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 least 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%,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
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 100 000 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 puerperal apoplexy from the primary outcome, the rate of any acute CVD was 14.6 per 100 000 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 100 000 patients (95% CI, 2.8–4.5). Intracranial hemorrhage alone was diagnosed in 117 patients, which translates to a rate of 5.7 per 100 000 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), and pregnancy-related hematologic disorders (OR, 1.8; 95% CI, 1.4–2.2).

### Table 1. Baseline Patient Characteristics

| Characteristic* | Postdischarge Acute Cerebrovascular Disease (n=306) | No Postdischarge Acute Cerebrovascular Disease (n=2 065 924) | P Value
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>30.2 (±6.6)</td>
<td>28.3 (±6.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>109 (36.2)</td>
<td>773 863 (39.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black</td>
<td>47 (15.6)</td>
<td>129 177 (6.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hispanic</td>
<td>103 (34.2)</td>
<td>762 774 (38.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>42 (41.0)</td>
<td>296 190 (15.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medicaid or uninsured</td>
<td>122 (39.9)</td>
<td>831 871 (40.3)</td>
<td>0.89</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>57 (18.6)</td>
<td>163 917 (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>92 597 (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>174 064 (8.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (2.6)</td>
<td>15 594 (0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>42 (13.7)</td>
<td>156 907 (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>41 566 (2)</td>
<td>0.95</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>4 (1.3)</td>
<td>14 161 (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.
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.2,4,11,14 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 2. Predictors of Postpartum Acute Cerebrovascular Disease After Hospital Discharge for Labor and Delivery*

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR (95% CI)</th>
<th>P Value</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 (1.0–6.3)</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 281000 deliveries recorded by the National Hospital Discharge Survey reported that postdischarge acute CVD accounted for 40% of all postpartum events.13 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,16 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.20–23 For instance, parity may slightly increase the risk of coronary heart disease.20–21 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.21 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.10,11,24,26 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.29,30 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, 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. For instance, in a large cross-sectional study involving several dozens of New England hospitals, the relative risk during the 6-week postpartum period alone was 7.9. 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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卒中存活者的体能锻炼推荐

A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

卒中后体能锻炼缺乏十分普遍。充分的证据表明支持卒中存活者的运动训练，包括有氧训练及力量性训练，是有效的。体能锻炼可降低再卒中风险，日常生活能力与生活质量，并且降低了与卒中相关的医疗保健资源使用。卒中存活者的体能康复应在具备适当训练环境的早期开始。

结论

有证据表明，卒中存活者存在运动失调及久坐不动的生活方式。因此，这些建议为卒中存活者制定体能锻炼计划提供证据概述。卒中存活者应以全身性有氧运动与力量性训练相结合的组合形式积极参与体能锻炼。有氧运动每周至少150分钟或75分钟的中等强度运动，或者等效的高强度运动。力量性训练应至少每周进行两次。卒中存活者应通过参与体育锻炼，加强肌肉锻炼，减少久坐不动的行为，同时进行卒中二级预防的风险管理。

关键词: 体能锻炼; 有氧运动; 力量性训练; 康复

卒中及其他急性脑血管疾病（CVD）是我们所担心的妊娠并发症。据报道非妊娠的育龄妇女卒中的发生率是10.7/10万女性年龄年。相比之下，妊娠期卒中的发生率是3.4/10万妊娠女性，而妊娠期卒中的发生率大约是妊娠前的3倍。妊娠期女性卒中的死亡率大约是妊娠期的2倍。分娩后6周内卒中的发生率正在不断增长。实际上，产后6周内卒中的发生率是妊娠期的约8倍。而且，最近的数据显示，这种高风险可能会延长至产后12周。产后6周内急性卒中的发生率约为22-23/10万分娩女性，有数据表明，产后6周内卒中的发生率并不呈显著下降。

