Risk Factors for Pregnancy-Associated Stroke in Women With Preeclampsia

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Background and Purpose—Preeclampsia affects 3% to 8% of pregnancies and increases risk of pregnancy-associated stroke (PAS). Data are limited on which women with preeclampsia are at highest risk for PAS.

Methods—Using billing data from the 2003 to 2012 New York State Department of Health inpatient database, we matched women with preeclampsia and PAS 1:3 to preeclamptic controls based on age and race/ethnicity. Pre-defined PAS risk factors included pregnancy complications, infection present on admission, vascular risk factors, prothrombotic states, and coagulopathies. We constructed multivariable conditional logistic regression models to calculate the odds ratios (ORs) and 95% confidence intervals (95% CIs) for independent risk factors for PAS.

Results—Among women aged 12 to 55 years admitted to New York State hospitals for any reason during the study period (n=3 373 114), 88 857 had preeclampsia, and 197 of whom (0.2%) had PAS. In multivariable analysis, women with preeclampsia and stroke were more likely than controls to have severe preeclampsia or eclampsia (OR, 7.2; 95% confidence interval [CI], 4.6–11.3), infections present on admission (OR, 3.0; 95% CI, 1.6–5.8), prothrombotic states (OR, 3.5; 95% CI, 1.3–9.2), coagulopathies (OR, 3.1; 95% CI, 1.3–7.1), or chronic hypertension (OR, 3.2; 95% CI, 1.8–5.5). Additional analyses matched and stratified by severity of preeclampsia confirmed these results.

Conclusions—Infections, chronic hypertension, coagulopathies, and underlying prothrombotic conditions increase PAS risk in women with preeclampsia. These women may warrant closer monitoring. **(*Stroke*. 2017;48:1752-1759. DOI: 10.1161/STROKEAHA.117.017374.)**

Key Words: cerebrovascular diseases ■ pregnancy ■ preeclampsia ■ risk factors ■ stroke ■ women

Preeclampsia is a multisystem hypertensive disorder unique to pregnancy, characterized by widespread endothelial dysfunction and immune dysregulation.[1] Approximately 36% of women with pregnancy-associated strokes (PASs) have comorbid preeclampsia,[2] and preeclampsia increases stroke risk during the puerperium up to 6-fold.[3] Among women with PAS, women with preeclampsia are at increased risk of complications and death.[4,5]

Although preeclampsia affects 3% to 8% of all pregnancies,[3,6] the overall occurrence of PAS remains rare (34.2 per 100 000 deliveries).[7] Older age, black race, and lack of private insurance are associated with PAS in women with preeclampsia,[4,8] and increased preeclampsia severity is associated with an increased risk of cardiovascular events.[9] The rarity of PAS makes it difficult to predict which preeclampsia patients are at highest risk for cerebrovascular complications. The American Heart Association/American Stroke Association found insufficient evidence to make recommendations on prevention of stroke in pregnancy complicated by hypertensive disorders.[10]

We sought to identify modifiable risk factors that put women with preeclampsia at highest risk of PAS.

Methods

Study Design and Data Description

We performed a case–control study using billing data, coded according to the *International Classification of Diseases, Ninth Revision*, from the 2003 to 2012 New York State Department of Health Statewide Planning and Research Cooperative System inpatient database. We identified all women aged 12 to 55 years old admitted with preeclampsia, including mild preeclampsia (642.4x [where x is any fifth digit from 0–9], 642.7x), severe preeclampsia (642.5x), or eclampsia (642.6x) from January 1, 2003, through December 31, 2012. Women without preeclampsia were not included in the study, regardless of whether they had strokes during or after pregnancy. Cases were

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defined as women with preeclampsia and PAS, including diagnosis codes for transient ischemic attack or ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage (SAH), cerebral venous thrombosis, and codes specific for nonspecified PAS. Pregnancy-specific stroke codes were validated using internal data sets (Table I in the online-only Data Supplement). In women with >1 stroke admission, we counted only the first admission. We characterized PAS in terms of timing and stroke subtype. Although stroke risk is increased up to 12 weeks after delivery,[11] a 6-week post-partum time frame was chosen because of limitations of *International Classification of Diseases, Ninth Revision*, coding.[12] Traumatic intracerebral hemorrhage and SAH and hospitalizations with a primary rehabilitation diagnosis (V57.89) were excluded. We matched each stroke case to 3 controls of the same age, race/ethnicity, and insurance status, selected randomly from the pool of women with preeclampsia without PAS.

