Antenatal Factors Associated With Perinatal Arterial Ischemic Stroke

Véronique Darmency-Stamboul, MD; Corinne Chantegret, MD; Cyril Ferdynus, PhD; Nathalie Mejean, MD; Christine Durand, MD; Paul Sagot, MD, PhD; Maurice Giroud, MD, PhD; Yannick Bejot, MD, PhD; Jean Bernard Gouyon, MD, PhD

Background and Purpose—Perinatal arterial ischemic stroke (PAIS) is a common cause of hemiplegic cerebral palsy in children. The diagnosis of PAIS is based on cerebral imaging. The objective of our study was to determine prenatal risk factors associated with PAIS.

Methods—A retrospective case–control study was nested in the whole population of Burgundy, France, from January 2000 to December 2007. Case patients were confirmed by review of brain imaging and medical records. Three control subjects per case were randomly selected from the study population by sex, term, place, and year of birth.

Results—PAIS was confirmed in 32 patients and its incidence was one per 4400 live births. In comparison to control subjects, clinical conditions significantly associated to cases were gestational diabetes (16.1% versus 4.2%; \(P=0.04\)), fetal heart rate abnormalities (35.5% versus 10.9%; \(P=0.001\)), and meconium-stained liquor (40% versus 12%; \(P<0.001\)). At the limit of statistical significance were found maternal smoking before (39.3% versus 22.9%; \(P=0.08\)) and during pregnancy (32.1% versus 16.7%; \(P=0.07\)), cord abnormalities (29% versus 14.1%; \(P=0.06\)), and cesarean delivery (28.1% versus 14.6%; \(P=0.08\)). In the multivariate analysis, maternal smoking during pregnancy (OR, 3.1; 95% CI, 1.1–8.8; \(P=0.04\)) was the only risk factor significantly associated with PAIS.

Conclusions—This study is the first to identify maternal smoking during pregnancy as an independent prenatal risk factor of PAIS. Additional prospective studies are needed to confirm this result and to investigate the role of maternal smoking in fetal and neonatal thrombogenesis. (Stroke. 2012;43:2307-2312.)

Key Words: antenatal risk factors maternal smoking perinatal arterial ischemic stroke

Perinatal arterial ischemic stroke (PAIS) is the most frequent type of pediatric stroke. Its incidence is estimated between one per 2500 and one per 4000 live births and could increase because of a better diagnosis allowed by the emergence of new prenatal and neonatal cerebral imaging techniques. PAIS is also the main cause of hemiplegic cerebral palsy in children and it has been recently shown to induce cognitive impairment. Several questions persist about the risk factors of PAIS and its prevention. Recent studies have suggested that maternal risk factors for PAIS include primiparity, infertility, chorioamnionitis, prolonged rupture of membranes, pre-eclampsia, and intrauterine growth retardation. Nevertheless, no risk factors for maternal thrombosis have been investigated as potential risk factors for PAIS. A recent study of 248 neonates with PAIS concluded that definitive causes for most PAIS have not been established, and case–control studies are required.

The aim of this study was to identify prenatal risk factors associated with symptomatic PAIS at a regional level.

Materials and Methods

The study included the 141879 live births with gestational age ≥28 weeks gestation recorded from January 1, 2000, to December 31, 2007, in Burgundy, a French region with approximately 18500 births annually. Neonatal care was provided in one Level III, 7 Level II, and 9 Level I hospitals. Pediatric care was provided in 14 of these hospitals.

Hospitalizations for PAIS during the 2000 to 2007 period were recorded in the French hospitalization database (Programme de Médicalisation des Systèmes d’Information), which was made available by the Hospital Information Agency. Each hospital stay was identified by an Anonymous Discharge Summary, defined by an anonymous record of medical and administrative information. Hospital stays for PAIS were identified by the code of the International Classification of Diseases, 10th Revision: R568 (seizures), P90 (neonatal seizures), P910 (neonatal cerebral infarct), G802 (congenital hemiplegia), P524 (neonatal hemorrhage intracerebral), and P526 (neonatal cerebellar hemorrhage). Anonymous Discharge Summaries for which the main related or associated diagnosis did not correspond to these codes were excluded.

