Maternal and Infant Characteristics Associated With Perinatal Arterial Stroke in the Infant

Janet Lee; Lisa A. Croen; Kendall H. Backstrand; et al.

JAMA. 2005;293(6):723-729 (doi:10.1001/jama.293.6.723)

http://jama.ama-assn.org/cgi/content/full/293/6/723

Maternal and Infant Characteristics Associated With Perinatal Arterial Stroke in the Infant

Janet Lee, MS
Lisa A. Croen, PhD
Kendall H. Backstrand, BA
Cathleen K. Yoshida, MS
Louis H. Henning, BA
Camilla Lindan, MD
Donna M. Ferriero, MD
Heather J. Fullerton, MD
A. J. Barkovich, MD
Yvonne W. Wu, MD, MPH

Context Perinatal arterial ischemic stroke (PAS) is a common cause of hemiplegic cerebral palsy. Risk factors for this condition have not been clearly defined.

Objective To determine maternal and infant characteristics associated with PAS.

Design, Setting, and Patients Case-control study nested within the cohort of all 199 176 infants born from 1997 through 2002 in the Kaiser Permanente Medical Care Program, a managed care organization providing care for more than 3 million residents of northern California. Case patients were confirmed by review of brain imaging and medical records (n=40). Three controls per case were randomly selected from the study population.

Main Outcome Measure Association of maternal and infant complications with risk of PAS.

Results The population prevalence of PAS was 20 per 100 000 live births. The majority (85%) of infants with PAS were delivered at term. The following prepartum and intrapartum factors were more common among case than control infants: primiparity (73% vs 44%, $P=.002$), fetal heart rate abnormality (46% vs 14%, $P<.001$), emergency cesarean delivery (35% vs 13%, $P=.002$), chorioamnionitis (27% vs 11%, $P=.03$), prolonged rupture of membranes (26% vs 7%, $P=.002$), prolonged second stage of labor (25% vs 4%, $P<.001$), vacuum extraction (24% vs 11%, $P=.04$), cord abnormality (22% vs 6%, $P=.01$), preeclampsia (19% vs 5%, $P=.01$), and oligohydramnios (14% vs 3%, $P=.01$). Risk factors independently associated with PAS on multivariate analysis were history of infertility (odds ratio [OR], 7.5; 95% confidence interval [CI], 1.3-45.0), preeclampsia (OR, 5.3; 95% CI, 1.3-22.0), prolonged rupture of membranes (OR, 3.8; 95% CI, 1.1-12.8), and chorioamnionitis (OR, 3.4; 95% CI, 1.1-10.5). The rate of PAS increased dramatically when multiple risk factors were present.

Conclusions Perinatal arterial ischemic stroke in infants is associated with several independent maternal risk factors. How these complications, along with their potential effects on the placenta and fetus, may play a role in causing perinatal stroke deserves further study.

JAMA. 2005;293:723-729 www.jama.com

PERINATAL ARTERIAL ISCHEMIC stroke (PAS) is an important cause of cerebral palsy and other neurologic disabilities, including epilepsy and cognitive impairment.[1-7] Arterial ischemic stroke is diagnosed primarily in neonates born at term[8,9] and is responsible for 50% to 70% of congenital hemiplegic cerebral palsy in this population.[10,11]

The cause of PAS is poorly understood. Investigators have reported a number of obstetric and neonatal complications in the setting of PAS, including birth asphyxia, preeclampsia, chorioamnionitis, cardiac anomalies, polycythemia, and systemic infection.[7,12-15] Others have failed to find a significant difference in the frequency of perinatal complications between infants with PAS and controls.[16] Hematologic disorders, including factor V Leiden mutation and hyperhomocysteinemia, may also play a role in the pathogenesis of PAS.[14,17-19]

Previous studies of PAS are subject to a number of important limitations. Most describe only a small number of children[7,12,16,20-22] or lack an adequate comparison group.[8,14,23] We found previously that preeclampsia and intrauterine growth restriction are independent risk factors for PAS.[15] However, our earlier

Author Affiliations: Departments of Neurology (Ms Lee, Mssrs Backstrand and Henning, and Drs Ferriero, Fullerton, Barkovich, and Wu), Pediatrics (Drs Ferriero, Fullerton, Barkovich, and Wu), and Radiology (Dr Barkovich), University of California, San Francisco; and Kaiser Permanente Division of Research (Dr Croen and Ms Yoshida) and Department of Radiology (Dr Lindan), Oakland, Calif.
Corresponding Author: Yvonne W. Wu, MD, MPH, UCSF Department of Child Neurology, Box 0137, 350 Parnassus Ave, Suite 609, San Francisco, CA 94117 (wuy@neuropeds.ucsf.edu).

study included only children with PAS who developed long-term motor impairment, and we did not confirm the diagnosis of PAS with review of brain imaging. Therefore, we set out to determine pregnancy complications associated with radiologically confirmed PAS in a defined population of infants.

METHODS

This case-control study was nested within the cohort of all 199 176 infants born from January 1, 1997, to December 31, 2002, in the Northern California Kaiser Permanente Medical Care Program (KPMCP). The KPMCP is a large managed care organization that provides care for more than 30% of the population in northern California. The members of KPMCP are demographically similar to the California population, except that the very poor and very wealthy are underrepresented.[24] All study procedures were approved by the institutional review boards at KPMCP and at the University of California, San Francisco, which waived requirement for informed consent.

