Stroke and Pregnancy
Cheryl Jaigobin, MD, FRCPC; Frank L. Silver, MD, FRCPC

Background and Purpose—We sought to characterize the subtypes of stroke associated with pregnancy and the puerperium, with emphasis on timing, etiology, risk factors, and outcome.

Methods—We conducted a retrospective analysis of patients admitted to the Toronto Hospital between January 1, 1980, and June 30, 1997, with a diagnosis of stroke during pregnancy or within 6 weeks postpartum. Strokes were classified as ischemic (arterial or venous) or hemorrhagic (subarachnoid or intracerebral). All patients were investigated with at least a CT scan of the head, and most had MRI and/or cerebral angiography.

Results—Of approximately 50 700 admissions for delivery, 34 patients with a diagnosis of stroke were identified (21 infarctions and 13 hemorrhages). Of patients with infarction, 13 were arterial and 8 were venous. Nine of 13 arterial events occurred in the third trimester or puerperium. Seven of 8 venous occlusions occurred postpartum. An etiologic diagnosis was made in 7 of 13 patients with arterial territory infarction, including cardiac emboli, coagulopathies, and carotid artery dissection. Of patients with hemorrhage, 7 were subarachnoid and 6 were intracerebral. The etiology was identified in 10 patients: 3 were due to ruptured aneurysms, 5 were associated with arteriovenous malformations, and 2 were associated with disseminated intravascular coagulation. All patients with infarction survived, but 3 patients with hemorrhage died.

Conclusions—The majority of strokes associated with pregnancy were arterial occlusions. Most presented during the third trimester and puerperium. (Stroke. 2000;31:2948-2951.)

Key Words: cerebral infarction • hemorrhage • pregnancy

Stroke is the second leading cause of death of women in Canada and the United States.¹ ² There is a higher incidence of stroke in young women than in men between the ages of 15 and 30 to 35 years.³ Stroke associated with pregnancy has been long recognized and may partly be responsible for this increased incidence. Stroke related to pregnancy is associated with significant morbidity and mortality. The American Maternal Mortality Collaborative reported cerebrovascular disease as the fifth cause of maternal deaths during 1980–1985.⁴ While stroke associated with pregnancy has been studied in both population-based and hospital-based studies, our understanding is limited by the exclusion of certain stroke subtypes and the limited use of investigations, particularly advanced neuroimaging techniques. We conducted a retrospective analysis of patients diagnosed with stroke during pregnancy and the puerperium (6 weeks postpartum) admitted to the Toronto Hospital between January 1, 1980, and June 30, 1997, with an analysis of timing, risk factors, etiology, and outcome for each stroke subtype.

Subjects and Methods
The total number of deliveries was determined from a review of obstetrical records (1980–1988) and from the medical records department (1989–1997).

Patients with a diagnosis of stroke during pregnancy and the puerperium admitted to the Toronto Hospital between January 1, 1980, and June 30, 1997, were identified by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) stroke codes 430 to 439 linked with pregnancy codes V22 and V23. To overcome coding errors for patients with diagnostic codes for stroke, we identified all patients in the pregnancy group who had procedure codes for CT, MRI, or cerebral angiogram. The medical record was reviewed by one author (C.J.), and the following data were abstracted: maternal age, parity, timing of presentation and presenting deficit, pregnancy-related risk factors for stroke (hypertension, diabetes, hyperlipidemia, and tobacco use). A history of eclampsia or preeclampsia was noted if it appeared in the hospital chart. Information regarding investigations (neuroimaging, cardiac investigations, hematologic assessment) was also abstracted. All patients had CT imaging of the brain. Most patients with infarction had MRI and cerebral angiography. All patients with hemorrhage, except 2 who died before investigations, were studied with cerebral angiography or had craniotomies. An etiologic diagnosis was made from the above investigations. Information regarding maternal and fetal outcome was abstracted if available.