Pre-defined exposures of interest, selected based on previously described associations with preeclampsia and PAS, included pregnancy-related variables, chronic vascular risk factors, comorbid prothrombotic states, coagulopathies/bleeding disorders, and infection of any type present on admission (POA), identified with a Statewide Planning and Research Cooperative System–specific indicator.[13,14] Infections acquired during the stroke hospitalization were not included. Coding details are in Table II in the online-only Data Supplement.

Cerebral symptoms are sufficient to classify preeclampsia as severe.[15,16] Because all our cases likely had neurological symptoms, this could create selection bias, confusing the relationship between severity of preeclampsia and stroke risk (ie, women with stroke and preeclampsia might by definition be coded as having severe preeclampsia). We therefore conducted a separate analysis matching each case to 3 controls of the same age, race/ethnicity, and severity of preeclampsia. Pre-specified subgroup analyses stratified the severity-matched cohort into 2 groups: those with mild preeclampsia and those with severe preeclampsia or eclampsia.

Statistical Analysis

We conducted univariable analyses comparing risk factors among cases and controls using χ^2 tests. Including only those PAS risk factors with $P<0.2$ from the univariable analysis,[17] we calculated unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (95% CI) using multivariable conditional logistic regression. Pre-specified subgroup analyses included a sensitivity analysis excluding all cases and controls with eclampsia (642.6x) and a subgroup analysis of post-partum strokes. All analyses were completed with SAS version 9.3 (SAS Institute, Cary, NC). A $P<0.05$ was set as the significance level.

Study Approvals

Approval was obtained from the Institutional Review Board of Columbia University Medical Center to conduct the analyses. Requirement for consent was waived because of the public, deidentified nature of the data.

Results

Baseline Characteristics of Women With Preeclampsia With and Without PAS

Among women aged 12 to 55 years admitted for any reason during the study period (n=3 373 114), 88 857 had preeclampsia, including eclampsia. Of these, 197 (0.2%) had PAS and were identified as cases, giving a cumulative incidence of PAS in women with preeclampsia of 222/100 000 during the study period. In the unmatched sample, compared with the 88 660 women with preeclampsia who did not have PAS, women with preeclampsia and PAS were older, had higher proportion of black race, lower proportion of Hispanic ethnicity, and higher proportion of severe preeclampsia (42.1% versus 29%) or eclampsia (28.9% versus 2%; Figure 1). Among cases, median age was 32 years (interquartile range, 26–36); 57 women (28.9%) had mild preeclampsia, 83 (42.1%) had severe preeclampsia, and 57 (28.9%) had eclampsia. The 197 stroke cases were matched with 591 nonstroke controls of the same age, race/ethnicity, and insurance status (Figure 2).

Timing and Characteristics of Strokes in Women With Preeclampsia and PAS

Among the 197 women with strokes, 55 (27.9%) strokes occurred antepartum; 8 (4.1%) occurred during the delivery hospitalization without further characterization in timing; 131 (66.5%) occurred post-partum; and 3 (1.5%) occurred during an admission without delivery, with no further characterization of timing. Of 131 post-partum strokes, 82 (62.6%) occurred after discharge (Figure 2). Stroke types included 92 (46.7%) hemorrhagic strokes, 26 (13.1%) ischemic, 8 (4.1%) transient ischemic attack, 5 (2.5%) cerebral venous thromboses, and 70 (35.5%) nonspecific PAS; 9 women had multiple subtypes (Figure I in the online-only Data Supplement). In-hospital mortality was 13.2% among cases, compared with 0.2% among controls. Details of discharge disposition/mortality are in Table III in the online-only Data Supplement.