Case Ascertainment

We searched electronically all head magnetic resonance imaging (MRI) and computed tomographic (CT) reports generated from January 1, 1997, through July 1, 2003 (all study infants were all at least 6 months of age when records were searched), and retrieved neuroimaging reports containing any of the following text strings: *stroke*, *infarct*, *thrombo*, *ischemi*, *middle cerebral artery*, *MCA*, *posterior cerebral artery*, *PCA*, *anterior cerebral artery*, *ACA*, *vascular insult*, *vascular injury*, *vascular event*, *porencephal*, or *hydranencephal*. We also retrieved all head MRI and CT reports generated for newborns admitted to the neonatal intensive care unit with seizures and for children who were given an inpatient or outpatient physician diagnosis of stroke, developmental delay, hemiparesis, or cerebral palsy before November 2003.

Two study investigators (K.H.B., J.L.) independently reviewed the head MRI and CT reports of 1970 patients to identify potential cases of PAS. They excluded neuroimaging studies that revealed (1) no mention of possible stroke; (2) an acute infarction occurring after 28 days of life; (3) isolated hemorrhagic lesions; (4) venous infarction; or (5) infarctions limited to the arterial watershed zones.[1] A study neuroradiologist (C.L.) then reviewed 141 head MRI or CT scans to confirm the presence of an arterial-distribution ischemic infarction. When the presence of an arterial infarction was not obvious, the imaging studies were reviewed by a second neuroradiologist (A.J.B.), and a consensus about the final neuroimaging diagnosis was reached through discussion. One child whose MRI scan could not be located was included because his MRI report described an unambiguous large posterior cerebral artery infarction.

Two investigators (K.H.B., J.L.) reviewed the medical records of children with radiologically confirmed arterial infarction to determine whether the stroke was perinatal. We defined a *perinatal* event as one that occurred in utero or up to 28 days after birth.[25] If the infant presented within the first 28 days after delivery, the stroke was considered to be *acute*. If an infant had been considered neurologically normal before 1 month of age but was later diagnosed with an old arterial infarction, the stroke was considered to be *presumed perinatal*.[3]

Three infants with PAS caused by a known neonatal event were excluded from the risk factor analysis but included in the prevalence calculation. One infant had an iatrogenic PAS after surgical evacuation of an intracranial hematoma, and 2 had acute arterial strokes in the setting of severe meningitis after 2 weeks of age.

Control Selection

We randomly selected 3 controls per case from the study population. Control infants were frequency matched to the infants with PAS on birth year, facility of birth, and gestational age stratum (<32 weeks, 32-35 weeks, and ≥36 weeks of gestation).

Data Abstraction

Two study investigators blinded to case status reviewed prenatal (J.L.), obstetric (J.L.), and neonatal (L.H.H.) medical records by using a standardized protocol. An infant born at or later than 41 weeks of gestation was considered postdates. Maternal body mass index was calculated from prepregnancy height and weight measurements, if available, or from the first prenatal visit. To evaluate the effect of ethnicity on risk of PAS, we abstracted maternal ethnicity according to self-report as noted in the medical records. Intrauterine growth restriction was defined as birth weight less than the 10th percentile for gestational age according to race- and sex-specific normative data compiled from California births.[26] The mother was considered to have a history of infertility if this was documented in a prenatal, obstetric, or neonatal record. Information about the use of infertility drugs for the index pregnancy was also abstracted from these records.

Preeclampsia was defined as a physician diagnosis of either preeclampsia or pregnancy-induced hypertension. We used the term *chorioamnionitis* to indicate a maternal temperature of at least 37.8°C or a physician diagnosis of chorioamnionitis according to clinical symptoms alone. The term *cord abnormalities* included tight nuchal cord, umbilical cord knot, and body cord. We used the term *birth asphyxia* to indicate a diagnosis made by a treating physician of either birth asphyxia or hypoxic-ischemic encephalopathy. The second stage of labor was coded as prolonged if it lasted more than 2 hours. Fetal heart rate abnormalities were considered present if a treating physician noted repetitive or prolonged late decelerations, fetal bradycardia, nonreassuring fetal heart tracing, or fetal distress according to electronic fetal heart rate monitoring. Decreased fetal movement referred to a maternal report of decreased fetal movement before labor or decreased fetal movement noted during a nonstress test.