Because our hospital is a tertiary referral center, we attempted to distinguish between patients who resided in the area served by the hospital and patients referred for specialized obstetrical and neurological care by their home address. Patients were considered outside of the catchment area of the Toronto Hospital if their home address indicated residence outside of the city of Toronto. The number of strokes per 100 000 deliveries was calculated for all patients. A

2948
corrected score was calculated by excluding patients referred from outside of the city of Toronto.

### Results

There were 50711 deliveries during 1980–1997. Fifty-one patients were identified by ICD-9-CM codes with a possible diagnosis of stroke associated with pregnancy. After review of the medical record, 34 patients had a final diagnosis of stroke. Two patients were excluded from this analysis because of incomplete investigations. The remaining patients were excluded because of nonstroke diagnoses, which included epilepsy, embolization for epistaxis, preceding neurological deficit, Bell’s palsy, cerebral abscess, delirium, neoplasm, and multiple sclerosis.

The number of strokes per 100 000 deliveries was calculated for all patients and corrected for patients within the catchment area. These data are summarized in Table 1. Of the 34 patients with stroke, 21 were ischemic (13 arterial, 8 venous) and 13 were hemorrhages (7 subarachnoid, 6 intracerebral). Patient age, parity, etiology, and risk factors for each stroke subtype are summarized in Table 2. In patients with infarction, an etiologic diagnosis was made in 7 of 13 patients with arterial territory stroke and 3 of 8 patients with venous thrombosis. In patients with an identifiable etiology, only 1 abnormality was identified. In patients without a known cause of stroke, vascular risk factors were identified in an additional 4 of 7 patients with arterial territory stroke and 3 of 8 patients with venous thrombosis. In patients with an identifiable etiology, only 1 abnormality was identified. In patients without a known cause of stroke, vascular risk factors were identified in an additional 4 of 7 patients with arterial territory stroke. Three patients had 1 risk factor, and 1 patient had 2 risk factors. These included preeclampsia (2), tobacco use (2), and hypertension (1). In patients with venous thrombosis of unknown cause, 2 were also diagnosed with preeclampsia. Of patients with subarachnoid hemorrhage, 3 were due to aneurysmal rupture. The 3 aneurysms were identified as posterior communicating artery aneurysms. Intracerebral hemorrhages were reported in the parietal and occipital regions in 4 of 6 patients; the other locations were frontal and cerebellar.

The timing of presentation of arterial territory infarction and venous thrombosis is shown in Figure 1. Most arterial strokes presented in the third trimester and puerperium. All but 1 venous infarction presented in the puerperium. The timing of subarachnoid hemorrhage and intracerebral hemorrhage is shown in Figure 2. Patients presented with subarachnoid hemorrhage during each trimester and the postpartum period. Patients presented with intracerebral hemorrhage after the first trimester. In patients with known causes of hemorrhage, the timing is shown in Figure 3. Patients presented with hemorrhage secondary to aneurysmal rupture during each trimester. Patients presented with bleeding from arteriovenous malformations (AVM) after the first trimester. Bleeding as a consequence of disseminated intravascular coagulation (DIC) occurred postpartum.

The outcome of patients with both infarction and hemorrhage was determined. All patients with infarction survived. However, 3 patients with hemorrhage (1 AVM, 2 unknown etiology) died during admission. Eight patients with infarction and 9 patients with hemorrhage presented before delivery. Of patients with infarction before delivery, there were 3 live deliveries, 1 miscarriage, and 1 termination. The outcome of 3 pregnancies was not available. Of patients with hemor-

### Table 1. Frequency of Stroke Associated With Pregnancy

<table>
<thead>
<tr>
<th>Frequency</th>
<th>All Strokes</th>
<th>Infarction</th>
<th>Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events per 100 000 deliveries</td>
<td>67</td>
<td>41</td>
<td>26</td>
</tr>
<tr>
<td>Corrected no. of events per 100 000 deliveries*</td>
<td>26</td>
<td>18</td>
<td>8</td>
</tr>
</tbody>
</table>

*Excluded referred patients.