The medical files of mothers and children with suspected PAIS in the Programme de Médicalisation des Systèmes d’Information database were reviewed by one of the authors (V.D.-S.) using a standardized protocol. Gestational data were obtained from medical files of mothers.

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From the Departments of Pediatrics (V.D.-S., C.C.), Radiology (N.M.), Obstetrics (P.S.), and Neurology (M.G., Y.B.), University Hospital, Dijon, France; the Department of Biostatistics (C.F.) and the Department of Pediatrics (GHSR; J.B.G.), University Hospital, Reunion Island, France (C.F.); the Dijon Stroke Registry, EA4184, Faculty of Medicine of Dijon, University of Burgundy, Burgundy, France (C.F., P.S., M.G., Y.B., J.B.G.); and the Department of Radiology, Hospital of Beaune, Beaune, France (C.D.).

Correspondence to Véronique Darmency-Stamboul, MD, Service de Pédiatrie, Hôpital d’Enfants, 10 Bd du Maréchal de Lattre de Tassigny, 21029 Dijon cédex, France. E-mail veronique.darmency-stamboul@chu-dijon.fr

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These files were filled in by obstetricians and midwives. Data from maternal files could not be modified after delivery.

The diagnosis of perinatal stroke (acute or retrospective, arterial or venous, ischemic, hemorrhagic) had to be ascertained by neuroimaging or by pathology. Therefore, newborns were excluded when neuroimaging was not performed or the report of the neuroimaging study did not reveal PAIS (particularly, patients with global ischemic encephalopathy, subarachnoid hemorrhage, perinatal intraventricular hemorrhage, and brain malformations).

Each case of PAIS was matched with 3 control subjects for sex, gestational age, place, and year of birth. The control subjects were selected using records contained in a regional perinatal database that includes all live births in Burgundy since 2000.5

Finally, 711 children were selected from the Programme de Médicalisation des Systèmes d’Information database and the corresponding obstetric and neonatal files were reviewed. Forty-six of the 711 medical records were identified as potential perinatal strokes or presumed perinatal strokes. The stroke was considered to be presumed perinatal if a child had been considered neurologically normal before 1 month of age but was later diagnosed with a remote arterial infarction. Then, 2 pediatric neuroradiologists (N.M. and C.D.) independently reviewed the brain MRI and CT scan reports of the 46 infants. The reviewers disagreed for 3 patients, who were therefore excluded. For more homogeneity, 2 hemorrhagic strokes without ischemia and 3 border zone infarcts were also excluded to allow an analysis strictly limited to PAIS. The Figure shows the selection process of the 32 cases of PAIS included in the case–control study.

The medical records of cases and control subjects provided the variables presented in Tables 1, 2, and 3. Maternal body mass index was calculated from weight and height measurements according to the formula: weight (kg)/height (cm)^2. Intrauterine growth restriction was defined as birth weight below the third percentile according to the fetal growth curves of Burgundy.6 Gestational diabetes was defined as a serum glucose level at the beginning of pregnancy of 0.95 g/L and/or a positive O’Sullivan test. Oligohydramnios was diagnosed by ultrasound examination and defined as a volume of amniotic liquid <250 mL from the 20th week of gestation. Seizures were defined when a physician diagnosed clinical seizures.

Neurological outcome was assessed by each physician referent of each infant and noted in the medical file. Then these data were collected by one of the author (V.D.-S.).

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**Figure.** Process of the study.