Stroke Risk Factors in Cases and Controls Matched on Age/Race-Ethnicity/Insurance

In univariable analysis, women with PAS had a higher proportion than controls of severe preeclampsia or eclampsia, infections POA, chronic hypertension, prothrombotic states, coagulopathies, migraine, and heart disease (Table 1). The difference in infections between cases and controls was driven by genitourinary infections: 71% of infections in cases were genitourinary, compared with 39% of infections in controls, and genitourinary infections occurred in 10% of cases compared with 2% of controls ($P<0.0001$). After adjusting for other risk factors, significant risk factors for stroke were severe preeclampsia or eclampsia (OR, 7.2; 95% CI, 4.6–11.3), infections POA (OR, 3.0; 95% CI, 1.6–5.8), chronic hypertension (OR, 3.2; 95% CI, 1.8–5.5), prothrombotic states (OR, 3.5; 95% CI, 1.3–9.2), and coagulopathies (OR, 3.1; 95% CI, 1.3–7.1; Table 2).

Demographics and Risk Factors in Severity-Matched Cohort

When cases were matched to controls by preeclampsia severity, similar risk factors emerged: infections POA (OR, 2.6; 95% CI, 1.4–4.6), prothrombotic states (OR, 2.9; 95% CI, 1.3–6.4), and chronic hypertension (OR, 4.2; 95% CI, 2.4–7.4) conferred greater risk of stroke after adjusting for other risk factors (Table 3). In the severity-stratified subgroup analysis, after adjusting for other variables, chronic hypertension (OR, 3.0; 95% CI, 1.4–6.3) and infection POA (OR, 4.5; 95% CI, 1.6–12.6) were significant stroke risk factors in the mild subgroup (n=57). In the severe subgroup (n=140), chronic hypertension (OR, 8.4; 95% CI, 3.1–22.5) and prothrombotic states (OR, 6.6; 95% CI, 2.5–17.5) increased stroke risk; the association of infection POA did not reach statistical significance

