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

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Perinatal arterial ischemic stroke (PAS) is an important cause of cerebral palsy and other neurologic disabilities, including epilepsy and cognitive impairment. Arterial ischemic stroke is diagnosed primarily in neonates born at term and is responsible for 50% to 70% of congenital hemiplegic cerebral palsy in this population.

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. Others have failed to find a significant difference in the frequency of perinatal complications between infants with PAS and controls. Hematologic disorders, including factor V Leiden mutation and hyperhomocysteinemia, may also play a role in the pathogenesis of PAS.

Previous studies of PAS are subject to a number of important limitations. Most describe only a small number of children or lack an adequate comparison group. We found previously that preeclampsia and intrauterine growth restriction are independent risk factors for PAS. However, our earlier study did not include a control group.

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 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.

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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 (KPMP). The KPMP is a large managed care organization that provides care for more than 30% of the population in northern California. The members of KPMP are demographically similar to the California population, except that the very poor and very wealthy are underrepresented. All study procedures were approved by the institutional review boards at KPMP 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. 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. 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.* 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. 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 χ² 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.

RESULTS
Among 1970 children who had either a head-imaging report containing a keyword suggestive of stroke, or who carried a physician diagnosis of stroke, cerebral palsy, neonatal seizures, or a related diagnosis.141 (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

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.

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Infant characteristics

Intrapartum complications

Birth weight, mean (SD), g 3127 (852) 3203 (923) .66

Gestational weeks, mean (SD) 38.5 (3.7) 37.9 (4.5) .49

Prepartum complications

PretermInfants Born at Kaiser Permanente Northern California, 1997-2002
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‡Data reflect the percentage of women delivering at term who had preterm labor earlier in the pregnancy.
†Data reflect the percentage of multigravida women who had a history of miscarriage.

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

<table>
<thead>
<tr>
<th>Maternal characteristics</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>2/37 (5) 9/111 (8) 0.7 (0.1-3.9)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>20-34</td>
<td>26/37 (70) 87/111 (78) Reference</td>
<td></td>
</tr>
<tr>
<td>≥35</td>
<td>9/37 (24) 15/111 (14) 2.0 (0.8-5.0)</td>
<td>.14</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>14/37 (39) 36/111 (32) Reference</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>4/37 (11) 16/111 (14) 0.6 (0.1-2.5)</td>
<td>.56</td>
</tr>
<tr>
<td>Hispanic</td>
<td>11/37 (30) 33/111 (30) 0.9 (0.3-2.1)</td>
<td>.74</td>
</tr>
<tr>
<td>Asian</td>
<td>8/37 (22) 25/111 (23) 0.8 (0.3-2.2)</td>
<td>.70</td>
</tr>
<tr>
<td>Other</td>
<td>0/37 1/111 (1)</td>
<td></td>
</tr>
<tr>
<td>High body mass index (≥30)</td>
<td>6/30 (20) 14/89 (16) 1.3 (0.5-3.8)</td>
<td>.59</td>
</tr>
<tr>
<td>Primiparity</td>
<td>27/37 (73) 49/111 (44) 3.4 (1.5-7.6)</td>
<td>.002</td>
</tr>
<tr>
<td>Previous miscarriage†</td>
<td>3/21 (14) 14/75 (19) 0.7 (0.1-3.0)</td>
<td>.76</td>
</tr>
<tr>
<td>History of infertility</td>
<td>4/37 (11) 4/111 (4) 3.2 (0.6-18.3)</td>
<td>.11</td>
</tr>
<tr>
<td>Ovarian stimulation</td>
<td>4/37 (11) 3/111 (3) 4.4 (0.7-30.9)</td>
<td>.07</td>
</tr>
</tbody>
</table>

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) 3/111 (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.

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.

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 min 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 placetas 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-based14,16,30 estimates range from 17 to 93 per 100000 live births, depending on the study design and case definition. We found that PAS was diagnosed in 20 per 100000 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 stroke31 and as high as the annual incidence of large-vessel ischemic stroke in adults older than 18 years (17-23 per 100000).32

Although infertility did not represent a significant risk factor in univariate analysis it was strongly associated with the presence of multiple risk factors identified in the multivariate analyses. Theornado that PAS was diagnosed in 20 per 100000 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 stroke31 and as high as the annual incidence of large-vessel ischemic stroke in adults older than 18 years (17-23 per 100000).32

<table>
<thead>
<tr>
<th>Risk Factors, No.*</th>
<th>Cases (n = 37)</th>
<th>Controls (n = 111)</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>Prevalence of PAS per 100000</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1</td>
<td>30/35 (86)</td>
<td>63/107 (59)</td>
<td>4.2 (1.4-14.8)</td>
<td>0.8</td>
</tr>
<tr>
<td>≤2</td>
<td>24/35 (69)</td>
<td>27/107 (25)</td>
<td>6.5 (2.6-16.5)</td>
<td>1.3</td>
</tr>
<tr>
<td>≤3</td>
<td>21/35 (60)</td>
<td>6/107 (6)</td>
<td>25.3 (7.9-87.1)</td>
<td>5.1</td>
</tr>
<tr>
<td>≥4†</td>
<td>11/35 (31)</td>
<td>2/107 (2)</td>
<td>24.1 (4.7-230.0)</td>
<td>4.8</td>
</tr>
</tbody>
</table>

*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).

*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.
characteristics associated with newborn stroke

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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 and the accuracy of the 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.

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