Perinatal arterial (ischemic) stroke (PAS) is more often recognized with the increased use of sophisticated neuroimaging techniques.\(^1\)\(^,\)\(^2\) In the full-term infant, PAS is the second most common underlying cause of neonatal seizures.\(^3\)\(^,\)\(^4\) Several reports restricted to full-term infants found diverse maternal, prenatal, and perinatal risk factors to be independently associated with the development of PAS.\(^4\)\(^,\)\(^5\) Infarct, preeclampsia, prolonged rupture of the membranes, and chorioamnionitis have been recently identified as independent maternal risk factors.\(^4\) Neonatal risk factors, such as congenital heart disease, infection, dehydration, polycythemia, prothrombotic factors, and others, have also been found to be associated with PAS.\(^6\)\(^–\)\(^10\)

There are hardly any data concerning PAS in preterm infants. A few reports included preterm infants in imaging studies,\(^1\)\(^1\)\(^–\)\(^1\)\(^3\) but no studies have so far been undertaken to investigate the risk factors for PAS in the preterm population. The aim of this study was to determine the antenatal and perinatal risk factors and postnatal complications in preterm infants with radiologically confirmed PAS in a hospital-based population.

**Results**

—Gestational age ranged between 27 and 36 weeks, and birth weight ranged between 580 and 3180 g. PAS was more common on the left side (61%), and 7% had bilateral PAS. The majority of strokes involved the middle cerebral artery distribution. Involvement of 1 or more lenticulostriate branches was most common among infants with a gestational age of 28 to 32 weeks, but main branch involvement was seen only in those with a gestational age of \(>32\) weeks. Twin-to-twin-transfusion syndrome, fetal heart rate abnormality, and hypoglycemia were identified as independent risk factors for PAS.

**Conclusions**

—Preterm PAS is associated with prenatal, perinatal, and postpartum risk factors. We were unable to identify any maternal risk factors. Involvement of the different branches of the middle cerebral artery changed with an increase in gestational age. (\textit{Stroke}. 2007;38:1759-1765.)

**Patients and Methods**

This case-control study was part of a cohort of preterm infants. Infants were admitted from January 1, 1990 to December 31, 2005 to the Wilhelmina Children’s Hospital. This tertiary-care, neonatal intensive care unit provides care for a population of 2 million people who live in the center of the Netherlands.

**Imaging and Infant Data**

Infants with congenital anomalies, chromosomal abnormalities, or infection of the central nervous system and with PAS beyond day 28 were excluded. Cerebral ultrasonography (cUS) was part of routine clinical care. Informed parental consent was obtained for magnetic resonance imaging (MRI) in all infants. All children are seen in the follow-up clinic until at least 5 years of age. (These data will be reported separately.)

An electronic search was performed of the US database; all infants were at least 9 months of age when records were searched. All records and images were retrieved for infants with a clinical diagnosis of hemiplegia and an imaging diagnosis of focal infarction, stroke, middle cerebral artery (MCA) infarction, and venous infarction. Two study investigators (F.G., R.A.J.N.) reviewed the cUS and MRI data of potential cases of PAS.

Imaging criteria for the cUS diagnosis of PAS were as follows: (1) presence of a wedge-shaped area of echogenicity, on coronal and
parasagittal views, in the region supplied by the MCA, anterior cerebral artery (ACA), or posterior cerebral artery (PCA) with a linear demarcation line and (2) cystic evolution of this area of increased echogenicity after 2 to 4 weeks. Echogenicity was sometimes noted to persist in the thalamic/basal ganglia region, despite observation of a cystic lesion on the MRI scan at term-equivalent age. Diagnosis was sometimes made in the cystic phase. After the site, shape, and evolution were taken into account, PAS was distinguished from cystic periventricular leukomalacia (PVL), which is usually bilateral, though not necessarily symmetric and not restricted to the territory of the MCA, and from parenchymal hemorrhage, which is unilateral but is associated with ipsilateral hemorrhage and shows a different shape and evolution, with formation of a porencephalic cyst that communicates with the lateral ventricle.

Neuroimaging studies that revealed intraventricular hemorrhage with a unilateral parenchymal hemorrhage (venous infarction), cystic PVL, or sinovenous thrombosis were excluded. One investigator (M.J.N.L.B.) reviewed the medical records of children with radiologically confirmed arterial infarction.

Three controls were randomly selected and were individually matched to the infants with PAS for date of birth (<2 weeks) and gestational age (GA) (<3 days). One study investigator (M.J.N.L.B.) reviewed the prenatal, obstetric, and neonatal medical records according to a standardized protocol.