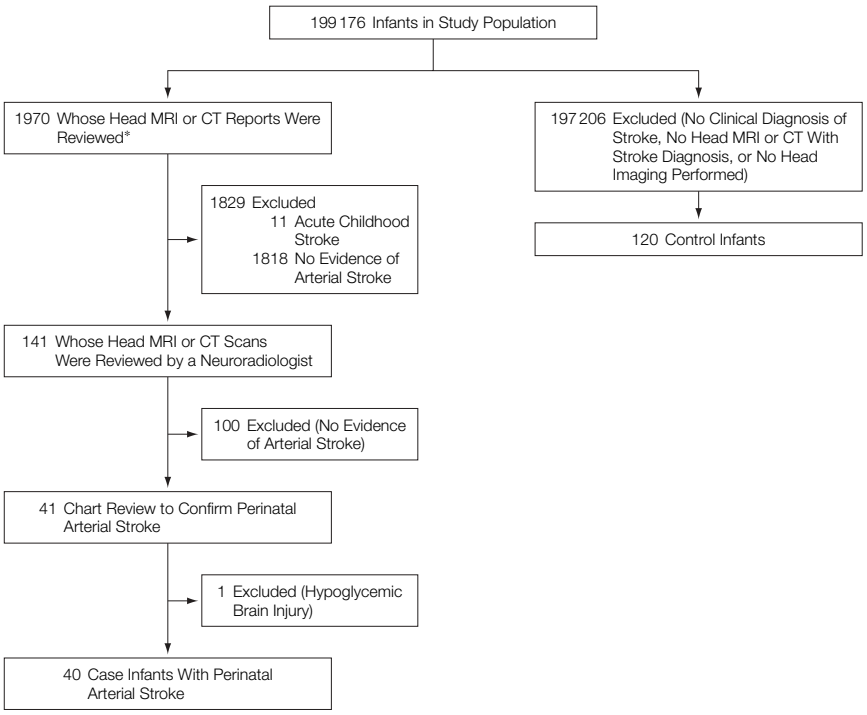
Data Analysis

We compared dichotomous variables by using χ^2 or Fisher exact test and continuous variables by using the *t* test. We calculated univariate odds ratios (ORs) and 95% confidence intervals (CIs) with the Cornfield or exact method, as appropriate, and multivariate ORs with backward stepwise logistic regression, with $P<.10$ used as the cutoff for retention in the model.[27] To determine whether risk factors differed for the acute-presentation group compared with the delayed-presentation group, we performed a polytomous logistic regression.[27] Odds ratios closely approximate the relative risk because the outcome of PAS is rare.

The multivariate model included maternal (primiparity and infertility), prepartum (preeclampsia, oligohydramnios), and intrapartum (chorioamnionitis, prolonged rupture of membranes, cord abnormality, and use of oxytocin) characteristics associated with PAS at a level of $P<.15$ in univariate analyses that were considered unlikely to be a result of the stroke. Infant characteristics such as neonatal seizures and low Apgar scores, as well as decreased fetal movement, were not included in the model because they most likely result from perinatal brain injury and do not play a causal role.

It is impossible to know where some variables lie on the causal pathway. For instance, fetal heart rate abnormalities may (1) play a primary causal role in PAS; (2) be on the causal pathway between a preceding risk factor and PAS; (3) be merely an adverse effect of an underlying causal factor without direct impact on PAS; (4) be a direct consequence of the stroke event; or (5) be a combination of the above. For this reason, intrapartum complications associated with PAS, including fetal heart rate abnormalities, prolonged second stage of labor, vacuum assistance, and emergency cesarean delivery, were not included in the main multivariate analysis but instead were added to the model separately to determine whether they contribute additional risk to PAS beyond that accounted for by the variables in the main model.

Figure. Selection of Study Cases



CT indicates computed tomography; MRI, magnetic resonance imaging.
*Patients with a neuroimaging report containing a keyword suggestive of stroke, or who carried a physician diagnosis of stroke, cerebral palsy, neonatal seizures, or a related diagnosis.

RESULTS

Among 1970 children who had either a head-imaging report or a clinical diagnosis suggesting possible PAS, 141 patients had a head MRI or CT scan that was reviewed by a neuroradiologist (FIGURE). A total of 40 cases of PAS were confirmed, providing a population prevalence of 20 per 100 000 live births. Infants with PAS were all singleton gestation, and the majority (85%) were delivered at term (mean [SD], 39.9 [1.0] weeks). The 6 preterm infants with PAS were born between 30 and 35 weeks of gestation, with the exception of 1 infant who was delivered at 24 weeks.

Clinical Presentation

Most infants with PAS (58%) presented during the acute neonatal period. Term infants presented frequently with neonatal seizures (70%), whereas 3 of 4 preterm infants with acute PAS were diagnosed incidentally when a routine head ultrasound showing intraventricular hemorrhage or white-matter abnormalities led to a head CT that diagnosed an arterial stroke. All children with presumed perinatal stroke presented after 2 months of age, with pathologic handedness (hand preference earlier than 1 year of age) as the most common presenting symptom, which was consistent with previous reports.[3]

Previously described causes of PAS were uncommon in our cohort. Although cardiac echocardiography was not performed routinely, none of the children with PAS were diagnosed with a major congenital heart abnormality. Minor cardiac findings in 4 patients with a heart murmur included a patent ductus arteriosus, a very mild muscular hypertrophy, and a small ventral septal defect that was thought to be clinically insignificant. One infant had a mild polycythemia (hematocrit level dropped from 70.5% to 65% during 20

hours) that did not require exchange transfusion. Few patients received a coagulation evaluation, and therefore we could not assess the role of prothrombotic disorders in PAS.

Neuroimaging Findings

The diagnosis of PAS was made on either head MRI (70%) or head CT (30%). Unilateral infarctions were more common on the left (53%) than on the right (35%), whereas 13% demonstrated bilateral arterial distribution infarcts. The majority of strokes involved only the middle cerebral artery distribution (74%), with an additional 4 strokes that involved the middle cerebral artery plus other arteries.

