admission. The clinical circumstances that led to each maternal admission and ultimately to each preterm delivery were operationally defined.¹⁹ A course of antenatal adrenal corticosteroids given to enhance fetal lung maturation was

considered complete if the gravida received 2 doses of betamethasone 24 hours apart and delivered at least 48 hours after the first dose, or if she received 4 doses of dexamethasone at 12-hour intervals. Neonatal data were collected from the newborn's medical record.

Variable Definitions

The gestational age estimates were based on a hierarchy of the quality of available information. Most desirable were estimates based on the dates of embryo retrieval or intrauterine insemination or fetal ultrasound before

the 14th week (62%). When these were not available, reliance was placed sequentially on a fetal ultrasound at 14 or more weeks (29%), last menstrual period without fetal ultrasound (7%), and gestational age recorded in the log of the NICU (1%). The birth weight z score is the number of standard deviations the infant's birth weight is above or below the median weight of infants at the same gestational age in a standard data set.²⁰ The 6 initiators of preterm delivery, preterm labor, prelabor rupture of the fetal membranes, placental abruption, cervical insufficiency, preeclampsia, and delivery for fetal indications, are defined elsewhere.¹⁹

Placentas

All who biopsied the placenta were trained to ensure sterile technique. A piece of the chorion and underlying trophoblast tissue was removed under sterile conditions from the placenta at the midpoint of the longest distance between the cord insertion and the edge of the disk, and then placed in liquid nitrogen until transfer to a –80°C freezer. Eighty-two percent of the placentas were sampled within 1 hour of delivery. The microorganism recovery rate was not influenced by the interval between birth and sampling. The microbiologic procedures are described in detail elsewhere,²¹ as are the procedures for the preparation and reading of histologic slides.²²

Fetal thrombi were recognized when fibrin was seen attached to a vessel wall with ingrowth of endothelial cells. This degree of organization excludes acute thrombi, but there are no accepted criteria for assigning an exact age to these thrombi. Villous injury was not required for the diagnosis of thrombi. Not all thrombi were occlusive. Many, but not all thrombi, were associated with demonstrable villous injury, such as hemorrhage or sclerosis, but villous injury was not explicitly coded.

TABLE 3 Risks of MDI Scores Associated With Delivery Characteristics

Delivery Characteristics		<55	55–69	≥70	Row <i>N</i>
Number of fetuses	1	12	10	78	609
	2+	9	12	79	312
Antenatal steroids	Complete course	12	11	77	593
	Partial course	9	12	79	234
	None	11	9	81	94
Magnesium	For tocolysis	11	10	80	503
	For PE	15	12	74	121
	No	10	13	77	288
Cesarean delivery	Yes	10	10	80	618
	No	14	12	74	303
Initiator of delivery	PTL	9	11	80	414
	pPROM	14	9	76	202
	Preeclampsia	16	11	74	121
	Abrupt	5	11	84	101
	Cervical insufficiency	15	10	75	48
Duration of labor	Fetal indication	17	20	63	35
	0 h	13	12	74	227
	≤12 h	17	9	74	211
	>12 h	8	11	82	483
Duration of ROM	<1 h	11	11	78	539
	1–24 h	10	10	79	144
	>24 h	12	11	78	238
Maximum no. of infants		103	99	719	921
Percent		11	11	78	

These are row percents. preeclampsia (PE); prolonged preterm rupture of membranes (pPROM); preterm labor (PTL); rupture of membranes (ROM).

Level 3 severity of chorionic plate inflammation was defined as >20 neutrophils/20×. Grade 3 inflammation of the amnion was defined as numerous large or confluent foci, whereas grade 4 was defined as necrosis. Inflammation in the chorion/decidua was similarly, but separately, graded.

Inflammation in the umbilical cord was graded from 0 to 5. Grade 3 required neutrophils in perivascular Wharton jelly, grade 4 required panvasculitis and umbilical cord vasculitis extending deep into Wharton jelly, and grade 5 required a “halo lesion” (ring of precipitate in Wharton jelly encircling each vessel). Neutrophilic infiltration into fetal stem vessels in the chorionic plate required that neutrophils appeared to have migrated toward the amnionic cavity.