Maternal Data
Maternal ethnicity was noted as recorded in the medical notes. Intrauterine growth restriction was defined as a birth weight less than the third percentile for GA according to the criteria of Kloosterman.14 The mother was considered to have a history of infertility if this was documented in a prenatal, obstetric, or neonatal record.

Preeclampsia was defined as either preeclampsia or pregnancy-induced hypertension, as diagnosed by the obstetrician. The term “choioamnionitis” was used in cases when either the mother’s temperature was at least 38°C or a diagnosis was made by the attending obstetrician according to clinical symptoms alone. Fetal heart rate abnormalities were considered present when a treating physician noted repetitive or prolonged late decelerations, fetal bradycardia, nonreassuring fetal heart tracing, or fetal distress by electronic fetal heart rate monitoring. Decreased fetal movements referred to maternal report of decreased fetal movements before labor.

Placental Examination
During the period from 1990 until December 1996, placentas arrived fixed in formalin in the pathology department. Routine histologic examination was done on at least 3 samples from the placenta; ie, 1 paraffin block from the umbilical cord and membranes, 1 from the insertion, and 1 from normal placental parenchyma (with additional blocks from macroscopic lesions). The angioarchitecture of monochorionic twin placentas (vascular anastomoses) were versus after fixation. From December 1996 onward, all placentas arrived fresh, and the angioarchitecture of monochorionic twin placentas was studied with the use of different color dyes for the venous and arterial circulations of both twins.15 At least 4 paraffin blocks of the placenta were studied, ie, 1 paraffin block from the umbilical cord and membranes, 1 from the insertion, and 2 from normal placental parenchyma (with additional blocks from macroscopic lesions). The following histologic abnormalities were observed: choioamnionitis, funisitis, chronic villitis, fetal thrombosis, and disturbed maternalplacental perfusion, ie, placental bed pathology. In monochorionic placentas, the typical histologic abnormalities in donor and recipient parenchymas were observed. The donor tissue showed an immature parenchyma with large vili, compared with the recipient parenchyma with small, mature villi.

Data Analysis
Maternal and infant characteristics were tabulated by disease status. Because patients with PAS were matched to controls, conditional logistic regression was used, with disease status (PAS or not) as the dependent variable and maternal and fetal characteristics and prepregnancy and intrapartum complications as independent variables. Univariate statistically significant predictors were included in a multivariate logistic-regression analysis. All results are expressed as odds ratios (ORs) and 95% CIs, with corresponding probability values. Cs not including 1 (P < 0.05) were considered statistically significant. SPSS for Windows, version 14, was used for all analyses.

Results
Among 3877 preterm infants with a GA of ≤34 6/7 weeks, a total of 26 cases of PAS were confirmed (0.7%). An additional 5 cases with a GA of 35 0/7 to 36 6/7 weeks were confirmed to have PAS.

Clinical Presentation
The GA ranged between 27 and 36 weeks; birth weight ranged between 580 and 3180 g (Table 1). One infant died in the neonatal period and 1 at the age of 21 months. Six infants were 1 of monzygous twins, with associated twin-to-twin transfusion syndrome (TTTS). Antenatal death of the cotwin occurred in 3 of the 6 monochorionic twinning pregnancies. One was part of a dichorionic triplet (2 male, 1 female).

Neuroimaging Findings
The diagnosis was initially made on cUS examination in all cases and subsequently confirmed by MRI in the neonatal period (n = 25; 81%) or later in infancy (n = 2). There were no infants with a diagnosis of PAS on cUS that was not confirmed by MRI (sensitivity of cUS = 100%). Eleven infants had an MRI scan performed on both occasions. Four infants were diagnosed by cUS and did not undergo MRI. Unilateral infarction was more common on the left side (61%) than on the right (32%), whereas 7% demonstrated bilateral arterial distribution infarcts. The majority of strokes involved the MCA (n = 25; 81%), 1 of whom had both an MCA and a PCA distribution, 4 infants had an ACA distribution, 1 infant had a PCA distribution, and 1 infant showed a unilateral watershed distribution between the ACA and MCA. Involvement of the MCA main branch was seen in 9 infants and a cortical branch in 4, and 1 or more lenticulostriate branches were involved in 12 infants. Involvement of the different branches changed with an increase in GA. Whereas only 1 of the 14 infants with a GA between 28 and 32 weeks showed involvement of the main branch, 8 of the 11 infants with a GA >32 weeks did (P < 0.02, Fisher’s exact test). Involvement of 1 or more lenticulostriate branches was most common among infants with a GA of 28 to 32 weeks (Figure 1). cUS and MRI images illustrate the different types of lesions in Figures 2 and 3. Associated intracranial lesions were found in 4 of our cases. All 4 had a lenticulostriate infarct, associated with cystic PVL in 2 and with a large, intraventricular hemorrhage in the other 2.