### Table 2. Baseline Demographic Variables

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=34)</th>
<th>Arterial Infarct (n=13)</th>
<th>Venous Thrombosis (n=8)</th>
<th>Subarachnoid Hemorrhage (n=7)</th>
<th>Intracerebral Hemorrhage (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>30 (20–40)</td>
<td>30</td>
<td>31</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td>Parity</td>
<td>11 primiparous</td>
<td>3 primiparous</td>
<td>3 primiparous</td>
<td>3 primiparous</td>
<td>3 primiparous</td>
</tr>
<tr>
<td></td>
<td>21 multiparous</td>
<td>10 multiparous</td>
<td>5 multiparous</td>
<td>3 multiparous</td>
<td>2 multiparous</td>
</tr>
<tr>
<td></td>
<td>2 unknown</td>
<td></td>
<td></td>
<td>1 unknown</td>
<td>1 unknown</td>
</tr>
<tr>
<td>Etiology</td>
<td>6 unknown</td>
<td>5 unknown</td>
<td>3 aneurysm</td>
<td>4 AVM</td>
<td>4 AVM</td>
</tr>
<tr>
<td></td>
<td>4 cardiac</td>
<td>3 coagulopathy</td>
<td>2 unknown</td>
<td>1 DIC</td>
<td>1 DIC</td>
</tr>
<tr>
<td></td>
<td>2 coagulopathy</td>
<td></td>
<td></td>
<td>1 AVM</td>
<td>1 unknown</td>
</tr>
<tr>
<td></td>
<td>1 large artery</td>
<td></td>
<td></td>
<td>1 DIC</td>
<td></td>
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<tr>
<td>Vascular risk factors</td>
<td>3 preeclampsia</td>
<td>3 preeclampsia</td>
<td>3 preeclampsia</td>
<td>1 preeclampsia</td>
<td>1 smoking</td>
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<td></td>
<td>3 smoking</td>
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<td>1 hypertension</td>
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rhage before delivery, there were 5 live deliveries, 3 deaths due to maternal death, and 1 termination.

Discussion

Despite both population-based and single-hospital studies, there is no consensus regarding the incidence of stroke associated with pregnancy. An early study in Rochester, Minn, reported an incidence of 3.5 ischemic strokes per 100 000 population.5 The incidence during pregnancy was reported to be 5 infarctions per 100 000 pregnancies in Glasgow, Scotland.6 More recently, Sharshar et al7 reported an incidence of 4.3 nonhemorrhagic strokes and 4.3 intracerebral hemorrhages per 100 000 deliveries. In the present study we report 69 strokes per 100 000 pregnancies. However, our hospital is a tertiary referral center for neurology, neurosurgery, and obstetrics. After exclusion of patients who were referred to our institution from outside hospitals, the incidence was 26/100 000 pregnancies. The incidence of stroke in nonpregnant women aged 15 to 44 years was reported to be 10.7/100 000 women years.8 While it is recognized that there is an increased risk of stroke associated with pregnancy, there is no consensus regarding the magnitude of risk. After review of a series of reports in the medical literature, Wiewers9 reported a 13-fold increase in the risk of stroke. This was subject to potential selection bias. More recently, in a population-based study of patients in Baltimore, Md, and Washington, DC, Kittner et al10 reported a relative risk of 0.7 of cerebral infarction during pregnancy. This increased to 8.7 during the postpartum period. The relative risk of intracerebral hemorrhage was 2.5 during pregnancy and 28.3 during the postpartum period.10

It has been long assumed that the majority of strokes associated with pregnancy were secondary to venous thrombosis. This belief was challenged by Cross et al,6 who investigated 31 patients with angiography or obtained an etiologic diagnosis at autopsy. Arterial occlusion was identified in 17 patients, and venous thrombosis was present in only 1 patient. Despite this report, a high incidence of cerebral venous thrombosis has been reported in subsequent studies. Of 113 patients diagnosed with venous thrombosis over a 20-year period in Mexico City, 73 were associated with pregnancy.11 As well, 20% of strokes in India in patients younger than 40 years are attributed to venous thrombosis.12,13 In the majority of patients, this diagnosis was made without confirmatory neuroimaging. The more recent population-based studies omitted cerebral venous thrombosis because of acknowledged difficulty in reaching this diagnosis. In our study, of 21 patients with infarction, 8 were secondary to venous thrombosis. The diagnosis of venous thrombosis was confirmed by MRI in 6 patients and by angiography in 2. Although venous thrombosis can present in association with pregnancy, most infarctions are attributed to arterial occlusion.