- **N: 141 879** children live-born in Burgundy from 2000 to 2007 with GA ≥28 weeks
- **N: 46** children with neuroimaging of potential PAIS reviewed by 2 neuroradiologists
- **N: 37** children with: Arterial infarct Venous infarct Hemorrhagic stroke
- **N: 665** Excluded No evidence of PAIS No neuroimaging performed
- **N: 9** excluded for global ischemic encephalopathy, SAH, PIH.
- **N: 5** excluded for Hemorrhagic stroke Venous and border zone infarct
- **N: 711** children with codes of ICD 10: R568; P90; P910; G802; P524; P526
- **N: 141 168** Excluded
- **N: 32 cases of PAIS and PPIS**
- **N: 96 controls**

GA: gestational age, ICD: International classification of diseases, SAH: subarachnoid hemorrhage, PIH: perinatal intraventricular hemorrhage, PPIS: presumed perinatal ischemic stroke
Table 1. Neuroimaging Features of 32 Cases of Perinatal Arterial Ischemic Stroke

<table>
<thead>
<tr>
<th>Cerebral imaging</th>
<th>Neonatal Presentation (N=24)</th>
<th>Delayed Presentation (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>23 96</td>
<td>7 87</td>
</tr>
<tr>
<td>CT</td>
<td>18 75</td>
<td>4 50</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>19 79</td>
<td>1 12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Side of the damage</th>
<th>No.</th>
<th>Percent</th>
<th>No.</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>11 46</td>
<td>2 25</td>
<td>11 46</td>
<td>2 25</td>
</tr>
<tr>
<td>Right</td>
<td>9 37</td>
<td>5 62</td>
<td>9 37</td>
<td>5 62</td>
</tr>
<tr>
<td>Bilateral</td>
<td>4 17</td>
<td>1 13</td>
<td>4 17</td>
<td>1 13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular location</th>
<th>One artery</th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Middle cerebral artery (MCA)</td>
<td>19 79</td>
<td>6 75</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anterior cerebral artery (ACA)</td>
<td>3 12</td>
<td>0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posterior cerebral artery (PCA)</td>
<td>0 0</td>
<td>1 12.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Two arteries</td>
<td>0 0</td>
<td>0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Three arteries (MCA and ACA)</td>
<td>2 8</td>
<td>1 12.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemorrhagic–ischemic lesions</td>
<td>5 18</td>
<td>0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Statistical Analysis
The qualitative and quantitative variables were expressed as percentages and means (SDs), respectively. Univariate analysis of quantitative data were performed using one-way analysis of variance or, if the normality assumption was violated, by the Kruskal-Wallis test. The qualitative and quantitative variables were expressed as percentages. ORs and their 95% CIs were estimated.

The multivariate analysis was performed using a conditional logistic regression model with a backward selection method. Covariables included in the initial model were those identified with a probability value <0.20 in the univariate analysis and also those considered as risk factors in other studies. Interactions were systematically tested and removed from the final model if they did not reach statistical significance. ORs and their 95% CIs were estimated.

All hypotheses were tested at the α risk of 0.05. Statistical analyses were performed using SAS 9.2 (SAS Institute Inc).

Table 2. Neurological Outcome of the 32 Cases of PAIS at 19 Mo of Median Age

<table>
<thead>
<tr>
<th>Neurological Outcome</th>
<th>No. of Cases/ Total No. of Cases</th>
<th>No. of Cases/ Total No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired walking</td>
<td>0/19</td>
<td>1/8</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>4/19</td>
<td>8/8</td>
</tr>
<tr>
<td>Dystonia</td>
<td>4/19</td>
<td>6/8</td>
</tr>
<tr>
<td>Cognitive disorders</td>
<td>0/19</td>
<td>2/8</td>
</tr>
<tr>
<td>Language disorder</td>
<td>2/19</td>
<td>1/8</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>3/19</td>
<td>1/8</td>
</tr>
<tr>
<td>Death</td>
<td>3/22</td>
<td>0/8</td>
</tr>
</tbody>
</table>

PAIS indicates perinatal arterial ischemic stroke.