Developmental Assessment at 24 Months

Families were invited to bring their child for a developmental assessment close to the time when he or she would be 24

months corrected age. Fully 91% of children had this developmental assessment, which included a neurologic examination^{19,23,24} and the BSID, second edition (BSID-II).²⁵ Of these children, 77% had their examination within the range of 23.5–27.9 months. All BSID-II assessments were age adjusted. Neurologic examiners were asked to rate the child on the Gross Motor Function Classification System (GMFCS)²⁶ separately from the neurologic examination. Certified examiners administered and scored the BSID-II. Before testing, examiners were told the child's age. After completion of testing, they were told the gestational age so that the unadjusted Mental Development Index (MDI) and Psychomotor Development Index could be obtained. Only 2% of examiners indicated at the time of the examination that they had more than a limited amount of information about the child.

Cognitive impairment was defined as an MDI <70. An MDI <55 was considered severe cognitive impairment.

The child was classified as nontestable on a scale if his or her impairments prohibited standardized administration, or if >2 items were judged to be “not applicable.”

Data Analysis

The generalized form of the null hypothesis that we evaluated states that the risk of a low BSID-II score is not associated with any maternal, pregnancy, or delivery characteristic. To avoid attributing cognition and perception deficits to motor impairments, we limited our analyses to children who were able to walk independently (GMFCS <1), and who, therefore, were unlikely to have functionally important fine-motor impairments.

Because our outcomes of interest (MDI <55 and MDI between 55 and 69) are mutually exclusive and each is appropriately compared with the same referent group (MDI ≥70), we used maximum-likelihood multinomial (polytomous) logistic regression (Stata command: mlogit; Stata Corp, College Station, TX) to calculate odds ratios. We selected variables as potential confounders if identified in the literature or if in our data they were associated with both another relevant exposure and low MDI with probabilities ≤0.25.²⁷

To adjust for potential confounders, we created 2 individual conditional logistic multivariable models, each comparing children in 1 of the 2 abnormal outcome groups to the same referent group (ie, those with MDI ≥70). These models contained a hospital cluster term to account for the possibility that infants born at a particular hospital are more like each other than like infants born at other hospitals.

RESULTS

A total of 1200 infants survived to 24 months and 85% of surviving study participants were assessed with BSID-II

and GMFCS (Fig 1). After excluding those with impaired gross motor function (GMFCS ≥ 1), 921 were included in the analyses described in this article. Placenta microbiology and histology were available for 85% ($n = 783$) of these 921 infants.

Maternal Prepregnancy Characteristics

Infants whose mother was black, single, or eligible for public insurance were at increased risk of MDI <55 , as were infants whose mother had less than a high school equivalent education, or a prepregnancy BMI of >30 (Table 1).

Pregnancy Characteristics and Exposures

Of all the factors listed in Table 2, only assisted conception was associated with a decreased risk of MDI <55 .

Delivery Characteristics

The highest risks of MDI <55 were found with shorter duration of labor and when infants were delivered for fetal indications or for maternal pre-eclampsia, and the lowest risk was found when delivery was due to placental abruption (Table 3).

Placental Cultures and Histologic Findings

Placental inflammation and presence of microorganisms were not associated with low MDI. The only placental finding associated with low MDI was thrombosis of fetal stem vessels; however, there were only 40 infants with this exposure (Tables 4 and 5).

Infant Characteristics

The risk of MDI <55 decreased with increasing gestational age, birth weight, birth weight z score, and head circumference z score. Boys were also at moderately higher risk than girls of MDI <55 (Table 6).

TABLE 4 Risks of MDI Scores Associated With Organisms Cultured From the Placenta

Organisms		<55	55–69	≥ 70	Row <i>N</i>
Total sample					
No. of organisms isolated	0	11	10	79	435
	1	10	11	78	201
	2+	11	11	78	198
Any anaerobe	Yes	8	10	81	224
	No	12	11	77	610
Any aerobe	Yes	13	11	76	260
	No	10	11	79	574
Any <i>Mycoplasma</i>	Yes	15	12	72	85
	No	10	11	79	749
Skin organisms ^a	Yes	10	11	79	154
	No	11	11	78	680
Vaginal organisms ^b	Yes	10	12	78	132
	No	11	11	78	702
Maximum no. of infants		91	90	653	834
Percent		11	11	78	
Cesarean delivery sample					
No. of organisms isolated	0	11	11	78	333
	1	8	9	83	142
	2+	10	9	81	81
Any anaerobe	Yes	5	10	84	116
	No	11	10	79	440
Any aerobe	Yes	12	7	81	129
	No	9	11	80	427
Any <i>Mycoplasma</i>	Yes	10	10	80	41
	No	10	10	80	515
Skin organisms ^a	Yes	7	12	81	69
	No	10	10	80	487
Vaginal organisms ^b	Yes	7	11	82	55
	No	10	10	80	501
Maximum no. of infants		55	57	444	556
Percent		10	10	80	

These are row percents.