Univariate Risk Factor Analysis
Maternal race, primiparity, and a history of previous miscarriages or infertility did not differ between case and control groups. None of the case or control infants had been exposed
to cocaine during pregnancy. Being part of monozygous twins with TTTS was associated with a 15 times higher risk of PAS. Intrauterine death of the cotwin occurred in 3 of the cases and none of the controls. Preeclampsia was associated with a 2 times higher risk of PAS, but the difference did not reach statistical significance ($P=0.12$).

Intrapartum complications associated with PAS included use of oxytocin, fetal heart rate abnormality, ventouse delivery, and emergency caesarean section. Only reduced fetal movements and fetal heart rate abnormalities were associated with a respective 6 ($P=0.04$) and 4 ($P=0.003$) times higher risk of PAS. At delivery, the umbilical artery pH was $<7.10$ in 4 of 16 (25%) infants with PAS compared with 11 of 51 (22%) controls ($P=0.53$) for whom a cord gas value was available.

In the neonatal period, there was no difference regarding ventilation, use of inotropic support, the presence of a ductus arteriosus requiring therapy, polycythemia, umbilical catheters, or peripheral arterial lines. Hypoglycemia yielded a 3.3 times higher risk of PAS than in controls ($P=0.01$). Eight

### TABLE 1. Univariate Predictors of PAS in Preterm Infants

<table>
<thead>
<tr>
<th>Maternal Characteristics and Prepartum Complications</th>
<th>Cases, n=31</th>
<th>Controls, n=93</th>
<th>OR (95% CI)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal characteristics, yes/no</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primiparity</td>
<td>13/31</td>
<td>40/92</td>
<td>0.9 (0.4–2.1)</td>
<td>0.86</td>
</tr>
<tr>
<td>History of infertility</td>
<td>2/31</td>
<td>12/91</td>
<td>0.5 (0.1–2.2)</td>
<td>0.34</td>
</tr>
<tr>
<td>Clomid</td>
<td>1</td>
<td>6/12</td>
<td>0.5 (0.06–4.2)</td>
<td>0.52</td>
</tr>
<tr>
<td>In vitro fertilization/intracytoplasmic sperm injection</td>
<td>6/12</td>
<td>NE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTTS</td>
<td>6/31</td>
<td>3/93</td>
<td>15.4 (1.8–130.6)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Death of cotwin</td>
<td>3/6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrauterine growth restriction; birth weight $&lt;$third percentile</td>
<td>7/31</td>
<td>22/93</td>
<td>0.9 (0.3–2.6)</td>
<td>0.90</td>
</tr>
<tr>
<td>Occipitofrontal circumference $&lt;$third percentile</td>
<td>5/27</td>
<td>14/84</td>
<td>1.1 (0.2–3.8)</td>
<td>0.87</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>9/31</td>
<td>14/92</td>
<td>2.1 (0.8–5.3)</td>
<td>0.12</td>
</tr>
<tr>
<td>Reduced fetal movement</td>
<td>4/30</td>
<td>2/93</td>
<td>6.0 (1.1–32.8)</td>
<td>0.04*</td>
</tr>
</tbody>
</table>