Results
Characteristics of PAIS
Within the birth cohort of 141,879 neonates, we identified 32 cases of PAIS. The incidence was therefore one case for 4,400 live births. The majority of the 32 children with symptomatic PAIS were delivered at term (87%), 59% were boys, and 75% were diagnosed in the neonatal period. Median gestational age was 40 weeks of gestation (range, 36–42 weeks). The 4 preterm infants were born at 36 weeks of gestation.

In the 24 cases with neonatal diagnosis, the median age at presentation was 36 hours (range, 24–72 hours). The major symptom in the neonatal period was seizure, which occurred in 23 cases (96%). Seizures were focal in 20 cases (83%) and/or generalized in 14 cases (58%). Other symptoms such as hypotonia (41.9%) or apnea (25.8%) were also observed.

In the 8 cases with delayed diagnosis, the median age at presentation was 8 months (range, 5–22 months). The major symptom was hemiplegia, which occurred in 7 cases. Dystonia was observed in 5 cases. Among these 8 cases, 6 presented no other neonatal diseases and did not require hospitalization at birth. The 2 remaining cases were hospitalized during the neonatal period: the first with anal imperforation and the second with congenital diaphragmatic hernia.

The diagnosis of PAIS was made using transfontanellar ultrasound (62%) and/or CT scan (69%) and/or MRI (94%; Table 1). In these 32 patients with PAIS, stroke was limited to the middle cerebral artery territory in 78% of cases. Lesions were left-sided in 40.6%, right-sided in 43.7%, and bilateral in 15.7%. Among the 32 strokes, 5 were initially ischemic and then hemorrhagic. An electroencephalogram was performed in 29 cases (91%) and was abnormal in 25 cases (86%) with slow waves or focal spikes.

In this cohort, 3 children died (9%) and 2 were lost to follow-up (Table 2). Neurological outcome was assessed at a median age of 19 months (range, 12–96) in the 27 other children. A single infant was still unable to walk at the last examination at 4 years. The average age of walking was 13.3 (±2.1) months. Four children developed epilepsy (one with West syndrome, one with severe refractory focal epilepsy, and 2 with well-controlled focal epilepsy). Hemiplegia was found in 12 of 27 infants and dystonia in 37% of cases. Four of the 19 children diagnosed with PAIS in the neonatal period had hemiplegia (21%) with no clinical or radiological symptoms predictive of this symptom.

A thrombophilia workup was available for 15 patients and 4 of them (27%) had abnormalities: one deficit in antithrombin III, protein C and S; one deficit in protein S and factor V Leiden; one deficit in proteins C and S; and one deficit in protein S. The thrombophilia workup was performed in the neonatal period for 3 newborns and between 1 and 12 months for 12 newborns. Infants with (n=15) and without (n=17) thrombophilia workup had similar clinical characteristics (data not shown).

Factors Associated With PAIS
In the univariate analysis comparing the 32 cases and their 96 control subjects, significant differences were observed for gestational diabetes (16.1% versus 4.2%; P=0.04), fetal heart...
rate abnormalities (35.5% versus 10.9%; \( P = 0.001 \)), and meconium-stained amniotic fluid (40% versus 12%; \( P < 0.001 \); Table 3). Maternal cigarette smoking before pregnancy (39.3% versus 22.9%; \( P = 0.08 \)) and during pregnancy (32.1% versus 16.7%; \( P = 0.07 \)) were associated with a nonsignificant increase in the likelihood of PAIS as were cord abnormalities (29% versus 14.1%; \( P = 0.06 \)) and cesarean delivery (28.1% versus 14.6%; \( P = 0.08 \)). Birth weights were similar in PAIS (3.18 ± 0.56 kilos) and control subjects (3.27 ± 0.5 kilos; \( P = 0.4 \)).