^a *Corynebacterium* sp, *Propionibacterium* sp, *Staphylococcus* sp.

^b *Prevotella bivia*, *Lactobacillus* sp, *Peptostreptococcus magnus*, *Gardnerella vaginalis*.

Multivariable Analyses

In multivariable models that included the total sample, heightened risk of MDI <55 was predicted by nonwhite race, maternal education <12 years, maternal BMI >30 , male gender, and birth weight z score >2 SDs below the mean. When the sample was limited to children for whom we had information about histologic characteristics, the same variables were predictive of MDI <55 , whereas thrombosis of fetal vessels provided additional information about increased risk (odds ratio 3.1, 95% confidence interval [CI] 1.2, 7.7). For both total sample and the histology-limited sample, the only significant risk factors for MDI 55 to 69 were male and nonwhite race. Multinomial

models without a hospital cluster term provided results that were very similar to those provided by individual logistic regression models that included a hospital cluster term (Table 7).

DISCUSSION

Three maternal attributes (obesity, nonwhite race, and maternal education) and 1 placental finding (thrombosis of fetal stem vessels) were associated with impaired early cognitive function in extremely preterm infants. Neonatal predictors of such impairment were birth weight z score < -2 (ie, below the third centile) and male gender. In general, stronger associations were found for MDI <55 than for MDI 55 to 69.

TABLE 5 Risks of MDI Scores Associated With Histologic Characteristics of the Placenta, Total Sample

Histologic Characteristic		< 55	55–69	≥70	Row <i>N</i>
Inflammation chorionic plate ^a	Yes	9	12	79	159
	No	11	11	78	679
Inflammation external membranes ^b	Yes	12	10	78	295
	No	11	12	78	547
Neutrophil infiltration fetal stem vessels	Yes	12	10	78	209
	No	10	11	78	621
Umbilical cord vasculitis ^c	Yes	11	13	76	137
	No	11	11	79	682
Thrombosis of fetal stem vessels	Yes	23	5	73	40
	No	10	11	79	789
Infarct	Yes	9	15	75	142
	No	11	10	78	705
Increased syncytial knots	Yes	12	14	74	174
	No	11	10	79	676
Decidual hemorrhage/ Fibrin deposition	Yes	11	12	77	129
	No	11	10	78	708
Maximum no. of placentas		94	94	669	857
Percent		11	11	78	

These are row percents.

^a Stage 3 and severity 3.

^b Grades 3 and 4.

^c Grades 3, 4, and 5.

TABLE 6 Risks of MDI Scores Associated With Characteristics of the Infants

Characteristics of the Infant		<55	55–69	≥70	Row <i>N</i>
Gender	Male	15	13	72	472
	Female	8	8	84	449
Gestational	23–24	15	11	74	163
Age, wk	25–26	12	10	78	435
	27	8	11	80	323
Birth weight, g	≤750	14	13	73	318
	751–1000	11	10	79	421
	>1000	5	10	85	182
Birth weight	< −2	22	14	68	51
	z score ^a				
	≥ −2, < −1	15	12	73	123
	≥ −1	10	10	80	747
Head	< −2	21	10	70	73
	z score ^a				
circumference	≥ −2, < −1	14	14	72	207
	≥ −1	9	18	81	609
Maximum number of infants		103	99	719	921
Percent		11	11	78	

These are row percents.

^a Birth weight and head circumference z scores based on Yudkin et al²⁰ standard.

Our finding that male gender was predictive of impaired early cognitive function agrees with most^{5,28} but not all²⁹ studies of extremely preterm infants.^{28,30,31} The mechanisms for this association are not well understood. Boys born prematurely have a greater risk of morbidities, such as cerebral white matter damage and chronic lung disease, and gender differences in brain

structure and response to injury might also be important.³²

In our multivariable regression models, fetal growth restriction is a predictor of an MDI <55, while not predicting a less severely low MDI. Others, too, have found that growth-restricted infants are at increased risk of cognitive limitations.^{33,34} One explanation invokes placental dysfunction, which can restrict

placental transfer of substrates for brain development.³⁵ An alternative explanation is that fetal growth restriction increases the risk of neonatal complications^{36,37} that are more proximally related to cognitive impairment.³⁸

Children who experience a major postnatal infection (including bacteremia and necrotizing enterocolitis) are more likely than others to have cerebral white matter injury³⁹ and cognitive impairment.^{15,17} Perinatal inflammation, as evidenced by chorioamnionitis, is also a risk factor for white matter injury and cerebral palsy.⁴⁰ We, however, did not find any evidence that antenatal inflammation predicts cognitive impairment.

