Acute Cerebrovascular Disease Occurring After Hospital Discharge for Labor and Delivery

Dominic A. Hovsepian, BS*; Nandita Sriram, BS*; Hooman Kamel, MD; Matthew E. Fink, MD; Babak B. Navi, MD

Background and Purpose—The risk of stroke and other postpartum cerebrovascular disease (CVD) occurring after hospital discharge for labor and delivery is uncertain.

Methods—We performed a retrospective cohort study using administrative databases to identify all pregnant women who were hospitalized for labor and delivery at nonfederal, acute care hospitals in California from 2005 to 2011 and who were discharged without an International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis of CVD. The primary outcome was an acute CVD composite defined as any ischemic stroke, intracranial hemorrhage, cerebral venous sinus thrombosis, pituitary apoplexy, carotid/vertebral artery dissection, hypertensive encephalopathy, or other acute CVD occurring after hospital discharge and before 6 weeks after labor and delivery. Descriptive statistics were used to estimate the incidence of postdischarge CVD. Multivariate logistic regression was used to evaluate the association between selected baseline factors and postdischarge CVD.

Results—The rate of any postdischarge acute CVD was 14.8 per 100,000 patients (95% confidence interval [CI], 13.2–16.5). Risk factors for any acute CVD were eclampsia (odds ratio [OR], 10.1; 95% CI, 3.09–32.8), chronic kidney disease (OR, 5.4; 95% CI, 2.5–11.8), black race (OR, 2.5; 95% CI, 1.9–3.3), preeclampsia (OR, 2.1; 95% CI, 1.6–2.8), pregnancy-related hematologic disorders (OR, 1.8; 95% CI, 1.3–2.5), and age (OR, 1.5 per decade; 95% CI, 1.3–1.8).

Conclusions—The incidence of postpartum acute CVD after hospital discharge for labor and delivery is similar to rates reported for all postpartum events in previous publications, suggesting that a substantial proportion of postpartum CVD occurs after discharge. (Stroke. 2014;45:1947-1950.)

Key Words: cerebral hemorrhage ■ postpartum period ■ pregnancy ■ stroke

Stroke and other acute cerebrovascular disease (CVD) are feared complications of pregnancy. The incidence of stroke in nonpregnant women of reproductive age has been reported to be 10.7 per 100,000 women-years.1 Compared with these women, pregnant women are at ≈3-fold increased risk of ischemic stroke, hemorrhagic stroke, and cerebral venous thrombosis.1,3 The mortality rate from pregnancy-related cerebrovascular disorders ranges from 4% to 29%2,4,5 and these events account for 5% to 14% of all maternal deaths during pregnancy.6,7

The majority of pregnancy-related CVD occur during delivery or in the 6 weeks immediately after delivery.2,8–10 In fact, the 6-week postpartum period is associated with an 8-fold increased risk of stroke compared with the nonpregnant state.11 Furthermore, recent data suggest that this increased risk may actually extend as long as 12 weeks postpartum.12 The absolute rate of postpartum acute CVD occurring 6 weeks after delivery ranges from 8 to 22 per 100,000 deliveries,2,4,8,11,13,14 and there are data to suggest that the incidence of postpartum CVD is rising.14

Although several previous studies have reported an increased risk of acute CVD during the postpartum period, none have focused on event rates after hospital discharge for labor and delivery, a time when women remain at risk but are monitored less frequently. Furthermore, these studies have not identified risk factors for events that occur during this specific time period. Therefore, we sought to determine the incidence of postpartum acute CVD after hospital discharge and to identify risk factors associated with acute CVD in this population.

Methods

Study Design, Subjects, and Setting
We conducted a retrospective cohort study using linked hospital discharge data from California administrative claims databases. The Office of Statewide Health Planning and Development, a division of the California Department of Health and Human Services, collects data on all emergency department visits and acute care hospital discharges at nonfederal health-care facilities throughout the state. These data undergo quality checks and are deidentified for use by the Agency for Healthcare Quality and Research for its Healthcare

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Cost and Utilization Project. Each patient in this database is given a unique record linkage number that allows for longitudinal tracking.

Using this database, we identified all pregnant women who were hospitalized for labor and delivery between January 1, 2005, and September 31, 2011, and discharged without any previous or concurrent International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis of CVD (430–438, 674.0, 671.5, 253.2, 443.21, and 443.24). Record linkage numbers were used to link subjects to any subsequent emergency department visit or hospitalization ≤6 weeks of labor and delivery. This study was certified as exempt from review by our institutional review board because our analysis was limited to publicly available deidentified data.