The timing of stroke associated with pregnancy is also controversial. It has been recently reported that the risk is greatest during the postpartum period.10 In our study most patients presented in the third trimester and the postpartum period. The reason for this is unclear. Two patients were diagnosed with arterial dissection in the postpartum period, which may be directly related to delivery. For other causes, it has been suggested that stroke in the postpartum period may be the indirect result of a large reduction in blood volume or secondary to hormonal changes.10 Venous thrombosis may be secondary to physiological changes in coagulation associated with pregnancy or secondary to dehydration.

In prior studies, an etiologic diagnosis was reached in a small proportion of patients. The most common identifiable causes of cerebral infarction reported in 2 recent studies are eclampsia and preeclampsia.7,10 The mechanism by which this results in cerebral infarction is unknown. It is for this reason that preeclampsia and eclampsia were considered risk factors instead of etiologic factors in our study. The identifiable causes of arterial territory infarction in our study included cardiac emboli or paradoxical emboli (valvular heart disease, coronary artery disease, patent foramen ovale), coagulopathy (deficiencies of protein C, protein S, and antithrombin III and activated protein C resistance), and arterial dissection. Arterial dissection was identified as the cause of stroke in 2 patients. In 1 patient there was dissection of the internal carotid artery. In the second patient coronary artery dissection resulted in myocardial infarction and subsequent stroke.

Maternal mortality following cerebral infarction has been reported in 0% to 25% of patients.14 Cross et al6 reported 26% maternal mortality immediately after stroke. In a more recent study there were no maternal deaths after arterial occlusions.7 Mortality has also been reported in association with venous thrombosis. Twenty percent mortality was reported in a study
from India, and 9% mortality was reported in a series from Mexico City. All patients with arterial and venous infarction in our series survived.

The most common causes of intracerebral hemorrhage are arterial aneurysms and AVM. In 1 study of 154 patients with intracerebral hemorrhage associated with pregnancy, 77% were secondary to aneurysmal rupture and 23% were due to AVM. Other reported causes have included preeclampsia, vasculitis, and cavernous angioma. An additional cause identified in our study was DIC. Five of our 13 patients had prior uneventful pregnancies. The patients in our series presented with hemorrhage secondary to ruptured aneurysms in each trimester. Most patients with hemorrhage from AVM presented in the second trimester. Although this is consistent with previous reports, the reason for this is unclear.

Maternal mortality has been reported in association with intracerebral hemorrhage. The reported mortality associated with subarachnoid hemorrhage is 27% to 40%. Three of our patients with intracerebral hemorrhage died shortly after presentation. Hemorrhage was caused by AVM in 1 patient and unknown in the remaining 2. Death was secondary to herniation in 2 patients and cardiac arrest in 1 patient.

In summary, our study is an attempt to characterize the spectrum of cerebrovascular disease associated with pregnancy assessed at our institution over a 17-year period. Our patients had complete vascular, cardiac, and hematologic assessments. We recognize that over time, the complexity of investigations increased with technological advancement. We also recognize that because our institution is a tertiary referral center for neurology, neurosurgery, and obstetrics, there is a potential for bias in estimating the incidence of stroke. We attempted to correct for this by eliminating patients who were referred to our institution in determining the incidence of stroke associated with pregnancy. Most of the strokes in our cohort were arterial infarction. The identifiable etiologies included cardiac emboli, coagulopathies, and arterial dissection. Most arterial territory and venous infarction occurred postpartum. Intracerebral hemorrhages occurred during each trimester and in the postpartum period. All patients with infarction survived, but 3 patients with hemorrhage died.

References
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