The only histologic characteristic of the placenta associated with cognitive impairment was thrombosis of fetal stem vessels, which is considered a lesion of uteroplacental circulation and has been associated with adverse neonatal outcomes.⁴¹ In addition to stillbirth,⁴² perinatal liver disease,⁴³ and intrauterine growth restriction in mono-chorionic twins,⁴⁴ fetal vessel thrombosis has been linked to adverse neurologic outcomes, including neonatal encephalopathy⁴⁵ and neonatal stroke.⁴⁶ In the ELGAN cohort, it has been associated with ventriculomegaly of the offspring,⁴⁷ which, in turn, is associated with low MDI.⁴

One antecedent that we identified, maternal obesity, is of particular interest because it is potentially modifiable and its prevalence is increasing.⁴⁸ Although maternal obesity is predictive of higher maternal blood levels of C-reactive protein⁴⁹ and interleukin-6,⁵⁰ we found no indirect evidence to support a link between maternal inflammation, as indicated by placental findings and initiators of preterm delivery, and subsequent impaired infant cognitive function. Maternal obesity is associated with multiple complications of pregnancy⁵¹ and with perinatal

TABLE 7 Multivariable Analysis of Variables Associated With Low MDI

Variables	<55	55–69
Total sample (<i>n</i> = 921)		
Gestational age 23–24 wk	1.9 (0.97, 3.6)	1.0 (0.5, 1.9)
Gestational age 25–26 wk	1.2 (0.7, 2.1)	0.8 (0.5, 1.3)
Single mother	1.3 (0.7, 2.2)	1.2 (0.7, 2.1)
BMI >30	1.9 (1.1, 3.1) ^a	1.3 (0.9, 2.3)
Vaginal/cervical infection	1.2 (0.6, 2.2)	1.4 (0.8, 2.6)
Cesarean delivery	0.8 (0.5, 1.2)	0.8 (0.5, 1.4)
BWZ < −2	2.2 (1.5, 7.5) ^a	1.9 (0.7, 4.8)
Male	2.5 (1.6, 4.1) ^a	2.0 (1.3, 3.2) ^a
Nonwhite race	2.3 (1.4, 3.8) ^a	2.1 (1.3, 3.5) ^a
Mother's education <12 y	2.8 (1.6, 4.9) ^a	0.9 (0.5, 1.8)
Mother's education >16 y	0.8 (0.4, 1.5)	0.7 (0.4, 1.2)
Total histology/BSID sample (<i>n</i> = 857)		
Gestational age 23–24 wk	1.9 (0.9, 3.9)	1.1 (0.6, 2.1)
Gestational age 25–26 wk	1.1 (0.6, 2.0)	0.8 (0.4, 1.3)
Single mother	1.2 (0.7, 2.2)	1.2 (0.7, 2.0)
BMI >30	2.0 (1.1, 3.5) ^a	1.2 (0.7, 2.1)
Vaginal/cervical infection	1.2 (0.6, 2.4)	1.4 (0.7, 2.7)
Cesarean delivery	0.9 (0.5, 1.5)	0.9 (0.5, 1.5)
BWZ < −2	2.8 (1.1, 6.9) ^a	1.9 (0.7, 5.0)
Male	2.7 (1.6, 4.5) ^a	2.1 (1.3, 3.4) ^a
Thrombosis fetal vessels	3.1 (1.2, 7.7) ^a	0.6 (0.1, 2.5)
Increased syncytial knots	1.4 (0.8, 2.5)	1.5 (0.9, 2.5)
Nonwhite race	2.2 (1.3, 3.8) ^a	2.2 (1.3, 3.7) ^a
Mother's education <12 y	3.4 (1.9, 6.2) ^a	1.1 (0.6, 2.2)
Mother's education >16 y	0.7 (0.4, 1.4)	0.7 (0.4, 1.3)

Risk ratios and 95% CIs. The referent group is infants with MDI ≥ 70 . BWZ, birthweight z score.

^a $p < .05$.

mortality.^{52–55} Perhaps most relevant to our study is the association with fetal growth restriction.^{19,56} In addition, obesity is linked to chronic illnesses^{57,58} and social disadvantage,⁵⁹ which might affect the mother-infant interaction and the resources available to enhance the home environment.