Table 1. Univariate Predictors of Perinatal Arterial Stroke in a Population of Term and Preterm Infants Born at Kaiser Permanente Northern California, 1997-2002

	No./Total (%)*			
	Cases (n = 37)	Controls (n = 111)	Odds Ratio (95% Confidence Interval)	*P* Value
Maternal characteristics				
Age, y				
<20	2/37 (5)	9/111 (8)	0.7 (0.1-3.9)	>.99
20-34	26/37 (70)	87/111 (78)	Reference	
≥35	9/37 (24)	15/111 (14)	2.0 (0.8-5.0)	.14
Race				
White	14/37 (38)	36/111 (32)	Reference	
Black	4/37 (11)	16/111 (14)	0.6 (0.1-2.5)	.56
Hispanic	11/37 (30)	33/111 (30)	0.9 (0.3-2.1)	.74
Asian	8/37 (22)	25/111 (23)	0.8 (0.3-2.2)	.70
Other	0/37	1/111 (1)		
High body mass index (≥30)	6/30 (20)	14/89 (16)	1.3 (0.5-3.8)	.59
Primiparity	27/37 (73)	49/111 (44)	3.4 (1.5-7.6)	.002
Previous miscarriage†	3/21 (14)	14/75 (19)	0.7 (0.1-3.0)	.76
History of infertility	4/37 (11)	4/111 (4)	3.2 (0.6-18.3)	.11
Ovarian stimulation	4/37 (11)	3/111 (3)	4.4 (0.7-30.9)	.07
Prepartum complications				
Intrauterine growth restriction	4/37 (11)	11/109 (10)	1.1 (0.2-4.0)	>.99
Gestational diabetes	4/37 (11)	14/111 (13)	0.8 (0.2-2.9)	>.99
Preeclampsia	7/37 (19)	5/111 (5)	4.9 (1.2-21.0)	.01
Oligohydramnios	5/37 (14)	3/111 (3)	5.6 (1.0-37.6)	.02
Decreased fetal movement	12/37 (32)	7/111 (6)	7.1 (2.6-19.4)	<.001
Preterm labor‡	1/31 (3)	3/93 (3)	1.0 (0.02-13.0)	>.90
Intrapartum complications				
Chorioamnionitis	10/37 (27)	12/111 (11)	3.1 (1.1-8.6)	.02
Prolonged rupture of membranes	9/35 (26)	7/107 (7)	4.9 (1.7-14.1)	.002
Breech presentation	2/37 (5)	10/111 (9)	0.6 (0.1-2.9)	.73
Use of oxytocin	22/36 (61)	51/111 (46)	1.8 (0.9-3.9)	.11
Prolonged second stage of labor	9/36 (25)	4/111 (4)	8.9 (2.2-41.9)	<.001
Fetal heart rate abnormality	17/37 (46)	16/111 (14)	5.0 (2.2-11.6)	<.001
Meconium (moderate to severe)	8/37 (22)	15/111 (14)	1.8 (0.7-4.5)	.24
Cord abnormality	8/37 (22)	7/111 (6)	4.1 (1.4-11.8)	.008
Forceps	1/37 (3)	0/111		.25
Vacuum	9/37 (24)	12/111 (11)	2.7 (1.0-6.8)	.04
Emergency cesarean delivery	13/37 (35)	14/111 (13)	3.8 (1.6-8.9)	.002
Diagnosis of birth asphyxia	6/37 (16)	0/110		<.001
Infant characteristics				
Male sex	15/37 (41)	47/111 (42)	0.9 (0.4-2.0)	.85
Apgar score <7 at 5 min	15/37 (41)	16/110 (15)	4.0 (1.7-9.2)	.01
Resuscitation at birth	23/37 (62)	29/109 (27)	4.5 (2.1-9.9)	<.001
Postdates (≥41 wk)	9/37 (24)	16/110 (15)	1.9 (0.8-4.7)	.17
Gestational weeks, mean (SD)	38.5 (3.7)	37.9 (4.5)		.49
Birth weight, mean (SD), g	3127 (852)	3203 (923)		.66

*Three infants with acute arterial stroke after 2 weeks of age because of meningitis (2) or intraoperative stroke (1) were excluded from this analysis, which excluded 9 frequency-matched controls as well.
†Data reflect the percentage of multigravida women who had a history of miscarriage.
‡Data reflect the percentage of women delivering at term who had preterm labor earlier in the pregnancy.

Univariate Risk Factor Analysis

Although maternal age, race, body mass index, and number of previous miscarriages did not differ between the case and control groups, case mothers were more likely to be primiparous (TABLE 1). Case mothers were also more likely to have a history of infertility, although the difference was not significant (11% vs 4%, $P=.11$). Other prepartum characteristics more commonly observed in case mothers included preeclampsia, oligohydramnios, and decreased fetal movement.

Intrapartum complications associated with PAS included chorioamnionitis, prolonged rupture of membranes, prolonged second stage of labor, fetal heart rate abnormality, cord abnormality, vacuum assistance, and emergency cesarean delivery. A clinical diagnosis of birth asphyxia or hypoxic ischemic encephalopathy was given to 6 infants with PAS (16%), whereas none of the control infants received this diagnosis ($P<.001$). After delivery, infants with PAS were significantly more likely to be given an Apgar score less than 7 at 5 minutes and to require resuscitation (Table 1). The umbilical artery pH was less than 7.0 in 3 of 11 infants with PAS for whom a cord gas result was available.

Chorioamnionitis was significantly associated with PAS only in the absence of fetal distress (OR, 5.4; 95% CI, 1.3-21.6). No other interactions were found in stratified analyses. Furthermore, chorioamnionitis was associated with acute stroke (OR, 6.1; 95% CI, 1.9-19.2) but not with presumed perinatal stroke (OR, 0.7; 95% CI, 0.1-6.0). The risk factors for acute and presumed perinatal stroke were otherwise similar.