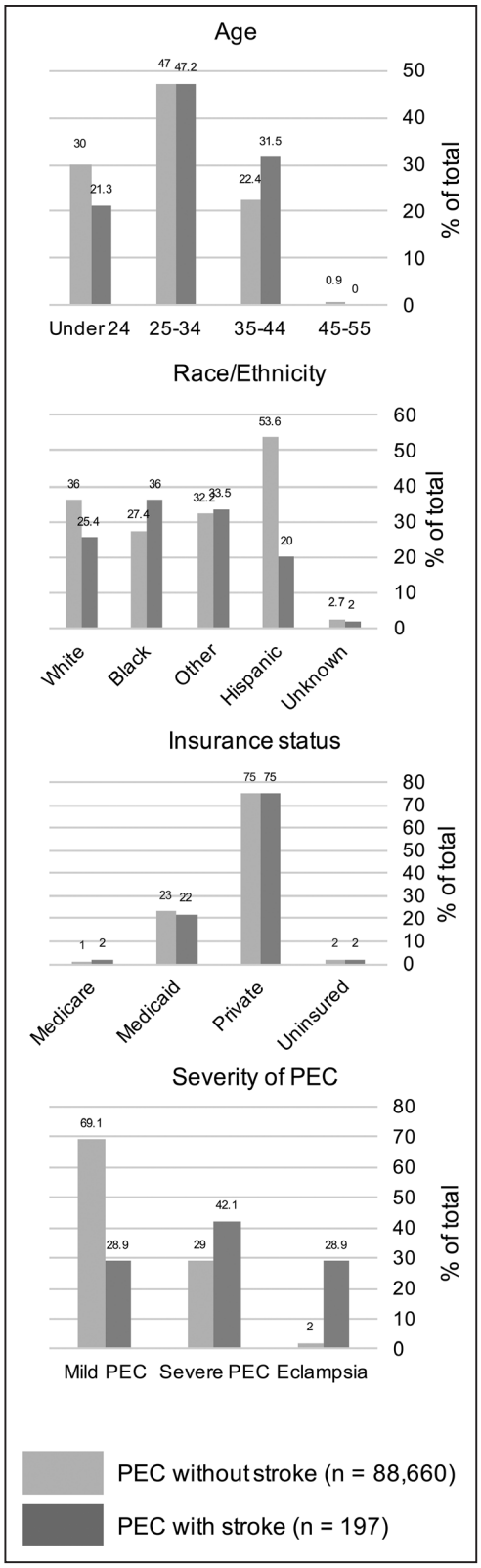

Figure 1. Baseline demographics of all women hospitalized with preeclampsia (PEC) in New York State 2003 to 2012 with and without pregnancy-associated stroke cases (women with PEC and stroke, n=197) are represented in dark gray. The unmatched sample of all women with PEC and without stroke (n=88 660) is represented in light gray. All columns represent percentages of total number in category.

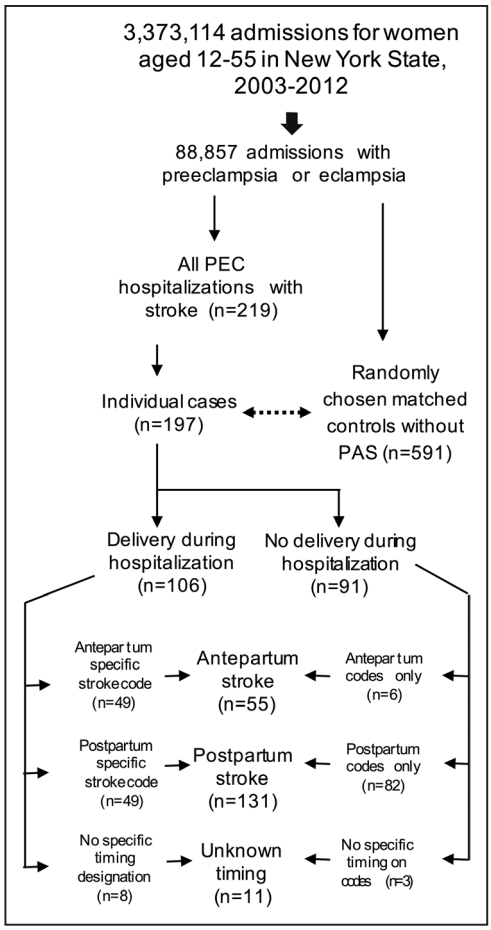

Figure 2. Patient selection, flow diagram. A total of 88 857 patients were admitted to hospitals in New York State between 2003 and 2012 with preeclampsia (PEC). Of these, 197 individual women had PEC and stroke. Strokes were classified as post-partum if they occurred either during a post-partum admission or during a delivery admission that included a pregnancy-specific stroke code with a fifth digit of 2 or 4 indicating a post-partum complication, in accordance with *International Classification of Diseases, Ninth Revision,* coding guidelines.[12] If the pregnancy-specific stroke code had a fifth digit of 3 indicating an antepartum complication, and the admission included a delivery, the stroke was categorized as antepartum.

after adjusting for other risk factors (OR, 1.9; 95% CI, 0.9–4.0; Table IV in the online-only Data Supplement). Demographics of mild versus severe cases and controls are shown in Table V in the online-only Data Supplement.

Subgroup Analyses

In the subgroup analysis excluding women with eclampsia (*International Classification of Diseases, Ninth Revision*, 642.6x), results were similar: women with chronic hypertension (adjusted OR, 4.2; 95% CI, 2.2–7.8), infection POA (adjusted OR, 3.7; 95% CI, 1.8–7.7), and prothrombotic states (adjusted OR, 2.6; 95% CI, 1.1–6.3) had higher risk of stroke (Table VI in the online-only Data Supplement). In the subgroup analysis, including only post-partum stroke, fewer cases than controls delivered via cesarean section (52% versus 65%; *P*=0.01). However, after adjusting for other risk factors, there was no significant association between cesarean