The association of assisted conception with a low MDI, seen in univariable analyses, was no longer significant in multivariable analyses. The most likely explanation is that the risk information provided by the assisted conception variable is more strongly conveyed by 2 other correlates of socioeconomic status: race and education.

We are not aware of any other large prospective studies relating early cognitive functioning in extremely preterm infants to placental findings or initiators of preterm delivery. A potential limitation of this study is that MDI <55 is only moderately predictive of cognitive impairment at school age.⁶⁰ The

strengths of this prospective study include the large number of infants, selection of participants based on gestational age rather than birth weight, and evaluations by individuals who were not aware of infants' medical or social histories.

This study has implications for efforts to prevent cognitive impairment among extremely premature infants. One antecedent identified here, maternal obesity, is potentially modifiable during the preconception period and pregnancy. The prevalence of another antecedent, fetal growth restriction, could be decreased by interventions to prevent severe preeclampsia, which occurred in 13% of our sample of extremely preterm infants.

To what extent the cognitive adversities associated with fetal growth restriction reflect postnatal phenomena (especially those associated with chronic lung disease) remains unclear. Postnatal disorders appear to be involved

in explaining some of the relationship between chronic lung disease and impaired development.⁷ If the occurrence of these disorders can be minimized, then there is hope that the influence of fetal growth restriction on cognitive deficiencies can be reduced.

CONCLUSIONS

Antenatal characteristics associated with impaired mental development include maternal BMI >30, nonwhite race, maternal education, thrombosis of fetal stem vessels, and male gender. Our findings do not support an important role of prenatal infection or inflammation in the development of impaired early cognitive function among extremely preterm infants.

ACKNOWLEDGMENTS

Participating institutions (site principal investigators, pathologists, and developmentalists): Baystate Medical Center, Springfield, MA (Bhavesh Shah, Solveg Pflueger, Susan McQuiston, Herbert Gilmore, Karen Christianson); Beth Israel Deaconess Medical Center, Boston, MA (Camilia R. Martin, Jonathan Hecht, Alaska Morgan, Haim Bassan, Cecil Hahn, Samantha Butler, Adre Duplessis, Colleen Hallisey); Brigham & Women's Hospital, Boston, MA (Linda J. Van Marter); Children's Hospital, Boston, MA (Alan Leviton); Massachusetts General Hospital, Boston, MA (Robert Insoft, Drucilla Roberts, Kalpathy Krishnamoorthy, Maureen Quill); Floating Hospital for Children at Tufts Medical Center, Boston, MA (Cynthia Cole/John Fiascone, Ina Bhan, Cecelia Keller, Karen Miller, Page Church, Caitlyn Hurley); University of Massachusetts Memorial Health Center, Worcester, MA (Francis Bednarek, Gamze Ayata, Robin Adair, Alice Miller, Rick Bream, Albert Scheiner, Beth Powers); Yale-New Haven Hospital, New Haven, CT (Richard Ehrenkranz, Miguel Reyes-Múgica, Eduardo Zambrano, Vinita Parkas,

Cindy Miller, Elaine Romano, Nancy Close, Linda Mayes, Joanne Williams); Wake Forest University Baptist Medical Center and Forsyth Medical Center, Winston-Salem, NC (T. Michael O'Shea, Dennis W. Ross, Gail Hounshell, Don Goldstein, Lisa Washburn, Cherrie Heller, Robert Dillard, Debbie Hiatt, Deborah Allred); University Health Systems of Eastern Carolina, Greenville, NC (Stephen Engelke, John Christie, Kathryn Kerkerling, Steve Engelke, Lynn Whitley, Rebecca Helms, Peter Resnik); North Carolina Children's

Hospital, Chapel Hill, NC (Carl Bose, Chad Livasy, Diane Marshall, Lisa Bostic, Janice Wereszczak, Mandy Taylor, Carol Torres, Kristi Milowic, Ginny Bose); DeVos Children's Hospital, Grand Rapids, MI (Mariel Portenga, Barbara Doss, Lynn Fagerman, Steve Pasynrnak, Victoria Caine, Wendy Burdo-Hartman, Dianah Sutton); Sparrow Hospital, Lansing, MI (Padmani Karna); Michigan State University, East Lansing, MI (Nigel Paneth, Madeleine Lenski, Nicholas Olomu, Padu Karna, Victoria Caine, Joan Price); University of Chicago Hospital, Chicago, IL (Michael

D. Schreiber, Aliya Husain, Sunila O'Connor, Michael Msall, Susan Plesha-Troyke, Leslie Caldarelli, Grace Yoon); William Beaumont Hospital, Royal Oak, MI (Daniel Batton, Chung-ho Chang, Karen Brooklier, Katie Solomon, Dan Batton, Melisa Oca, Beth Kring); and pathologists not at participating sites (Harvey Kliman, Pat Senagore).