Outcome Measurements
The primary outcome was an acute CVD defined as any hospitalization for ischemic stroke (ICD-9-CM 433.x1, 434.x1, 436), intracerebral hemorrhage (431), subarachnoid hemorrhage (430), subdural or epidural hemorrhage (432), cerebral venous thrombosis (437.6, 671.5), pituitary apoplexy (253.2), carotid/vertebral artery dissection (443.21, 443.24), hypertensive encephalopathy (437.2), or other acute cerebrovascular disorders (437, 674.0). We included only events occurring after the initial hospital discharge and before 6 weeks after labor and delivery. However, in light of recent data demonstrating that the increased risk of postpartum thrombosis extends to ≤12 weeks, we also performed a post hoc analysis that included events occurring after the initial hospital discharge and before 12 weeks after labor and delivery. In addition, because pituitary apoplexy is not a typical cerebrovascular event, we performed a sensitivity analysis that excluded pituitary apoplexy from our primary outcome composite. Secondary outcomes were ischemic stroke alone or intracerebral hemorrhage alone, defined as any intracerebral, subarachnoid, subdural, or epidural hemorrhage during this same time period.

Statistical Analysis
Descriptive statistics with exact confidence intervals (CIs) were used to estimate the crude incidence of postpartum acute CVD after hospital discharge. Multivariate logistic regression was used to evaluate the association between postpartum acute CVD and the following 12 weeks, the increased risk of postpartum thrombosis extends to ≤12 weeks. We also performed a post hoc analysis that included events occurring after the initial hospital discharge and before 12 weeks after labor and delivery. However, in light of recent data demonstrating that the increased risk of postpartum thrombosis extends to ≤12 weeks, we also performed a post hoc analysis that included events occurring after the initial hospital discharge and before 12 weeks after labor and delivery. In addition, because pituitary apoplexy is not a typical cerebrovascular event, we performed a sensitivity analysis that excluded pituitary apoplexy from our primary outcome composite. Secondary outcomes were ischemic stroke alone or intracerebral hemorrhage alone, defined as any intracerebral, subarachnoid, subdural, or epidural hemorrhage during this same time period.

**Table 1. Baseline Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>Postdischarge Acute Cerebrovascular Disease (n=306)</th>
<th>No Postdischarge Acute Cerebrovascular Disease (n=2065924)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y, mean (SD)</strong></td>
<td>30.2 (±6.6)</td>
<td>28.3 (±6.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Race†</strong></td>
<td></td>
<td></td>
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<tr>
<td>White</td>
<td>109 (36.2)</td>
<td>773863 (39.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black</td>
<td>47 (15.6)</td>
<td>129177 (6.6)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>103 (34.2)</td>
<td>762774 (38.9)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>42 (14.0)</td>
<td>296190 (15.1)</td>
<td></td>
</tr>
<tr>
<td>Medicaid or uninsured</td>
<td>122 (39.9)</td>
<td>831871 (40.3)</td>
<td>0.89</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>57 (18.6)</td>
<td>163917 (7.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>3 (1.0)</td>
<td>1679 (0.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripartum hemorrhage</td>
<td>20 (6.5)</td>
<td>92957 (4.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>Peripartum infection</td>
<td>5 (1.6)</td>
<td>9025 (0.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Pregnancy-related hematologic disorders</td>
<td>52 (17)</td>
<td>174064 (8.4)</td>
<td>&lt;0.001</td>
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<tr>
<td>Hypertension</td>
<td>8 (2.6)</td>
<td>15594 (0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>42 (13.7)</td>
<td>156907 (7.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2 (0.7)</td>
<td>993 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>8 (2.6)</td>
<td>4595 (0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>0 (0)</td>
<td>248 (0)</td>
<td>0.85</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0 (0)</td>
<td>328 (0)</td>
<td>0.83</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>0 (0)</td>
<td>143 (0)</td>
<td>0.88</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>6 (2)</td>
<td>41566 (2)</td>
<td>0.95</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>4 (1.3)</td>
<td>14161 (0.7)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*All data are reported as number (%) unless otherwise indicated.
†Percentages reflect all patients for whom racial data were available. Information regarding race was unavailable for 5% of patients.