Table 1. Demographics and Baseline Characteristics in New York State Women With Preeclampsia, With and Without Pregnancy-Associated Stroke, 2003 to 2012

Prevalence of Characteristics	Cases (Preeclampsia and PAS) n=197 (%)	Controls (Preeclampsia Without PAS) n=591 (%)	*P* Value
Age, y			n/a (matched)
≤24	42 (21)	126 (21)	
25–34	93 (47)	279 (47)	
35–44	62 (31)	186 (31)	
Race/ethnicity			n/a (matched)
Non-Hispanic white	50 (25)	150 (25)	
Non-Hispanic black	71 (36)	213 (36)	
Non-Hispanic other	33 (17)	99 (17)	
Hispanic	39 (20)	117 (20)	
Unknown	4 (2)	12 (2)	
Insurance status			n/a (matched)
Uninsured	4 (2)	12 (2)	
Medicare	43 (22)	129 (22)	
Medicaid	148 (75)	444 (75)	
Private	2 (1)	6 (1)	
Severity of preeclampsia			*P*<0.0001
Mild preeclampsia	73 (37)	435 (74)	*P*<0.0001
Severe preeclampsia	90 (46)	157 (27)	*P*<0.0001
Eclampsia	57 (29)	19 (3)	*P*<0.0001
Chronic hypertension	44 (22)	81 (14)	*P*=0.004
Prothrombotic states (includes following)	26 (13)	15 (3)	*P*<0.0001
Hypercoagulable state	15 (8)	7 (1)	*P*<0.0001
Sickle cell disease	5 (3)	1 (0)	*P*=0.005
Systemic lupus erythematosus	2 (1)	0 (0)	*P*=0.06
DVT/PE (acute, chronic, or history of prior)	10 (5)	7 (1)	*P*=0.003
Infection present on admission (includes following)	28 (14)	33 (6)	*P*<0.0001
Genitourinary infection	20 (10)	13 (2)	*P*<0.0001
Chorioamnionitis	4 (2)	7 (1)	*P*=0.5
Nonspecified pregnancy-related infection	6 (3)	17 (3)	*P*=1.0
Respiratory infection	0 (0)	2 (0)	*P*=1.0
Gastrointestinal infection	1 (1)	1 (0)	*P*=0.4
Sexually transmitted infection (includes HIV)	1 (1)	7 (1)	*P*=0.7
Sepsis	3 (2)	2 (0)	*P*=0.1
Other infection	4 (2)	12 (2)	*P*=1.0
Coagulopathy	29 (15)	16 (3)	*P*<0.0001
Migraine	6 (3)	1 (0)	*P*=0.001
Heart disease (includes following)	6 (3)	5 (1)	*P*=0.02
Congestive heart failure	1 (1)	0 (0)	*P*=0.3
Chronic ischemic heart disease	1 (1)	0 (0)	*P*=0.3
Congenital heart disease	1 (1)	1 (0)	*P*=0.4
Valvular heart disease	3 (2)	4 (1)	*P*=0.4
Chronic renal disease	1 (1)	4 (1)	*P*=1.0
Drug abuse or dependence	4 (2)	9 (2)	*P*=0.7
Alcohol abuse	4 (2)	10 (2)	*P*=0.2
HIV/AIDS (SPARCS indicator)	0 (0)	1 (0)	*P*=1.0
Diabetes mellitus	7 (4)	22 (4)	*P*=1.0
Active smoking	4 (2)	8 (1)	*P*=0.5
Obesity	8 (4)	15 (3)	*P*=0.3
Gestational hypertension	7 (4)	21 (4)	*P*=1.0
Multiple gestation	4 (2)	34 (6)	*P*=0.03
Multigravida	35 (18)	137 (23)	*P*=0.1

Cases and controls matched on age, race/ethnicity, and insurance status. See Table II in the online-only Data Supplement for complete details of diagnostic codes. DVT indicates deep vein thrombosis; PAS, pregnancy-associated stroke; PE, pulmonary embolism; and SPARCS, Statewide Planning and Research Cooperative System.

delivery and stroke risk (adjusted OR, 0.7; 95% CI, 0.4–1.1). Otherwise, similar risk factors were found in women with post-partum stroke (Tables VII and VIII in the online-only Data Supplement).