我们仅纳入首次出院后及分娩后前6周内发生的CVD。然而，根据最近的数据表明产后血栓形成的高风险可延伸至12周。我们还进行了事后分析，纳入首次出院后及分娩后前12周内发生的CVD。此外，由于利用这个数据库，我们确认了所有在2005年1月1日至2011年9月31日期间因分娩住院的妊娠女性，且出院诊断中没有按照国际疾病分类临床修订版（ICD-9-CM）定义的任何脑血管病。住院的可以使用编码与出院和分娩时诊断编码诊断6周内住院和住院的。因此，我们将住院的出院后、分娩后前12周内发生的CVD作为主要结局。

统计分析

利用这个数据库，我们确认了所有在2005年1月1日至2011年9月31日期间因分娩住院的妊娠女性，且出院诊断中没有按照国际疾病分类临床修订版（ICD-9-CM）定义的任何脑血管病。住院的可以使用编码与出院和分娩时诊断编码诊断6周内住院和住院的。因此，我们将住院的出院后、分娩后前12周内发生的CVD作为主要结局。

统计分析

我们使用行政数据库相关的出院数据进行了一项回顾性队列研究以确定从2005年至2011年在加利福尼亚非联邦急诊医院因分娩住院的所有孕妇，且不少于90天的医院住院。

方法

我们使用行政数据库相关的出院数据进行了一项回顾性队列研究以确定从2005年至2011年在加利福尼亚非联邦急诊医院因分娩住院的所有孕妇，且不少于90天的医院住院。

结果

统计分析

我们使用行政数据库相关的出院数据进行了一项回顾性队列研究以确定从2005年至2011年在加利福尼亚非联邦急诊医院因分娩住院的所有孕妇，且不少于90天的医院住院。
吸烟和酗酒。这些基线因素包括常见的妊娠并发症，均在本次分析中。

结果

最终分析纳入了2066230例患者，每位患者特征包括人口信息以及孕产史，均在纳入患者前选择的。通过逐步回归分析删掉了与结果无相关性。

主要结局是住院期间产后2周内发生的任何急性脑血管病，其300例患者特征分析中，因慢性肾脏疾病(OR, 4.7; 95% CI, 1.2–17.7)、子痫前期(OR, 12.9; 95% CI, 3.1–53.7)与颅内出血的风险增加有关，对于产后急性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

讨论

在一个大的研究和社区合作的人群中，我们发现分娩患者出院后6周内急性CVD的发病率与10%的死亡率。在我们的文献

在住院期间产后2周内发生的任何急性脑血管病，其中12.9%为颅内出血。住院期间急性CVD占所有住院事件的2.3%，而产后CVD占所有急性CVD的9.6%。

关于分娩患者出院后急性CVD的发病率、危险因素的预测价值较少，导致了来自不同研究的2010年协和研究的危险因素，出院后急性CVD的患者占所有事件的30%，然而，对于住院患者住院48小时内的危险因素，我们选择入院前2周的风险因素。这些风险因素可能有助于理解出院后的急性CVD。

在我们的分析中，分娩患者的急性CVD的发病率分别为7.5%，而住院患者急性CVD的发病率分别为17.2%。

因此，分娩患者出院后急性CVD的危险因素包括:子痫(优势比

年龄(每十年的OR, 1.5; 95% CI, 1.3–1.8)，吸烟和饮酒。这些基线因素包括常见的妊娠并发症，均在本次分析中。

在住院期间产后2周内发生的任何急性脑血管病，其中12.9%为颅内出血。住院期间急性CVD占所有住院事件的2.3%。然而，对分娩患者住院期间急性CVD的高危患者，这可以部分解释这部分人得到的及时监测和针对危险因素

这些人群中传统的血管危险因素比较罕见。比如年龄，岁，30.2(+6.6) 28.3(+6.5) <0.001。对分娩患者住院期间急性CVD的高危患者，这可以部分解释这部分人得到的及时监测和针对危险因素。

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文献

前人在卒中研究中发现，子痫是卒中的独立危险因素。这可能解释于住院期间产后2周内发生的任何急性脑血管病，其中12.9%为颅内出血。住院期间急性CVD占所有住院事件的2.3%。然而，对分娩患者住院期间急性CVD的高危患者，这可以部分解释这部分人得到的及时监测和针对危险因素。