Results
A total of 2066230 patients were included in the final analysis. Baseline patient characteristics, including demographic data and medical comorbidities, are outlined in Table 1. Notably, mean age was 28.3 (±6.5) years, and most patients were white (39.4%) or Hispanic (38.9%). Among the entire cohort, 8.4% had a comorbid diagnosis of a pregnancy-related hematologic disorder, 7.9% had preeclampsia, and 0.1% had eclampsia. Traditional vascular risk factors were rare in this population.

The primary outcome of any postpartum acute CVD occurring 6 weeks after hospital discharge for labor and delivery was diagnosed in 306 patients, which translates to a rate of 14.8 per 100000 patients (95% CI, 13.2–16.5). The in-hospital mortality rate from any postdischarge acute CVD was 5.9% (95% CI, 3.2–8.5%). The mean age of patients with any postdischarge acute CVD was 30.2 years (95% CI, 29.5–30.9) as compared with 28.3 years (95% CI, 28.3–28.3) in patients without any postdischarge acute CVD (P=0.001). In a sensitivity analysis excluding pituitary apoplexy from the primary outcome, the rate of any acute CVD was 14.6 per 100000 patients with an in-hospital mortality of 6.0%.

Ischemic stroke alone was diagnosed in 75 patients, which translates to a rate of 3.6 per 100000 patients (95% CI, 2.8–4.5). Intracranial hemorrhage alone was diagnosed in 117 patients, which translates to a rate of 5.7 per 100000 patients (95% CI, 4.6–6.7). The in-hospital mortality rates for ischemic stroke and intracranial hemorrhage were 6.7% (95% CI, 0.9–12.4%) and 10.3% (95% CI, 4.7–15.8%), respectively.

Statistically significant risk factors for any acute CVD were eclampsia (odds ratio [OR], 10.1; 95% CI, 3.1–32.8), chronic kidney disease (OR, 5.4; 95% CI, 2.5–11.8), black race (OR, 2.5; 95% CI, 1.9–3.3), preeclampsia (OR, 2.1; 95% CI, 1.6–2.8), pregnancy-related hematologic disorders (OR, 1.8; 95% CI, 1.5–2.1), and preeclampsia alone (OR, 2.1; 95% CI, 1.6–2.6). The increased risk of postpartum thrombosis extends to ≤12 weeks. We also performed a post hoc analysis that included events occurring after the initial hospital discharge and before 12 weeks after labor and delivery. However, in light of recent data demonstrating that the increased risk of postpartum thrombosis extends to ≤12 weeks, we also performed a post hoc analysis that included events occurring after the initial hospital discharge and before 12 weeks after labor and delivery. In addition, because pituitary apoplexy is not a typical cerebrovascular event, we performed a sensitivity analysis that excluded pituitary apoplexy from our primary outcome composite. Secondary outcomes were ischemic stroke alone or intracerebral hemorrhage alone, defined as any intracerebral, subarachnoid, subdural, or epidural hemorrhage during this same time period.
CI, 1.2–2.5), and age (OR, 1.5 per decade; 95% CI, 1.3–1.8). There were nonsignificant but suggestive associations with several other baseline factors (Table 2).

Risk factors for ischemic stroke were eclampsia (OR, 12.9; 95% CI, 1.5–113.9), chronic kidney disease (OR, 4.7; 95% CI, 1.2–17.7), preeclampsia (OR, 3.7; 95% CI, 2.2–6.1), black race (OR, 2.6; 95% CI, 1.4–4.8), pregnancy-related hematologic disorders (OR, 2.3; 95% CI, 1.3–3.9), and age (OR, 1.6 per decade; 95% CI, 1.1–2.1), whereas eclampsia (OR, 24.2; 95% CI, 6.0–97.2), black race (OR, 4.2; 95% CI, 2.5–7.1), preeclampsia (OR, 1.9; 95% CI, 1.2–3.0), and age (OR, 2.0 per decade; 95% CI, 1.4–2.7) were associated with an increased risk of intracranial hemorrhage.

In a post hoc analysis evaluating the incidence of acute CVD within the 12-week postpartum period, 356 patients were diagnosed with any postdischarge acute CVD among the 2066230 total patients, equating to a rate of 17.2 events per 100000 patients (95% CI, 15.4–19.0). The in-hospital mortality rate from any postdischarge acute CVD was 5.6% (95% CI, 3.2–8.0%). Ischemic stroke alone was diagnosed in 93 patients, which translates to a rate of 4.5 per 100000 patients (95% CI, 3.6–5.4). Intracranial hemorrhage alone was diagnosed in 137 patients, which translates to a rate of 6.6 per 100000 patients (95% CI, 5.5–7.7). The in-hospital mortality rates for ischemic stroke and intracranial hemorrhage were 5.4% (95% CI, 0.7–10.0%) and 10.2% (95% CI, 5.1–15.4%), respectively.