In the final multivariate model, smoking during pregnancy was significantly associated with an increase in the risk of PAIS (OR, 3.1; 95% CI, 1.1–8.8; \( P = 0.04 \)). Moreover, 2 other independent factors were found associated with a marginally nonsignificant increase in the risk of PAIS and were kept in the final model: diabetes (OR, 3.2; 95% CI, 0.8–13.5; \( P = 0.10 \)) and cord abnormalities (OR, 2.9; 95% CI, 0.9–9.1; \( P = 0.07 \)).

It is worthy to note that 33 women smoked before pregnancy; 25 of these women (75.8%) continued smoking during pregnancy until the end of gestation and 8 (24.2%) stopped smoking either before getting pregnant or early in pregnancy when pregnancy was diagnosed.

### Discussion

This population-based study has many similarities with previous studies for the incidence, clinical symptoms, neurolog-
tical imaging, and outcomes of PAIS. However, this study identified for the first time the potential deleterious role of maternal smoking as a promoter of symptomatic PAIS. This adds a new adverse effect of tobacco smoking in young women to the already long list.

The incidence of symptomatic PAIS in this study was one per 4400 live births. The consensus of the National Institute of Neurological Disorders and Stroke previously concluded that this incidence ranges between one per 2300 and one per 5000 births. Our study could have slightly underestimated the incidence of symptomatic PAIS because home births, children not diagnosed because neurological symptoms were mild, and children only cared for in an ambulatory setting were not recorded in the Programme de Médicalisation des Systèmes d’Information database. However, the rarity of births at home in Burgundy (40 annually) and the organization of perinatal and pediatric care in France make these biases more theoretical than reality.

The preponderance of boys (59%) in this cohort was also found in other recent studies: 62% in a French study and 57% in an International study. Golomb et al found that boys with PAIS had a higher birth weight, and they hypothesized that a traumatic and complicated delivery could be a cause of PAIS. This assumption was not confirmed in our study because no infant presented macrosomia at birth.

Epileptic seizures, among which 83% were focal, were the leading neurological symptom, occurring in 96% of children with symptomatic PAIS. Other frequent symptoms were hypotonia (41.9%) and apnea (25.8%). This clinical picture seems to be characteristic of PAIS according to previous studies. For instance, Chabrier et al found seizures in 91% of PAIS (74% of focal seizures), hypotonia in 46%, and apnea in 7%. The diagnosis of PAIS in cases of hemiplegia was delayed in 25% of cases at a median age of 8 months. A delayed presentation after the age of 2 months was observed in 40% to 65% of PAIS in previous studies.

The radiological presentation of PAIS in this cohort showed that most strokes (78%) were limited to the middle cerebral artery territory (with classical late thalamic atrophy). This finding is in keeping with other studies with corresponding rates of 74% or 89%. The retrospective nature of this study precluded precise information about the incidence of thrombophilia in symptomatic PAIS. Although the incidence of thrombophilic disorders (27%) was higher than the 0.02% to 5% observed in the global population without thrombosis, 3 of the abnormal results were obtained in the first week of life at a time when interpretation of results was uncertain. It is worthy to note that Simchen et al reported thrombophilic abnormalities in 64% of PAIS and the presence of either a factor V Leiden or antiphospholipid antibodies appeared to be major pathogenetic risk factors of PAIS. Currently, the need for a thrombophilia workup in PAIS is controversial as is the age at which such tests should be done. Indeed, the standard values differ according to the measurement method used. Monagle et al demonstrated the need for laboratories to develop age-related reference ranges specific to their own analyzer systems.

To our knowledge, this is the first clinical report to identify maternal smoking during pregnancy as an independent risk factor for PAIS. Very few studies have provided a reliable analysis of the impact of maternal smoking during pregnancy because of insufficient data. The case–control study conducted by Chabrier et al in French newborns found 16.0% of maternal smoking during pregnancy in cases and 14.7% in control subjects. Maternal smoking may have been underestimated in Chabrier et al’s study because the incidence smoking in pregnant French women was measured at 25% in a prospective study and was 22% in our control group.