Discussion

In this case–control study in a diverse population of women with preeclampsia, we found that risk factors for PAS included infections (predominantly genitourinary), chronic hypertension, prothrombotic conditions, and coagulopathies. The cumulative incidence of stroke in our preeclamptic

Table 2. Independent Stroke Risk Factors in Women With Preeclampsia, With and Without Pregnancy-Associated Stroke, Matched by Age, Race/Ethnicity, and Insurance Status

Risk Factors: Multivariable Analysis		Odds Ratio (95% Confidence Interval)
Infection present on admission	Unadjusted	2.7 (1.6–4.7)
	Adjusted	3.0 (1.6–5.8)
Chronic hypertension	Unadjusted	1.9 (1.2–2.9)
	Adjusted	3.2 (1.8–5.5)
Prothrombotic state*	Unadjusted	7.5 (3.5–16.1)
	Adjusted	3.5 (1.3–9.2)
Coagulopathy†	Unadjusted	6.0 (3.1–11.3)
	Adjusted	3.1 (1.3–7.1)
Severe preeclampsia or eclampsia	Unadjusted	6.6 (4.4–9.8)
	Adjusted	7.2 (4.6–11.3)
Heart disease‡	Unadjusted	3.6 (1.1–11.8)
	Adjusted	1.7 (0.3–9.4)
Multiple gestation	Unadjusted	0.3 (0.1–1.0)
	Adjusted	0.3 (0.1–0.9)
Multigravida	Unadjusted	0.7 (0.5–1.1)
	Adjusted	1.1 (0.6–1.9)

See Table II in the online-only Data Supplement for complete details of diagnostic codes.

*Includes primary hypercoagulable state, history of deep vein thrombosis or pulmonary embolism, systemic lupus erythematosis, and sickle cell disease.

†Includes bleeding diatheses and thrombocytopenia.

‡Includes congenital, valvular, and ischemic heart diseases and congestive heart failure.

population was 222/100 000, >6 times the incidence of stroke in the overall pregnant population, consistent with prior studies.[3,4] Two thirds of cases of PAS (131 of 197) were diagnosed post-partum, consistent with prior research.[7] More than 1 in 10 women with preeclampsia and PAS died during their admission for stroke, likely reflecting the large proportion of hemorrhagic strokes.[18] In comparison, overall US maternal mortality in 2011 was 17.8 per 100 000 deliveries, or 0.02%,[5,19–21] emphasizing the importance of identifying women at the highest risk of PAS and targeting them for closer monitoring.

Infection

Infection is increasingly recognized as a trigger for stroke, particularly in young people.[14,22] Proposed mechanisms include increased levels of inflammatory cytokines leading to platelet aggregation and impaired endothelial function. Infections may also provoke cardiac arrhythmias or dehydration-induced thrombosis; in 1 study, infections tripled the odds of peripartum cerebral venous thrombosis.[23] The pathophysiology of preeclampsia remains incompletely understood[1] although imbalance of pro- and antiangiogenic factors and an increase in proinflammatory cytokines seem to play roles.[24] Animal models of preeclampsia have demonstrated impaired cerebral autoregulation, increased blood-brain barrier permeability, and neuronal hyperexcitability, mediated by elevated levels of tumor necrosis factor-α.[25–28] In the setting of preeclampsia-associated inflammation and puerperial hypercoagulability, superimposed infection could trigger stroke by exacerbating inflammation and coagulopathy.[11]

Although we included only infections POA in our analysis, it is important to acknowledge that we cannot be certain that the infection preceded the stroke without a prospective study. Nevertheless, a possible association between infection and preeclampsia-associated stroke has important clinical implications because it may represent a modifiable risk factor. The difference in infections between cases and controls in our cohort was driven entirely by genitourinary infections. Symptoms of urinary infections, such as dysuria or incontinence, may go unrecognized in post-partum women because similar symptoms may occur with normal post-partum recovery. Women with preeclampsia undergo post-partum blood pressure checks; screening for urinary tract infections at these visits and monitoring those with infections more closely for neurological symptoms may be warranted. The role for prophylactic antibiotics could be considered on a case by case basis and may be a target in clinical trials.