**Discussion**

In a large and ethnically and socioeconomically diverse population, we found the incidence of postpartum acute CVD 6 weeks after hospital discharge for labor and delivery to be ≈15 per 100000 deliveries. Previous publications have reported the incidence of postpartum acute CVD to be anywhere from 8 to 22 per 100000 deliveries.\(^2\)\(^4\)\(^8\)\(^11\)\(^13\)\(^14\) Therefore, the incidence of postdischarge, postpartum acute CVD from our study falls within the range of incidences reported for all postpartum acute CVD. This suggests that a substantial proportion of postpartum cerebrovascular complications occur after hospital discharge.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR (95% CI)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eclampsia</td>
<td>10.1 (3.1–32.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>5.4 (2.5–11.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black race</td>
<td>2.5 (1.9–3.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>2.1 (1.6–2.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pregnancy-related hematologic disorders</td>
<td>1.8 (1.2–2.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age, per decade</td>
<td>1.5 (1.3–1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>3.4 (0.8–14.9)</td>
<td>0.110</td>
</tr>
<tr>
<td>Peripartum infection</td>
<td>2.5 (1.0–4.3)</td>
<td>0.052</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.4 (1.0–2.0)</td>
<td>0.060</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and OR, odds ratio.

*A list of baseline clinical factors was selected a priori for inclusion in the model. Covariates that were not associated with the outcome at a significance level of P<0.20 were eliminated via stepwise reverse selection; the remaining covariates are shown here.

Few data exist regarding the incidence, mortality, and risk factors for acute CVD after hospital discharge for labor and delivery. One study examining data from 280000 deliveries recorded by the National Hospital Discharge Survey reported that postdischarge acute CVD accounted for 40% of all postpartum events.\(^1\) However, for a large proportion (36.5%) of pregnancy-related events in that study, the exact timing of the event (ie, antepartum, intrapartum, or postpartum) was unknown, and this may have skewed the true postdischarge event rate. In light of the fact that the average length of stay for labor and delivery is 2.6 days,\(^1\) our finding that a sizeable proportion of postpartum acute CVD occurs after hospital discharge is consistent with results from a previous study, which reported that the median onset of postpartum acute CVD is 8 days after delivery.\(^19\)

Previous studies have suggested that pregnancy itself may predispose to certain stroke risk factors, which could partly explain the increased stroke risk in the postpartum period.\(^2\)\(^3\)\(^4\)\(^8\)\(^11\)\(^13\)\(^14\) For instance, parity may slightly increase the risk of coronary heart disease.\(^2\)\(^3\)\(^4\)\(^8\)\(^11\)\(^13\)\(^14\) In addition, pregnancy is associated with increased serum cholesterol and triglyceride levels, which, although potentially adaptive to fetal–maternal needs, could theoretically increase the risk of atherosclerotic diseases.\(^2\)\(^5\) We found that eclampsia, preeclampsia, black race, chronic kidney disease, pregnancy-related hematologic disorders, and older age were independently associated with an increased risk of any postpartum acute CVD after hospital discharge. These risk factors are intuitive and consistent with those previously reported for all pregnancy-related acute CVD. Of note, the absolute rate of eclampsia was low in our study population, which may have been because of aggressive management of preeclampsia with magnesium sulfate administration. However, the relative risk of any postdischarge acute CVD in patients with eclampsia was increased >10-fold. This increased risk may partly be explained by the fact that eclampsia can manifest with posterior reversible encephalopathy syndrome, which is often interpreted or diagnosed as an acute CVD. In addition, hypertension, which is part of the eclampsia syndrome and a major risk factor for posterior reversible encephalopathy syndrome, has been found in multiple previous studies to be a significant risk factor for postpartum acute CVD.\(^2\)\(^4\)\(^13\)\(^24\)\(^28\) Although we cannot establish a causal relationship between postdischarge acute CVD and the risk factors we identified, these risk factors may be helpful in identifying patients at high risk of CVD after discharge who may potentially benefit from close monitoring and targeted efforts at risk factor modification.