#### Intrapartum Complications and Infant Characteristics

<table>
<thead>
<tr>
<th>Intrapartum complications, yes/no</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature rupture of membranes</td>
<td>9/31</td>
<td>23/93</td>
<td>1.3 (0.5–3.2)</td>
<td>0.63</td>
</tr>
<tr>
<td>Vaginal blood loss</td>
<td>2/31</td>
<td>17/92</td>
<td>0.3 (0.1–1.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>Oxytocin induction</td>
<td>2/31</td>
<td>1/91</td>
<td>6.0 (0.5–66.2)</td>
<td>0.14</td>
</tr>
<tr>
<td>Fetal heart rate abnormalities</td>
<td>18/31</td>
<td>24/92</td>
<td>3.7 (1.6–8.8)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Ventouse delivery</td>
<td>2/31</td>
<td>1/91</td>
<td>6.0 (0.5–66.2)</td>
<td>0.14</td>
</tr>
<tr>
<td>Breach delivery</td>
<td>0/31</td>
<td>8/93</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>Emergency caesarean section</td>
<td>14/31</td>
<td>28/95</td>
<td>1.8 (0.8–3.9)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infant characteristics</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>13/31</td>
<td>51/93</td>
<td>0.5 (0.2–1.3)</td>
<td>0.17</td>
</tr>
<tr>
<td>Umb.artern pH $&lt;7.10$</td>
<td>4/16</td>
<td>11/51</td>
<td>1.8 (0.3–12.2)</td>
<td>0.53</td>
</tr>
<tr>
<td>Apgar score at 5 minutes $\leq 5$</td>
<td>2/31</td>
<td>7/93</td>
<td>1.0 (0.2–5.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>GA, wk, mean±SD</td>
<td>31.7±2.5</td>
<td>31.7±2.5</td>
<td>1.0 (0.4–2.5)</td>
<td>0.99</td>
</tr>
<tr>
<td>Birth weight, g, mean±SD</td>
<td>1599±633</td>
<td>1607±720</td>
<td>1.000 (0.999–1.001)</td>
<td>0.96</td>
</tr>
<tr>
<td>Intermittent positive-pressure ventilation</td>
<td>18/31</td>
<td>47/93</td>
<td>1.4 (0.6–3.5)</td>
<td>0.43</td>
</tr>
<tr>
<td>Hypoglycemia ($&lt;2$ mmol/L)</td>
<td>13/31</td>
<td>16/90</td>
<td>3.3 (1.3–8.3)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Umbilical lines</td>
<td>21/31</td>
<td>71/89</td>
<td>1.1 (0.7–3.5)</td>
<td>0.85</td>
</tr>
<tr>
<td>Inotropic support</td>
<td>5/31</td>
<td>23/95</td>
<td>0.6 (0.2–1.7)</td>
<td>0.30</td>
</tr>
<tr>
<td>Ductus (Indocin/surgery)</td>
<td>1/31</td>
<td>8/93</td>
<td>0.4 (0.1–3.0)</td>
<td>0.36</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>3/31</td>
<td>4/93</td>
<td>2.3 (0.5–10.1)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

EUG indicates ectopic pregnancy; IUD, intrauterine demise; Umb.artern pH, umbilical arterial pH; and NE, could not be estimated. Other abbreviations are as defined in text. Values are given as frequencies. *Statistically significant.
case infants developed seizures (26%) compared with 4 controls ($P=0.007$).

**Multivariate Risk Factor Analysis**

The following variables were entered into the main logistic-regression model: TTTS, decreased fetal movements, abnormal heart rate pattern, and hypoglycemia (Table 2). The risk factors that remained independently associated with PAS were TTTS (OR=31.2, 95% CI=2.9 to 340.0), abnormal heart rate pattern (OR=5.2, 95% CI=1.5 to 17.6), and hypoglycemia (OR=3.9; 95% CI=1.2 to 12.6).

**Placental Pathology**

Nineteen placental pathologic examinations were performed among the 31 cases (Table 3). Extensive placental thrombosis was noted in 1 case. This infant showed lack of flow in the internal carotid artery on neonatal MR angiography and infarction in both the MCA and PCA distribution. Fifty-one control placentas were available for pathologic examination. Comparison between cases and controls could be done for placentas of 18 case infants and 33 control infants. One case infant could not be included in the statistical analysis because there was no matched control. No significant differences were found between case infants and control infants.

**Thrombophilia**

Only 11 cases have so far been tested for the presence of a genetic thrombophilia, because the remaining infants were born before these tests became routinely available at our institution. Seven infants were diagnosed with a genetic thrombophilia, including 2 with factor V Leiden heterozygosity, 5 with a methylene tetrahydrofolate reductase mutation (2 homozygous, 3 heterozygous), and 1 with increased lipoprotein(a).16

**Preterm Infants With <32 Weeks GA**

Because the preterm infants with a GA of <32 weeks were a more homogeneous group (most will be inborn, after in utero transfer), this subgroup was also analyzed separately. In the univariate risk factor analysis, case infants were noted to have fetal heart rate abnormalities and hypoglycemia significantly more often than controls. TTTS could no longer be estimated as a risk factor, because this problem was present in 2 of 19 case infants compared with 0 of 57 controls (Fisher exact
For the multivariate analysis, an abnormal heart rate pattern (OR 11.7, 95% CI 2.2 to 61.6; *P*=0.004) and hypoglycemia (OR 8.6, 95% CI 1.7 to 43.9; *P*=0.01) remained independently associated with PAS.