Chronic Hypertension

The role of chronic hypertension in preeclampsia-associated stroke is poorly characterized. Chronic hypertension shifts the cerebral autoregulatory curve[29] but is not associated with loss of dynamic cerebral autoregulatory capacity because of rapid adaptation of the cerebral vasculature.[30] However, acute malignant hypertension in chronically hypertensive patients severely impairs dynamic cerebral autoregulation.[31] Preeclampsia may cause impairment of cerebrovascular autoreactivity,[32] leading to hyperemia, hypertensive leukoencephalopathy, and the reversible cerebral vasoconstriction syndrome,[33] all of which can be associated with stroke.[34] Reversible cerebral vasoconstriction syndrome is highly associated with post-partum stroke.[35] Unfortunately, we were unable to assess investigate the role of reversible cerebral vasoconstriction syndrome and stroke in our population because reversible cerebral vasoconstriction syndrome is not reliably captured by *International Classification of Diseases, Ninth Revision,* coding.

Prothrombotic Conditions and Coagulopathies

Women with an underlying propensity to thrombosis are at increased risk of stroke when pregnancy, itself a hypercoagulable state, is complicated by preeclampsia.[4,36] Only 2.5% of strokes in our cohort were because of cerebral venous thrombosis, suggesting that prothrombotic states may put women at risk of arterial thrombosis and hemorrhagic stroke as well. However, cerebral venous thrombosis, which may also present with hemorrhage, may be underdiagnosed. Women with underlying thrombophilia may have been on antithrombotic treatment during or after their pregnancy, increasing their intracerebral hemorrhage/SAH risk. Patients with preeclampsia and a history of coagulopathy likely warrant increased vigilance in the peripartum period.

Table 3. Investigation of Risk Factors for Stroke, New York State Women With Preeclampsia, Matched on Severity of Preeclampsia

Risk Factors: Multivariable Analysis		All Cases Odds Ratio (95% CI)	Mild Cases Only Odds Ratio (95% CI)	Severe Cases Only Odds Ratio (95% CI)
Chronic hypertension	Unadjusted	4.8 (2.8–8.3)	3.3 (1.6–6.5)	8.6 (3.4–21.7)
	Adjusted	4.2 (2.4–7.4)	3.0 (1.4–6.3)	8.4 (3.1–22.5)
Infection present on admission	Unadjusted	2.8 (1.6–4.7)	4.3 (1.7–10.6)	2.1 (1.1–4.1)
	Adjusted	2.6 (1.4–4.6)	4.5 (1.6–12.6)	1.9 (0.9–4.0)
Prothrombotic state*	Unadjusted	3.6 (2.0–6.5)	n/a	6.1 (3.1–12.2)
	Adjusted	2.9 (1.3–6.4)	n/a	6.6 (2.5–17.5)
Coagulopathy†	Unadjusted	2.8 1.7–4.7	n/a	3.0 (1.7–5.4)
	Adjusted	1.5 (0.8–3.1)	n/a	1.3 (0.5–2.9)
Obesity	Unadjusted	n/a	9.0 (1.8–44.6)	n/a
	Adjusted	n/a	4.9 (0.9–26.5)	n/a
Heart disease‡	Unadjusted	4.5 (1.3–15.9)	n/a	3.8 (1.0–14.0)
	Adjusted	2.1 (0.5–9.9)	n/a	1.0 (0.2–5.4)
Migraine	Unadjusted	3.6 (1.1–11.8)	n/a	n/a
	Adjusted	3.6 (0.9–14.5)	n/a	n/a
Multiple gestation	Unadjusted	0.3 (0.1–0.8)	n/a	0.3 (0.1–0.9)
	Adjusted	0.2 (0.1–0.9)	n/a	0.2 (0.04–0.7)
Multigravida	Unadjusted	0.5 (0.3–0.7)	n/a	0.3 (0.2–0.5)
	Adjusted	0.6 (0.4–0.9)	n/a	0.3 (0.2–0.6)

See Table II in the online-only Data Supplement for complete details of diagnostic codes. CI indicates confidence interval; and n/a, not applicable.