In our secondary outcome analysis, we found that hemorrhagic strokes are more common than ischemic strokes after hospital discharge, which is consistent with results for all postpartum events in previous studies.\(^10\)\(^11\)\(^13\)\(^24\)\(^26\) The mortality rate from our study for postdischarge hemorrhagic events was ≈1.5 times greater than that for ischemic events, which is also supported by previous literature comparing pregnancy-related ischemic and hemorrhagic strokes.\(^2\)\(^5\)\(^20\) Several risk factors, including eclampsia, preeclampsia, black race, and older age, were common to both ischemic and hemorrhagic postdischarge acute CVD. However, chronic kidney disease and hematologic disorders were additional risk factors for postpartum ischemic strokes after hospital discharge, which may indicate mechanistic differences between these events.
The limitations of our study include the dependence on administrative data, which may have resulted in inaccuracies in diagnostic coding or misclassification of patients. Many of the ICD-9-CM codes used to identify risk factors and outcomes in this study have not been validated, which could have led to incorrect associations between comorbidities and postpartum acute CVD. However, similar associations in previous literature suggest that some correlation does exist between postdischarge acute CVD and the risk factors examined in our study. We also did not use data from federal healthcare facilities, which make up 3.1% of California facilities,10 but it is unlikely that the lack of data from this small percentage of facilities would have changed our numbers significantly. Finally, although our study contained a large number of postpartum women, the absolute rate of acute CVD was low, so our analysis of potential risk factors may have been underpowered, particularly for our subgroup analyses.

Previous work has shown that pregnancy confers a 3-fold increased risk of stroke compared with the nonpregnant state, and that the postpartum state is associated with an even higher risk.1-3,11,12 For instance, in a large cross-sectional study involving several dozens of New England hospitals, the relative risk of stroke during pregnancy and the 6-week postpartum period was 2.4, whereas the relative risk during the 6-week postpartum period alone was 7.9.11 Therefore, it is important for neurologists, obstetricians, and primary care physicians to be mindful of the incidence of acute CVD during the postpartum period. Our study expands on this message by demonstrating that many postpartum strokes occur after hospital discharge, when women are monitored less frequently and may be less cognizant of potential postpartum complications. The predominance of hemorrhagic strokes, coupled with their higher mortality rates, makes the consequences of these events even more clinically relevant. Clinicians should be aware that postpartum women remain at risk for stroke even if they have been discharged from their initial labor and delivery hospitalization without complication.

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Disclosures
Dr Kamel serves on the speaker’s bureau and consultant/advisory board for Genentech; this disclosed relationship is considered modest. Dr Fink serves as the Editor for Neurology:Alert; this disclosed relationship is considered modest. The other authors report no conflicts.

References
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http://stroke.ahajournals.org/content/45/7/1947

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卒中存活者
终模型中显著性定义为 P<0.5。所有的分析均采用数据管理统计绘图软件（Stata MP）。

结果

最终分析纳入了 2066230 例患者，患妊娠相关急性 CVD 的患者为 306 例（0.0015）。根据患者性别、种族、年龄以及我们所确定的危险因素，将所有患者分为两组进行比较。最后，10.9% 的患者合并妊娠相关的血液疾病，7.9% 有先兆子痫，0.1% 有子痫。

在 2062030 例 (99.8%) 的患者中，得出控制。使用逐步反向选择去掉在阈值 P<0.20 内的非显著因素。最终分析共纳入 2066230 例患者。患者基线特征包括人口统计学特征*。

关于分娩患者出院后急性 CVD 发病率、死亡率、危险因素的数据缺失。没有使用联邦政府医疗机构的数据，它占有加利福尼亚州机构的 3.1%，可能造成有偏的估计。

讨论

在 306 例 (0.0015%) 的患者中，我们发现分娩患者出院后急性 CVD 发病率的十分之二十分之一。之前文献报道出院后急性 CVD 发病率为十分之二十分之一。在医院，我们进行的临床研究可能低估了患者的出院后急性 CVD 发病率。我们发现分娩患者出院后急性 CVD 发病率的十分之二十分之一。在分娩期间，这些产后妇女很少被监测，也很少意识到潜在的产后并发症。研究中出院后急性 CVD 的发病率在报道的范围内。这表明，出院后急性 CVD 在分娩后的发病率比之前报道的要高。这可能提示我们应进一步研究出院后急性 CVD 的病因学和发病率。

分娩后急性 CVD 的高危患者，这可以使这部分人得到密切监测和针对危险因素的靶向治疗。

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