Multivariate Risk Factor Analysis

The following variables were entered into the main logistic regression model:

history of infertility, oligohydramnios, preeclampsia, prolonged rupture of membranes, cord abnormality, chorioamnionitis, primiparity, and use of oxytocin (TABLE 2). The risk factors that remained independently associated with PAS were infertility (OR, 7.5; 95% CI, 1.3-45), preeclampsia (OR, 5.3; 95% CI, 1.3-22.0), chorioamnionitis (OR, 3.4; 95% CI, 1.1-10.5), and prolonged rupture of membranes (OR, 3.8; 95% CI, 1.1-12.8). Seven of the 8 infertile women received ovarian-stimulation medications before the conception of the index child. When ovarian stimulation was entered into the model in the place of infertility, the adjusted OR was 13.2 (95% CI, 1.8-98.3).

Although fetal heart rate abnormalities, vacuum extraction, and emergency cesarean delivery were all significantly associated with increased risk of PAS in univariate analyses, none of these factors remained independently associated with PAS after adjustment for the other variables in the multivariate model. Prolonged second stage of labor was a significant univariate predictor of PAS but was also strongly correlated with primiparity. As expected, when primiparity was removed from the model to avoid collinearity, prolonged second stage of labor was an independent predictor of PAS (OR, 5.0; 95% CI, 1.2-21.1; $P=.03$).

Multiple Risk Factors

The following factors were significantly associated with PAS on either univariate or multivariate analysis and could be identified before delivery: primiparity, infertility, oligohydramnios, preeclampsia, chorioamnionitis, prolonged rupture of membranes, decreased fetal movement, prolonged second stage of labor, and fetal heart rate abnormalities. As expected, the risk of PAS increased with the number of these risk factors present (TABLE 3). Only 6% of controls had 3 or more risk factors present compared with 60% of case children (OR, 25.3; 95% CI, 7.9-87.1). When 3 or more risk factors are present, the probability of delivering a child with PAS is as high as 1 in 200.

Placental Pathology

Only 3 placental pathologic examinations were performed in the 40 infants with PAS. Findings included a positive staphylococcus culture on the fetal side (1 term infant), funisitis (1 preterm infant), and acute chorioamnionitis, together with a placental infarction (1 preterm infant). Eleven control placentas were submitted for pathologic examination. Findings among the 3 control infants born at term included a chorangioma (1), placental abruption (1), and a normal placenta (1), whereas for the 8 preterm control infants, findings included acute chorioamnionitis (3) and a normal placenta (5).

COMMENT

Perinatal arterial stroke is the most common cause of hemiplegic cerebral palsy, yet the etiology is poorly understood. To our knowledge, this is the first controlled study of risk factors for PAS within a population that includes all cases diagnosed by neuroimaging, and we found several significant risk factors identified during pregnancy. Intrapartum complications were also more common in infants with PAS, and the risk of PAS was dramatically higher in the presence of multiple risk factors.

The prevalence of PAS has not been clearly determined. Previous population-[15,28,29] and hospital-based[14,16,30] estimates range from 17 to 93 per 100 000 live births, depending on the study design and case definition. We found that PAS was diagnosed in 20 per 100 000 live births. The exclusion of periventricular and watershed distribution infarctions, as well as infarctions that appear to be venous in origin, may explain why our prevalence estimate is within the lower range of previous estimates. Our findings confirm, however, that the rate of PAS is 17 times higher than the incidence of childhood ischemic stroke[31] and as high as the annual incidence of large-vessel ischemic stroke in adults older than 18 years (17-23 per 100 000).[32]

Although infertility did not represent a significant risk factor in univari-

Table 2. Multivariate Odds Ratios for Perinatal Arterial Stroke in a Population of Term and Preterm Infants Born at Kaiser Permanente Northern California, 1997-2002*

	Odds Ratio (95% Confidence Interval)	*P* Value
History of infertility	7.5 (1.3-45.0)	.03
Oligohydramnios	5.4 (0.9-31.3)	.06
Preeclampsia	5.3 (1.3-22.0)	.02
Prolonged rupture of membranes	3.8 (1.1-12.8)	.03
Cord abnormality	3.6 (1.0-12.7)	.05
Chorioamnionitis	3.4 (1.1-10.5)	.03
Primiparity	2.5 (1.0-6.4)	.05

*The variables included in the backward stepwise logistic regression were all those listed above, as well as use of oxytocin, which was dropped from the final model ($P = .49$).

Table 3. Risk of Perinatal Arterial Stroke (PAS) Stratified by the Number of Risk Factors Present Before Delivery

Risk Factors, No.*	No. (%)		Odds Ratio (95% Confidence Interval)	Prevalence of PAS per 1000
	Cases (n = 37)	Controls (n = 111)		
≥1	30/35 (86)	63/107 (59)	4.2 (1.4-14.8)	0.8
≥2	24/35 (69)	27/107 (25)	6.5 (2.6-16.5)	1.3
≥3	21/35 (60)	6/107 (6)	25.3 (7.9-87.1)	5.1
≥4†	11/35 (31)	2/107 (2)	24.1 (4.7-230.0)	4.8

*Includes risk factors that can be identified before delivery: infertility, preeclampsia, chorioamnionitis, prolonged rupture of membranes, primiparity, oligohydramnios, decreased fetal movement, prolonged second stage of labor, and fetal heart rate abnormalities.

†The proportion of case children with 5 or more risk factors was 11%. None of the control children had 5 or more risk factors, so an odds ratio could not be calculated.

ate analysis, it was an independent predictor of PAS after adjustment for confounders. This discrepancy is explained by the fact that infertile women were less likely to have other significant risk factors such as preeclampsia and oligohydramnios, and this negative confounding was largely removed by multivariate analysis. All 4 mothers with infertility who had a child with PAS in our study were treated with ovarian-stimulation drugs. Ovarian hyperstimulation syndrome is known to cause a hypercoagulable state that may lead to arterial and venous thrombosis in the mother.[33,34] To our knowledge, this is the first report of infertility treatment with ovarian stimulation associated with thrombotic complications in the newborn; whether placental thrombosis underlies this relationship requires further study. Others have reported an increased risk of cerebral palsy after infertility treatment.[35,36] Larger studies are needed to confirm the association between infertility and PAS and to determine whether the underlying infertility or its treatment might be responsible.