The mechanisms by which smoking during pregnancy could increase the risk of stroke in the fetus or the newborn are unknown and can only be a matter of speculation. Maternal exposure to drugs and toxins has been investigated and may cause neonatal arterial ischemic strokes. For instance, Domínguez et al identified the consumption of cocaine as a risk factor of PAIS probably due to cerebral artery vasoconstriction in the fetus.

It can be also assumed that maternal smoking may promote thrombosis and inflammation of the placenta, a condition that could favor PAIS in the fetus, who presents besides a physiological state of hypercoagulability.

During pregnancy, the levels of protein S and of protein C are low, whereas the levels of factors VIII, V, and I are increased. Therefore, pregnancy promotes maternal hypercoagulability and contributes to maternal thrombosis. High maternal age, obesity, lupus, infection, inflammatory conditions, diabetes, and also smoking have been reported as risk factors of maternal thrombosis. Cigarette smoking predisposes the individual to atherosclerosis and increases the relative risk of ischemic stroke by approximately 2-fold. Toxicity is higher among female smokers, especially when they have several risk factors such as pregnancy. Cigarette smoking could promote vasomotor dysfunction (with decreased availability of nitric oxide), atherogenesis (by free radical-mediated oxidative stress), and inflammation (with an increase in C-reactive protein and interleukin).

This study also showed that gestational maternal diabetes is associated with an increase in the odd of PAIS. Curry et al reported 3 mothers with gestational diabetes and 2 with pre-existing insulin-dependent diabetes among 60 cases of PAIS. It was claimed that diabetes could increase the risk of PAIS by increasing the hemoglobin concentration in blood and the size of the fetus, a condition favoring a difficult birth. In this cohort, the children born to mothers with diabetes were no heavier than those born to mothers without diabetes (data not shown) and this series provided no evidence to support the traumatic birth hypothesis.

Fetal heart rate abnormalities, meconium-stained amniotic fluid, and cesarean delivery, all of which are recognized markers of perinatal asphyxia, were more common in cases than in control subjects. Complications during labor were also more frequent in cases than in control subjects in other studies. It is worthy of note that the focal character distinguishes PAIS from hypoxic–ischemic encephalopathy, although these 2 pathological conditions share many risk factors and can coexist in the same patient.

Cord abnormalities (mainly tight umbilical cord) were associated with a nonsignificant increase in the likelihood of PAIS in this study. Lee et al also reported a significant
difference between PAIS and control subjects for cord abnormalities (22% versus 6%). According to Cheong et al., a tight umbilical cord could contribute to a decrease in cerebral blood flow that favors arterial thrombosis in the fetus.

Other maternal risk factors of PAIS previously reported were not found in this study, that is, pre-eclampsia or infertility, chorioamnionitis, and prolonged rupture of membranes, 3,8,11,24,28–33 This is not a surprising finding because risk factors of PAIS, with complex multifactorial relationship, were no systematically found in the literature. Evidence for true causation of perinatal stroke was lacking for most cases, even in large multinational studies.

Finally, this study was subject to a number of limitations related to a relatively small sample of final cases. However, the case–control design of the study partially overcome this limit and allowed the identification of maternal smoking as an important risk factor of PAIS. The retrospective character of this study also precluded any identification of radiological factors associated with development of hemiplegia in patients with PAIS. For instance, 4 of the 19 children diagnosed with PAIS in the neonatal period and who developed hemiplegia did not have diffusion-weighted imaging in the neonatal period.

Conclusions

To our knowledge, this study is the first to identify maternal smoking during pregnancy as an independent prenatal risk factor of PAIS. Our results emphasize the major role of prevention in pregnant women exposed to cigarette smoke. Additional prospective studies are needed to confirm this result and investigate the role of maternal smoking in fetal and neonatal thrombogenesis.

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References

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