The authors gratefully acknowledge the contributions of our subjects and their families, as well as those of our colleagues.

REFERENCES

- Doyle LW; Victorian Infant Collaborative Study Group. Neonatal intensive care at borderline viability—is it worth it? *Early Hum Dev.* 2004;80(2):103–113
- Washburn LK, Dillard RG, Goldstein DJ, Klinepeter KL, Jackson BG, O'Shea TMD. Survival and developmental impairment in extremely low gestational age newborns born 1980–2000. *Pediatr Res.* 2002;51(4):288A
- Kuban K, Allred E, O'Shea TM, et al. Cranial ultrasound lesions in the NICU predict cerebral palsy at age 2 years in children who were born at extremely low gestational age. *J Child Neurol.* 2008;24:63–72
- O'Shea TM, Kuban KC, Allred EN, et al; Extremely Low Gestational Age Newborns Study Investigators. Neonatal cranial ultrasound lesions and developmental delays at 2 years of age among extremely low gestational age children. *Pediatrics.* 2008; 122(3). Available at: www.pediatrics.org/cgi/content/full/122/3/e662
- Wood NS, Costeloe K, Gibson AT, Hennessy EM, Marlow N, Wilkinson AR; EPICure Study Group. The EPICure study: associations and antecedents of neurological and developmental disability at 30 months of age following extremely preterm birth. *Arch Dis Child Fetal Neonatal Ed.* 2005;90(2):F134–F140
- Roberts G, Anderson PJ, Doyle LW; Victorian Infant Collaborative Study Group. The stability of the diagnosis of developmental disability between ages 2 and 8 in a geographic cohort of very preterm children born in 1997. *Arch Dis Child.* 2010;95(10):786–790
- Laughon M, O'Shea TM, Allred EN, et al. Chronic lung disease and the risk of developmental delay at two years of age in children born before 28 weeks' gestation. *Pediatrics.* 2009;124(2):637–648
- Kiechl-Kohlendorfer U, Ralser E, Pupp Peglow U, Reiter G, Trawöger R. Adverse neurodevelopmental outcome in preterm infants: risk factor profiles for different gestational ages. *Acta Paediatr.* 2009;98(5):792–796
- Cheng SW, Chou HC, Tsou KI, Fang LJ, Tsao PN. Delivery before 32 weeks of gestation for maternal pre-eclampsia: neonatal outcome and 2-year developmental outcome. *Early Hum Dev.* 2004;76(1):39–46
- Schmidt B, Roberts RS, Davis P, et al; Caffeine for Apnea of Prematurity Trial Group. Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med.* 2007; 357(19):1893–1902
- Bozynski ME, Nelson MN, Matalon TA, et al. Prolonged mechanical ventilation and intracranial hemorrhage: impact on developmental progress through 18 months in infants weighing 1200 grams or less at birth. *Pediatrics.* 1987;79(5):670–676
- Vohr BR, Poindexter BB, Dusick AM, et al; National Institute of Child Health and Human Development National Research Network. Persistent beneficial effects of breast milk ingested in the neonatal intensive care unit on outcomes of extremely low birth weight infants at 30 months of age. *Pediatrics.* 2007;120(4). Available at: www.pediatrics.org/cgi/content/full/120/4/e953
- Whitaker A, Johnson J, Sebris S, et al. Neonatal cranial ultrasound abnormalities: association with developmental delay at age one in low birth weight infants. *J Dev Behav Pediatr.* 1990;11(5):253–260
- Ehrenkranz RA, Walsh MC, Vohr BR, et al; National Institutes of Child Health and Human Development Neonatal Research Network. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. *Pediatrics.* 2005;116 (6):1353–1360
- Stoll BJ, Hansen NI, Adams-Chapman I, et al; National Institute of Child Health and Human Development Neonatal Research Network. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. *JAMA.* 2004;292(19):2357–2365
- Arnold CC, Kramer MS, Hobbs CA, McLean FH, Usher RH. Very low birth weight: a problematic cohort for epidemiologic studies of very small or immature neonates. *Am J Epidemiol.* 1991;134(6):604–613
- Shah DK, Doyle LW, Anderson PJ, et al. Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormalities on magnetic resonance imaging at term. *J Pediatr.* 2008;153(2):170–175
- O'Shea TM, Allred EN, Dammann O, et al; ELGAN study Investigators. The ELGAN study of the brain and related disorders in extremely low gestational age newborns. *Early Hum Dev.* 2009;85(11):719–725
- McElrath TF, Hecht JL, Dammann O, et al; ELGAN Study Investigators. Pregnancy disorders that lead to delivery before the 28th week of gestation: an epidemiologic approach to classification. *Am J Epidemiol.* 2008;168(9):980–989
- Yudkin PL, Aboualfa M, Eyre JA, Redman CWG, Wilkinson AR. New birthweight and head circumference centiles for gestational ages 24 to 42 weeks. *Early Hum Dev.* 1987;15 (1):45–52