Preeclampsia, a strong risk factor for PAS in our population, is thought to result from a vascular defect in the placenta bed, leading to reduced uteroplacental blood flow.[37,38] Preeclampsia has been associated with maternal prothrombotic disorders, thrombotic lesions in the placenta, and a maternal history of thromboembolism.[39-41] Furthermore, preeclampsia increases the risk of neonatal sinovenous thrombosis, neonatal encephalopathy, and motor impairment related to PAS.[15,42-44] The relationship between prothrombotic disorders, preeclampsia, placental dysfunction, and PAS deserves further study.

Chorioamnionitis, a diagnosis that is usually based on the presence of maternal intrapartum fever, has received much attention as a predictor for cerebral palsy.[45] However, to our knowledge, this is the first report of clinical chorioamnionitis acting as an independent risk factor for PAS. Interestingly, chorioamnionitis was associated only with PAS that was diagnosed in the neonatal period and not with PAS diagnosed later in infancy, which suggests that the pathogenesis of PAS may differ for infants with earlier presentation compared with those with a later presentation. Alternatively, the presence of chorioamnionitis may increase the likelihood of neonatal symptoms, thus prompting earlier recognition of PAS.

We found that intrapartum complications were more common in infants with PAS than in control infants, which was consistent with previous reports.[20,21,46] However, complications such as fetal heart rate abnormalities were no longer independently associated with PAS after adjustment for maternal variables. Furthermore, although fetal distress and low Apgar scores often lead to a clinical diagnosis of birth asphyxia, these complications do not always reflect a global hypoxic-ischemic event, as implied by the term *birth asphyxia*. In our study, all 6 infants with PAS who were diagnosed with birth asphyxia had a focal arterial infarction as opposed to the more typical neuroimaging findings of hypoxic-ischemic brain injury, such as deep gray-matter or arterial-watershed injury, reminding us that the clinical diagnosis of birth asphyxia is not specific for any single pathogenetic mechanism of brain injury.

Our study was subject to a number of limitations. Despite the large source population, the number of final cases was relatively small, resulting in wide CIs for several effect estimates. There may be underascertainment of PAS because 11% of our cohort was lost to follow-up by 1 year of age, and children with subtle neurologic deficits may not have received a neuroimaging study to identify a PAS. Insufficient information was available on possible risk factors such as smoking, drug use, and socioeconomic indicators. Given the retrospective nature of the study, we lacked a uniform neuroimaging protocol and relied on medical record documentation for determining the presence of risk factors. However, physicians typically document maternal complications in the medical records before knowing the outcome of the child, thus minimizing potential reporting bias. Strengths of our study include the population-based setting; blinded evaluation of maternal, prepartum, and intrapartum factors; and the selection of an appropriate control group.

Perinatal arterial stroke has been attributed to etiologies such as congenital heart disease,[47] polycythemia,[13] in utero cocaine exposure,[48] and neonatal meningitis.[49] Among our cases, only 2 infants had neonatal meningitis, 1 had an iatrogenic stroke from brain surgery, no infants had major congenital heart disease, and 1 infant had a mild polycythemia that resolved without intervention. If one makes an assumption that the 4 independent risk factors found in this study do in fact play a causal role, the population-attributable fractions (chorioamnionitis, 21%; infertility, 19%; preeclampsia, 16%; and prolonged rupture of membranes, 16%) suggest that these factors may account for a significant proportion of PAS cases.

A thromboembolic event originating from an intracranial vessel, extracranial vessel, the heart, or the placenta may lead to an arterial stroke that occurs in the perinatal period.[1] Although placental findings have rarely been described in PAS, pathologic studies have suggested that placental infarction and inflammation may be related to cerebral palsy, a long-term outcome of PAS.[50-53] We found similar placental abnormalities in our infants with PAS, although only 3 placentas were examined. Maternal conditions that affect placental function, such as preeclampsia and chorioamnionitis, were found to be independent risk factors for PAS. Together, these data suggest that the placenta may play an important role in the pathogenesis of PAS, although no conclusions can be drawn from this study, given the small number of placentas examined.

Future studies that provide additional data on placental pathology, coagulation disorders in the mother and fetus, and comprehensive neuroimaging findings may further elucidate the underlying pathogenetic mechanisms

of PAS. Only with an improved understanding of what causes PAS will we determine how to prevent this important cause of neurologic disability in children.