**Preterm Singletons**

After exclusion of all case and control infants belonging to multiple births, 23 case infants and 69 control infants could be compared for the risk factors mentioned earlier. Because in the univariate risk factor analysis reduced fetal movements (OR = 3.8, 95% CI = 0.7 to 21.6, *P*=0.03) were more often present among the case infants, this variable was also entered into the main logistic-regression model, together with abnormal heart rate pattern and hypoglycemia. Only the latter 2 remained independently associated with PAS (respectively, OR = 6.2, 95% CI = 1.7 to 22.1; *P*=0.005 and OR = 3.6, 95% CI = 1.0 to 12.9; *P*=0.05).

**Discussion**

Studies about PAS in preterm infants are scarce, with usually only a few preterm infants having been reported as part of a group consisting mainly of term infants. To our knowledge, this is the first controlled study of risk factors for PAS in

**TABLE 2. Multivariate ORs for PAS in Preterm Infants**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR (95% CI)</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTTS, yes/no</td>
<td>31.2 (2.9–340.0)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Reduced fetal movement, yes/no</td>
<td>1.6 (0.2–12.8)</td>
<td>0.64</td>
</tr>
<tr>
<td>Abnormal fetal heart rate, yes/no</td>
<td>5.2 (1.5–17.6)</td>
<td>0.008*</td>
</tr>
<tr>
<td>Hypoglycemia (&lt;2 mmol/L)</td>
<td>3.9 (1.2–12.6)</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

*Statistically significant.

**TABLE 3. Placental Examination in a Subgroup of Cases and Controls**

<table>
<thead>
<tr>
<th>Placental pathology</th>
<th>Cases, n=19</th>
<th>Controls, n=51</th>
<th>OR (95% CI)</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorioamnionitis</td>
<td>1/19</td>
<td>13/51</td>
<td>0.1 (0.02–1.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>Infarct/hypoxia</td>
<td>7/19</td>
<td>19/51</td>
<td>1.5 (0.4–5.4)</td>
<td>0.49</td>
</tr>
<tr>
<td>Normal</td>
<td>5/19</td>
<td>18/51</td>
<td>0.5 (0.2–1.9)</td>
<td>0.35</td>
</tr>
<tr>
<td>Vascular anastomoses</td>
<td>6/19</td>
<td>1/51</td>
<td>NE</td>
<td>...</td>
</tr>
</tbody>
</table>

NE indicates could not be estimated.
preterm infants. Except for the presence of TTTS, antenatal risk factors like a history of infertility, preeclampsia, and chorioamnionitis could not be identified as significant risk factors. Decreased fetal movements, abnormalities of fetal heart rate, and an emergency caesarean section were more often present among the cases than the controls, but only fetal heart rate abnormalities were identified as an independent risk factor. Hypoglycemia was the only independent risk factor identified in the neonatal period. Because preterm infants with a GA of ≤32 weeks are a more homogeneous group, this subgroup was analyzed separately. Abnormal heart rate pattern and hypoglycemia were both independently associated with PAS.

We found that PAS is not uncommon in preterm infants with a GA of ≤34 weeks, with an incidence of 7/1000, compared with an incidence of 1/4000 in full-term infants. This incidence is similar to our value of 0.9% for cystic PVL (authors’ unpublished data) but higher than the incidence for cystic PVL reported by Hamrick et al.17 The higher incidence of PAS in our cohort of preterm infants may be explained by the use of routine cUS in all preterm infants, many of whom did not present with clinical symptoms, whereas only those full-term infants who presented with (hemi)convulsions would have undergone neuroimaging. Furthermore, preterm infants are more often exposed to invasive procedures during their stay in the neonatal intensive care unit (eg, umbilical lines) than are infants born at term. Because suspected parenchymal lesions detected by cUS examinations are always verified by MRI in both preterm and term infants, it is unlikely that varying diagnostic criteria are a reason for the discrepancy in incidence between preterm and term infants. Our PAS data are hospital based, obtained from a level-3 neonatal intensive care unit that serves a population of 2 million people. The incidence for preterm infants born at 35 to 36 weeks was not calculated because they represent a select population of very sick preterm infants.