21. Onderdonk AB, Delaney ML, DuBois AM, Allred EN, Leviton A; Extremely Low Gestational Age Newborns (ELGAN) Study Investigators. Detection of bacteria in placental tissues obtained from extremely low gestational age neonates. *Am J Obstet Gynecol*. 2008;198(1):110–, e1–e7
22. Hecht JL, Allred EN, Kliman HJ, et al; Elgan Study Investigators. Histological characteristics of singleton placentas delivered before the 28th week of gestation. *Pathology*. 2008;40(4):372–376
23. Kuban KC, Allred EN, O'Shea M, Paneth N, Pagano M, Leviton A; ELGAN Study Cerebral Palsy-Algorithm Group. An algorithm for identifying and classifying cerebral palsy in young children. *J Pediatr*. 2008;153(4):466–472
24. Kuban KC, O'Shea M, Allred E, et al. Video and CD-ROM as a training tool for performing neurologic examinations of 1-year-old children in a multicenter epidemiologic study. *J Child Neurol*. 2005;20(10):829–831
25. Bayley N. *Bayley Scales of Infant Development*. 2nd ed. San Antonio, TX: Psychological Corporation; 1993
26. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol*. 1997;39(4):214–223
27. Dales LG, Ury HK. An improper use of statistical significance testing in studying covariables. *Int J Epidemiol*. 1978;7(4):373–375
28. Hintz SR, Kendrick DE, Vohr BR, Kenneth Poole W, Higgins RD; Nichd Neonatal Research Network. Gender differences in neurodevelopmental outcomes among extremely preterm, extremely-low-birthweight infants. *Acta Paediatr*. 2006;95(10):1239–1248
29. Beaino G, Khoshnood B, Kaminski M, et al; EPIPAGE Study Group. Predictors of the risk of cognitive deficiency in very preterm infants: the EPIPAGE prospective cohort. *Acta Paediatr*. 2011;100(3):370–378
30. Shankaran S, Johnson Y, Langer JC, et al. Outcome of extremely-low-birth-weight infants at highest risk: gestational age < or =24 weeks, birth weight < or =750 g, and 1-minute Apgar < or =3. *Am J Obstet Gynecol*. 2004;191(4):1084–1091
31. Stoelhorst GM, Rijken M, Martens SE, et al; Leiden Follow-Up Project on Prematurity. Developmental outcome at 18 and 24 months of age in very preterm children: a cohort study from 1996 to 1997. *Early Hum Dev*. 2003;72(2):83–95
32. Johnston MV, Hagberg H. Sex and the pathogenesis of cerebral palsy. *Dev Med Child Neurol*. 2007;49(1):74–78
33. Leitner Y, Fattal-Valevski A, Geva R, et al. Neurodevelopmental outcome of children with intrauterine growth retardation: a longitudinal, 10-year prospective study. *J Child Neurol*. 2007;22(5):580–587
34. Leitner Y, Fattal-Valevski A, Geva R, et al. Six-year follow-up of children with intrauterine growth retardation: long-term, prospective study. *J Child Neurol*. 2000;15(12):781–786
35. Reuss ML, Paneth N, Susser M. Does the loss of placental hormones contribute to neurodevelopmental disabilities in preterm infants? *Dev Med Child Neurol*. 1994;36(8):743–747
36. Bose C, Van Marter LJ, Laughon M, et al; Extremely Low Gestational Age Newborn Study Investigators. Fetal growth restriction and chronic lung disease among infants born before the 28th week of gestation. *Pediatrics*. 2009;124(3). Available at: www.pediatrics.org/cgi/content/full/124/3/e450
37. Engineer N, Kumar S. Perinatal variables and neonatal outcomes in severely growth restricted preterm fetuses. *Acta Obstet Gynecol Scand*. 2010;89(9):1174–1181
38. Anderson PJ, Doyle LW. Neurodevelopmental outcome of bronchopulmonary dysplasia. *Semin Perinatol*. 2006;30(4):227–232
39. Glass HC, Bonifacio SL, Chau V, et al. Recurrent postnatal infections are associated with progressive white matter injury in premature infants. *Pediatrics*. 2008;122(2):299–305