Author Contributions: Dr Wu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Croen, Backstrand, Ferriero, Fullerton, Wu.
Acquisition of data: Lee, Croen, Backstrand, Yoshida, Henning, Lindan, Barkovich, Wu.
Analysis and interpretation of data: Lee, Croen, Backstrand, Ferriero, Wu.
Drafting of the manuscript: Lee, Backstrand, Henning, Wu.
Critical revision of the manuscript for important intellectual content: Croen, Backstrand, Yoshida, Lindan, Ferriero, Fullerton, Barkovich, Wu.
Statistical analysis: Lee, Wu.
Obtained funding: Ferriero, Wu.
Administrative, technical, or material support: Lee, Croen, Yoshida, Henning, Wu.
Study supervision: Croen, Barkovich, Wu.
Financial Disclosures: None reported.
Funding/Support: This study was funded by the United Cerebral Palsy Foundation. Dr Wu was supported in part by NS35902 from the National Institutes of Health and the National Institute of Neurological Disorders and Stroke, and Ms Lee was supported by the Doris Duke Clinical Research Training Program.
Role of the Sponsor: The United Cerebral Palsy Foundation had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.
Acknowledgment: We thank Carla Stelling, BS, Roxana Odouli, MSPH, Rick Riordan, BS, and Kim Detels for their research assistance, as well as Karin Nelson, MD, S. Claiborne Johnston, MD, PhD, and Thomas B. Newman, MD, MPH, for their mentorship and careful reviews of the manuscript.

