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Acute Cerebrovascular Disease Occurring after Hospital Discharge for Labor and Delivery

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Abstract

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 through 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 prior to 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% CI 13.2-16.5). Risk factors for any acute CVD were eclampsia (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).

Conclusion—The incidence of postpartum acute CVD after hospital discharge for labor and delivery is similar to rates reported for all postpartum events in prior publications, suggesting that a substantial proportion of postpartum CVD occurs after discharge.

Keywords

postpartum; pregnancy; stroke; intracerebral hemorrhage; cerebrovascular disease

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Introduction

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 to these women, pregnant women are at an approximately 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 following delivery.^{2,8-10} In fact, the 6-week postpartum period is associated with an 8-fold increased risk of stroke compared to 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

While several prior 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 healthcare 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 Cost and Utilization Project.¹⁵ Each patient in this database is given a unique record linkage number that allows for longitudinal tracking.¹⁶

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 prior 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 within 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 disorder (437, 674.0). We included only events occurring after the initial hospital discharge and prior to 6 weeks after labor and delivery. However, in light of recent data demonstrating that the increased risk of postpartum thrombosis extends to at least 12 weeks,¹² we also performed a post-hoc analysis that included events occurring after the initial hospital discharge and prior to 12 weeks after labor and delivery. In addition, since 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 intracranial hemorrhage alone, defined as any intracerebral, subarachnoid, subdural, or epidural hemorrhage during this same time period.

Statistical Analysis

Descriptive statistics with exact confidence intervals 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 *a priori* selected baseline factors: age, race, insurance status, preeclampsia (*ICD-9-CM* 642 except for 642.6), eclampsia (*ICD-9-CM* 642.6), peripartum hemorrhage (*ICD-9-CM* 666), peripartum infection (*ICD-9-CM* 659.2, 659.3, 670, 672), pregnancy-related hematologic disorders which consisted of primary hypercoagulable states and anemia and coagulation defects complicating pregnancy, childbirth, or the puerperium (*ICD-9-CM* 289.81, 648.2, 649.3), hypertension (*Clinical Classification Software [CCS]* codes 98, 99),¹⁷ diabetes mellitus (*CCS* 45, 50, 186), congestive heart failure (*ICD-9-CM* 674.5, *CCS* 108), chronic kidney disease (*ICD-9-CM* 646.2, 669.3; *CCS* 157, 158), coronary heart disease (*CCS* 101), peripheral vascular disease (*CCS* 114, 115, 116), atrial fibrillation (*ICD-9-CM* 427.3x), tobacco use (*ICD-9-CM* 305.1, 649.0, 989.84, V15.82), and alcohol abuse (*ICD-9-CM* 303, 305.0). These baseline factors, which included common pregnancy-related complications, were the only factors that were controlled for in this analysis. Stepwise reverse selection was used to eliminate factors not significant at a threshold of $p < 0.20$. Significance for the final model was defined as a p-value of < 0.05 . All analyses were performed using Stata MP (Version 13, College Station, Texas).

Results

A total of 2,066,230 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 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 to 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 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 (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 1.2-2.5), 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); while 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 post-discharge acute CVD among the 2,066,230 total patients, equating to a rate of 17.2 events per 100,000 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 100,000 patients (95% CI 3.6-5.4). Intracranial hemorrhage alone was diagnosed in 137 patients, which translates to a rate of 6.6 per 100,000 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 approximately 15 per 100,000 deliveries. Prior publications have reported the incidence of postpartum acute CVD to be anywhere from 8 to 22 per 100,000 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.

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 281,000 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 (i.e. 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,¹⁸ our findings that a sizeable proportion of postpartum acute CVD occurs after hospital discharge are consistent with results from a previous study, which reported that the median onset of postpartum acute CVD is 8 days after delivery.¹⁹

Prior 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.²⁰⁻²² 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.²³ 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 very low in our study population, which may have been due to aggressive management of preeclampsia with magnesium sulfate administration. However, the relative risk of any postdischarge acute CVD in patients with eclampsia was increased more than 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 prior 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 prior studies.^{10,11,24,26} The mortality rate from our study for postdischarge hemorrhagic events was approximately 1.5 times greater than that for ischemic events, which is also supported by previous literature comparing pregnancy-related ischemic and hemorrhagic strokes.^{25,29} 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,³⁰ 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.

Prior work has shown that pregnancy confers an approximately 3-fold increased risk of stroke compared to 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 dozen New England hospitals, the relative risk of stroke during pregnancy and the 6-week postpartum period was 2.4, while 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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Table 1

Baseline Patient Characteristics

Characteristic [*]	Postdischarge Acute Cerebrovascular Disease (n = 306)	No Postdischarge Acute Cerebrovascular Disease (n = 2,065,924)	P Value
Age in years, mean (SD)	30.2 (±6.6)	28.3 (±6.5)	<0.001
Race [†]			<0.001
White	109 (36.2)	773,863 (39.4)	
Black	47 (15.6)	129,177 (6.6)	
Hispanic	103 (34.2)	762,774 (38.9)	
Other	42 (14.0)	296,190 (15.1)	
Medicaid or uninsured	122 (39.9)	831,871 (40.3)	0.89
Preeclampsia	57 (18.6)	163,917 (7.9)	<0.001
Eclampsia	3 (1.0)	1,679 (0.1)	<0.001
Peripartum hemorrhage	20 (6.5)	92,597 (4.5)	0.08
Peripartum infection	5(1.6)	9,025 (0.4)	0.002
Pregnancy-related hematologic disorders	52 (17)	174,064 (8.4)	<0.001
Hypertension	8(2.6)	15,594 (0.8)	<0.001
Diabetes	42 (13.7)	156,907 (7.6)	<0.001
Congestive heart failure	2 (0.7)	993(0)	<0.001
Chronic kidney disease	8 (2.6)	4,595 (0.2)	<0.001
Coronary heart disease	0 (0)	248(0)	0.85
Atrial fibrillation	0 (0)	328 (0)	0.83
Peripheral vascular disease	0 (0)	143 (0)	0.88
Tobacco use	6 (2)	41,566 (2)	0.95
Alcohol abuse	4 (1.3)	14,161 (0.7)	0.19

Abbreviations: SD, standard deviation.

* All data are reported as Number (%) unless otherwise indicated.

[†] Percentages reflect all patients for whom racial data was available. Information regarding race was unavailable for 5% of all patients.

Table 2

Predictors of Postpartum Acute Cerebrovascular Disease after Hospital Discharge for Labor and Delivery*

	Odds Ratio (95% CI)	P Value
Eclampsia	10.1 (3.1-32.8)	<0.001
Chronic kidney disease	5.4 (2.5-11.8)	<0.001
Black race	25 (1.9-3.3)	<0.001
Preeclampsia	2.1 (1.6-2.8)	<0.001
Pregnancy-related hematologic disorders	1.8 (1.2-2.5)	0.001
Age, per decade	1.5 (1.3-1.8)	<0.001
Congestive heart failure	3.4 (0.8-14.9)	0.110
Peripartum infection	2.5 (1.0-6.3)	0.052
Diabetes	1.4 (1.0-2.0)	0.060

* 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.