Lenticulostriate infarcts appeared to be especially common in this preterm population and can be well visualized by cUS, as they are well within the field of view. Because sequential US examinations were performed until term-equivalent age, it is unlikely that infarcts in this region were missed. Cortical infarcts were uncommon in our cohort. Because cUS is known to miss smaller cortical infarcts, it is likely that some cases with cortical PAS were missed over the years, especially because they do not necessarily lead to neurologic symptoms later in infancy.3,18,19

In our register, a total of 6 infants were diagnosed during this 16-year period with mild hemiplegia that could not be explained by a unilateral parenchymal hemorrhage. Five of these 6 infants did not belong to the group of infants described here. They had undergone MRI in infancy and did not have a lesion that could be attributed to PAS. Instead, they were noted to have mild, predominantly unilateral PVL that was not detected in the neonatal period by cUS. In the other infant, cUS findings were normal, and the parents did not give permission for an MRI scan. Because the child is 1 of monozygous twins and the cotwin died before birth, it is likely that this infant has as-yet-to-be-confirmed PAS.

The clinical presentation was very different from reports in the literature dealing with term infants. Whereas presentation with hemiconvulsions was the presenting symptom in 75% of the term infants studied by Kurnik et al.,10 seizures and/or apnea was observed in only 8 of our 31 cases, and 5 of these had main branch involvement and a GA of >32 weeks. Identification of the preterm infant with PAS will therefore be based mostly on dedicated sequential cUS. In contrast to the data of Golomb et al.,20 we did not find boys to be more commonly affected than girls.

Placental examination could be performed in about half of both case and control infants. There was no difference in the presence of chorioamnionitis.21 Monochorionic placentaion with vascular interconnections was more common among the case infants. This finding has been reported to lead to antenatal brain injury, such as antenatal cystic PVL and porencephaly.22–24 There are 2 case reports of PAS after death of a cotwin.25,26 The case reported by de Laveaucoupet et al.,25 however, was an infant with cystic PVL and not focal infarction. Death of a cotwin may further lead to the redistribution of thromboplastic material and/or emboli into the circulation of the surviving twin, or it may lead to a sudden drop in blood pressure due to the lack of resistance of the circulation of the deceased twin.27,28 Increased use of antenatal laser therapy appears to be associated with a reduced risk of TTTS-associated brain injury and may therefore also reduce the risk of PAS in this subgroup of preterm infants.29

In a recent study by Golomb et al.,30 4 of 35 children diagnosed with presumed PAS were part of twins. There was no death of the cotwin, and 2 were known to be dizygotic twins. The neonatal problems were evenly distributed among both groups, except for the presence of hypoglycemia, which was significantly more common among cases. Owing to the delay in visualizing US abnormalities in infants who develop PAS, it is uncertain whether the hypoglycemia did indeed precede PAS. Bilateral occipital infarction has been noted to be associated with symptomatic hypoglycemia in full-term infants.31,32 Indirect evidence for occipital regional vulnerability was studied in a newborn dog model.33 That study demonstrated increased regional cerebral blood flow (to 250% in the thalamus) during hypoglycemia. Regional glucose utilization was relatively unchanged or even reduced compared with a normoglycemic situation in the brain. This might make this region more vulnerable.

Furthermore, it is not uncommon to visualize small air bubbles on cUS shortly after insertion of an umbilical venous catheter, which might pass the heart via the foramen ovale to the arterial circulation. It has been shown that these small, “silent” air bubbles do not immediately cause obstruction of arterioles or capillaries; however, a decrease in cerebral blood flow has been described owing to the effects that gases have on vascular endothelial cells. This may cause a reduction in regional perfusion and an exaggerated response to vasoconstrictor agents.34

The role of prothrombotic disorders in preterm infants with PAS still needs to be determined. Only one third of our cases had a mutation analysis performed, and those data were unavailable for the controls. It was interesting to note that 7
of the 11 infants tested had a mutation, with the methylene tetrahydrofolate reductase mutation being especially prominent. Permission for performing mutation analysis is asked when case children visit the follow-up clinic. Retrospective analysis of DNA obtained from Guthrie cards will also be performed in the control children in the near future and will help to clarify the potential role of these prothrombotic factors. Our findings suggest that prothrombotic disorders are relatively more common in preterm neonates with PAS, and therefore, they should undergo extensive testing.

Conclusions
Fetal heart rate abnormalities, but especially the presence of TTTS, were independent risk factors for preterm PAS. Hypoglycemia was the only independent risk factor identified in the immediate neonatal period. In contrast to full-term infants with PAS, we were unable to identify any maternal risk factors. Involvement of the different branches of the MCA changed with an increase in GA.

Disclosures
None.

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

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