40. Wu YW, Colford JM Jr. Chorioamnionitis as a risk factor for cerebral palsy: a meta-analysis. *JAMA*. 2000;284(11):1417–1424
41. Redline RW, Pappin A. Fetal thrombotic vasculopathy: the clinical significance of extensive avascular villi. *Hum Pathol*. 1995;26(1):80–85
42. Saleemuddin A, Tantbirojn P, Sirois K, et al. Obstetric and perinatal complications in placentas with fetal thrombotic vasculopathy. *Pediatr Dev Pathol*. 2010;13(6):459–464
43. Dahms BB, Boyd T, Redline RW. Severe perinatal liver disease associated with fetal thrombotic vasculopathy. *Pediatr Dev Pathol*. 2002;5(1):80–85
44. Chan MP, Hecht JL, Kane SE. Incidence and clinicopathologic correlation of fetal vessel thrombosis in mono- and dichorionic twin placentas. *J Perinatol*. 2010;30(10):660–664
45. McDonald DG, Kelehan P, McMenamin JB, et al. Placental fetal thrombotic vasculopathy is associated with neonatal encephalopathy. *Hum Pathol*. 2004;35(7):875–880
46. Elbers J, Viero S, MacGregor D, DeVeber G, Moore AM. Placental pathology in neonatal stroke. *Pediatrics*. 2011;127(3). Available at: www.pediatrics.org/cgi/content/full/127/3/e722
47. McElrath TF, Allred EN, Bogges KA, et al; ELGAN Study Investigators. Maternal antenatal complications and the risk of neonatal cerebral white matter damage and later cerebral palsy in children born at an extremely low gestational age. *Am J Epidemiol*. 2009;170(7):819–828
48. Kim SY, Dietz PM, England L, Morrow B, Callaghan WM. Trends in pre-pregnancy obesity in nine states, 1993–2003. *Obesity (Silver Spring)*. 2007;15(4):986–993
49. Madan JC, Davis JM, Craig WY, et al. Maternal obesity and markers of inflammation in pregnancy. *Cytokine*. 2009;47(1):61–64
50. Roberts KA, Riley SC, Reynolds RM, et al. Placental structure and inflammation in pregnancies associated with obesity. *Placenta*. 2011;32(3):247–254
51. Catalano PM, Ehrenberg HM. The short- and long-term implications of maternal obesity on the mother and her offspring. *BJOG*. 2006;113(10):1126–1133
52. Chu SY, Kim SY, Lau J, et al. Maternal obesity and risk of stillbirth: a metaanalysis. *Am J Obstet Gynecol*. 2007;197(3):223–228
53. Kristensen J, Vestergaard M, Wisborg K, Kesmodel U, Secher NJ. Pre-pregnancy weight and the risk of stillbirth and neonatal death. *BJOG*. 2005;112(4):403–408
54. Leddy MA, Power ML, Schulkin J. The impact of maternal obesity on maternal and fetal health. *Rev Obstet Gynecol*. 2008;1(4):170–178
55. Vasudevan C, Renfrew M, McGuire W. Fetal and perinatal consequences of maternal obesity. *Arch Dis Child Fetal Neonatal Ed*. 2011;96(5):F378–F382
56. Sebastián Manzanares G, Angel Santalla H, Irene Vico Z, López Criado MS, Alicia Pineda L, José Luis Gallo V. Abnormal maternal body mass index and obstetric and neonatal outcome. *J Matern Fetal Neonatal Med*. 2011; Early online, 1–5
57. Jungheim ES, Moley KH. Current knowledge of obesity's effects in the pre- and periconceptional periods and avenues for future research. *Am J Obstet Gynecol*. 2010;203(6):525–530
58. Messier SP. Obesity and osteoarthritis: disease genesis and nonpharmacologic weight management. *Rheum Dis Clin North Am*. 2008;34(3):713–729
59. Brown A, Siahpash M. Risk factors for overweight and obesity: results from the 2001 National Health Survey. *Public Health*. 2007;121(8):603–613
60. Hack M, Taylor HG, Drotar D, et al. Poor predictive validity of the Bayley Scales of Infant Development for cognitive function of extremely low birth weight children at school age. *Pediatrics*. 2005;116(2):333–341