REFERENCES

1. Nelson KB, Lynch JK. Stroke in newborn infants. *Lancet Neurol*. 2004;3:150-158.
2. Mercuri E, Rutherford M, Cowan F, et al. Early prognostic indicators of outcome in infants with neonatal cerebral infarction: a clinical, electroencephalogram, and magnetic resonance imaging study. *Pediatrics*. 1999;103:39-46.
3. Golomb MR, MacGregor DL, Domi T, et al. Presumed pre- or perinatal arterial ischemic stroke: risk factors and outcomes. *Ann Neurol*. 2001;50:163-168.
4. deVeber GA, MacGregor D, Curtis R, Mayank S. Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. *J Child Neurol*. 2000;15:316-324.
5. de Vries LS, Groenendaal F, Eken P, van Haastert IC, Rademaker KJ, Meiners LC. Infarcts in the vascular distribution of the middle cerebral artery in preterm and fullterm infants. *Neuropediatrics*. 1997;28:88-96.
6. Humphreys P, Whiting S, Pham B. Hemiparetic cerebral palsy: clinical pattern and imaging in prediction of outcome. *Can J Neurol Sci*. 2000;27:210-219.
7. Koelfen W, Freund M, Varnholt V. Neonatal stroke involving the middle cerebral artery in term infants: clinical presentation, EEG and imaging studies, and outcome. *Dev Med Child Neurol*. 1995;37:204-212.
8. Sreenan C, Bhargava R, Robertson CM. Cerebral infarction in the term newborn: clinical presentation and long-term outcome. *J Pediatr*. 2000;137:351-355.
9. Wulfeck BB, Trauner DA, Tallal PA. Neurologic, cognitive, and linguistic features of infants after early stroke. *Pediatr Neurol*. 1991;7:266-269.
10. Uvebrant P. Hemiplegic cerebral palsy: aetiology and outcome. *Acta Paediatr Scand Suppl*. 1988;345:1-100.
11. Wu YW, Escobar GJ, Grether JK, Croen LA, Greene JD, Newman TB. Chorioamnionitis and cerebral palsy in term and near-term infants. *JAMA*. 2003;290:2677-2684.
12. Jan MM, Camfield PR. Outcome of neonatal stroke in full-term infants without significant birth asphyxia. *Eur J Pediatr*. 1998;157:846-848.
13. Amit M, Camfield PR. Neonatal polycythemia causing multiple cerebral infarcts. *Arch Neurol*. 1980;37:109-110.
14. Govaert P, Matthys E, Zecic A, Roelens F, Oostra A, Vanzieleghem B. Perinatal cortical infarction within middle cerebral artery trunks. *Arch Dis Child Fetal Neonatal Ed*. 2000;82:F59-F63.
15. Wu YW, March WM, Croen LA, Grether JK, Escobar GJ, Newman TB. Perinatal stroke in children with motor impairment: a population-based study. *Pediatrics*. 2004;114:612-619.
16. Estan J, Hope P. Unilateral neonatal cerebral infarction in full term infants. *Arch Dis Child Fetal Neonatal Ed*. 1997;76:F88-F93.
17. Hagstrom JN, Walter J, Bluebond-Langner R, Amatniek JC, Manno CS, High KA. Prevalence of the factor V Leiden mutation in children and neonates with thromboembolic disease. *J Pediatr*. 1998;133:777-781.
18. Hogeveen M, Blom HJ, Van Amerongen M, Boogmans B, Van Beynum IM, Van De Bor M. Hyperhomocysteinemia as risk factor for ischemic and hemorrhagic stroke in newborn infants. *J Pediatr*. 2002;141:429-431.
19. Mercuri E, Cowan F, Gupte G, et al. Prothrombotic disorders and abnormal neurodevelopmental outcome in infants with neonatal cerebral infarction. *Pediatrics*. 2001;107:1400-1404.
20. Ment LR, Duncan CC, Ehrenkranz RA. Perinatal cerebral infarction. *Ann Neurol*. 1984;16:559-568.
21. Mannino FL, Trauner DA. Stroke in neonates. *J Pediatr*. 1983;102:605-610.
22. Lien JM, Towers CV, Quilligan EJ, de Veciana M, Toohey JS, Morgan MA. Term early-onset neonatal seizures: obstetric characteristics, etiologic classifications, and perinatal care. *Obstet Gynecol*. 1995;85:163-169.
23. deVeber G; for the Canadian Paediatric Ischemic Stroke Study Group. Canadian Paediatric Ischemic Stroke Registry: analysis of children with arterial ischemic stroke. *Ann Neurol*. 2000;48:514.
24. Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. *Am J Public Health*. 1992;82:703-710.
25. Lynch JK, Nelson KB. Epidemiology of perinatal stroke. *Curr Opin Pediatr*. 2001;13:499-505.
26. *Intrauterine Growth and Neonatal Risk in California*. Sacramento: State of California Dept of Health; 1976.
27. Stata Corp. *STATA 7 Reference Manual*. College Station, Tex: Stata Press; 2000.
28. Lynch JKL, Nelson KB. Neonatal stroke in the United States: results of the National Hospital Discharge Survey, 1980-1998. *Neurology*. 2001;56:A10.
29. Andrew ME, Monagle P, deVeber G, Chan AK. Thromboembolic disease and antithrombotic therapy in newborns. *Hematology (Am Soc Hematol Educ Program)*. 2001:358-374.
30. Perlman JM, Rollins NK, Evans D. Neonatal stroke: clinical characteristics and cerebral blood flow velocity measurements. *Pediatr Neurol*. 1994;11:281-284.
31. Fullerton HJ, Wu YW, Zhao S, Johnston SC. Risk of stroke in children: ethnic and gender disparities. *Neurology*. 2003;61:189-194.
32. Schneider AT, Kissela B, Woo D, et al. Ischemic stroke subtypes: a population-based study of incidence rates among blacks and whites. *Stroke*. 2004;35:1552-1556.
33. Yoshii F, Ooki N, Shinohara Y, Uehara K, Mochimaru F. Multiple cerebral infarctions associated with ovarian hyperstimulation syndrome. *Neurology*. 1999;53:225-227.
34. Rogolino A, Coccia ME, Fedi S, et al. Hypercoagulability, high tissue factor and low tissue factor pathway inhibitor levels in severe ovarian hyperstimulation syndrome: possible association with clinical outcome. *Blood Coagul Fibrinolysis*. 2003;14:277-282.
35. Stromberg B, Dahlquist G, Ericson A, Finnstrom O, Koster M, Stjernqvist K. Neurological sequelae in children born after in-vitro fertilisation: a population-based study. *Lancet*. 2002;359:461-465.
36. Ericson A, Nygren KG, Olausson PO, Kallen B. Hospital care utilization of infants born after IVF. *Hum Reprod*. 2002;17:929-932.
37. Roberts JM, Cooper DW. Pathogenesis and genetics of preeclampsia. *Lancet*. 2001;357:53-56.
38. Shah DM. Perinatal implications of maternal hypertension. *Semin Pediatr Neurol*. 2001;8:108-119.
39. Kupferminc MJ, Eldor A, Steinman N, et al. Increased frequency of genetic thrombophilia in women with complications of pregnancy [published correction appears in *N Engl J Med*. 1999;341:384]. *N Engl J Med*. 1999;340:9-13.
40. Salafia CM, Pezzullo JC, Lopez-Zeno JA, Simmens S, Minior VK, Vintzileos AM. Placental pathologic features of preterm preeclampsia. *Am J Obstet Gynecol*. 1995;173:1097-1105.
41. Pabinger I, Grafenhofer H, Kaider A, et al. Preeclampsia and fetal loss in women with a history of venous thromboembolism. *Arterioscler Thromb Vasc Biol*. 2001;21:874-879.
42. Hunt RW, Badawi N, Laing S, Lam A. Preeclampsia: a predisposing factor for neonatal venous sinus thrombosis? *Pediatr Neurol*. 2001;25:242-246.
43. Badawi N, Kurinczuk JJ, Keogh JM, et al. Antepartum risk factors for newborn encephalopathy: the Western Australian case-control study. *BMJ*. 1998;317:1549-1553.
44. Hnat MD, Sibai BM, Caritis S, et al. Perinatal outcome in women with recurrent preeclampsia compared with women who develop preeclampsia as nulliparas. *Am J Obstet Gynecol*. 2002;186:422-426.
45. Wu YW, Colford JM. Chorioamnionitis as a risk factor for cerebral palsy: a meta-analysis. *JAMA*. 2000;284:1417-1424.
46. Ramaswamy V, Miller SP, Barkovich AJ, Partridge JC, Ferriero DM. Perinatal stroke in term infants with neonatal encephalopathy. *Neurology*. 2004;62:2088-2091.
47. Pellicer A, Cabanas F, Garcia-Alix A, Perez-Higueras A, Quero J. Stroke in neonates with cardiac right-to-left shunt. *Brain Dev*. 1992;14:381-385.
48. Heier LA, Carpanzano CR, Mast J, Brill PW, Winchester P, Deck MD. Maternal cocaine abuse: the spectrum of radiologic abnormalities in the neonatal CNS. *AJNR Am J Neuroradiol*. 1991;12:951-956.
49. Ment LR, Ehrenkranz RA, Duncan CC. Bacterial meningitis as an etiology of perinatal cerebral infarction. *Pediatr Neurol*. 1986;2:276-279.
50. Kraus FT, Acheen VI. Fetal thrombotic vasculopathy in the placenta: cerebral thrombi and infarcts, coagulopathies, and cerebral palsy. *Hum Pathol*. 1999;30:759-769.
51. Kraus FT. Cerebral palsy and thrombi in placental vessels of the fetus: insights from litigation. *Hum Pathol*. 1997;28:246-248.
52. Redline RW, O'Riordan MA. Placental lesions associated with cerebral palsy and neurologic impairment following term birth. *Arch Pathol Lab Med*. 2000;124:1785-1791.
53. Burke CJ, Tannenberg AE, Payton DJ. Ischaemic cerebral injury, intrauterine growth retardation, and placental infarction. *Dev Med Child Neurol*. 1997;39:726-730.