*Includes primary hypercoagulable state, history of deep vein thrombosis or pulmonary embolism, systemic lupus erythematosis, and sickle cell disease.

†Includes bleeding diatheses and thrombocytopenia.

‡Includes congenital, valvular, and ischemic heart diseases and congestive heart failure.

Other Vascular Risk Factors

Heart disease has been identified as a risk factor for PAS in women with preeclampsia.[4] After adjusting for other risk factors, our results failed to show significant between-group differences in heart disease. Similarly, we found no significant differences in stroke risk comparing other traditional vascular risk factors, such as diabetes mellitus, obesity, chronic renal disease, smoking, and other substance abuse. In fact, proportions of these risk factors were low in both cases and controls. Our study may have been underpowered to detect between-group differences in some risk factors because other studies have found otherwise; alternatively, the pathophysiology of PAS in women with preeclampsia may bear little relationship to traditional vascular risk factors.

Preeclampsia Severity

Preeclampsia is regarded as a disease along a continuum; women with gestational hypertension may go on to develop preeclampsia and then severe preeclampsia.[37] Women with severe preeclampsia were over-represented in our cases compared with the overall population of women with preeclampsia; however, it is difficult to interpret this finding because any cerebral symptom in a woman with preeclampsia is considered a severe feature, creating a significant selection bias. Further complicating interpretation of our data is the updating of diagnostic criteria for severe preeclampsia in 2013, after our study period.[16] The lack of data on the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome , a variant of preeclampsia, is a limitation of our study because these women may be at particularly high stroke risk.[38]

Research in Context: Study Strengths and Limitations

Two prior population-based studies compared women with preeclampsia and stroke to women with preeclampsia without stroke.[39,40] Neither study was designed to identify multiple independent risk factors for stroke in this population: one compared only mortality outcomes and the other compared methods of anesthesia during delivery. The ethnic and regional diversity of New York State increases the generalizability of our findings. Matching of cases and controls allowed for nuanced analysis of other risk factors. We conducted multiple subgroup analyses to explore possible biasing factors in our results.

Our study has limitations. Data were drawn from a large administrative database, and there may be coding errors. Some preeclampsia cases may not have been formally diagnosed and thus not included in the study. Pregnancy-specific

stroke codes do not distinguish between stroke subtypes, limiting the granularity of the data, although the majority of patients had additional codes to identify stroke subtypes with more precision (Figure I in the online-only Data Supplement). Although the proportion of each of the prothrombotic conditions individually (hypercoagulable states, history of thromboembolic events, systemic lupus erythematosis, and sickle cell disease) was higher in cases than controls, grouping them together may overestimate their effects. Diagnosis of prothrombotic conditions or coagulopathies may have occurred only after the stroke, leading to ascertainment bias. Although we included only infections POA for stroke, exact timing of infections in relation to stroke onset cannot be confirmed without a prospective study. Causality cannot be inferred from this observational study, and results should be interpreted cautiously.

In summary, urinary tract infections, chronic hypertension, prothrombotic conditions, and coagulopathies increased stroke risk in women with preeclampsia. Infections may be an important treatable risk factor in this population; similarly, screening for coagulopathies and prothrombotic conditions may be warranted in women with preeclampsia. Prospective studies are needed to confirm these findings and develop interventions aimed at preventing strokes in this uniquely vulnerable group.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Risk Factors for Pregnancy-Associated Stroke in Women with Preeclampsia: a Case-Control Study

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Supplemental Table I. Pregnancy-specific stroke ICD-9 code validation

Background: Pregnancy-specific stroke ICD-9 codes have been used in epidemiological studies to identify pregnancy-associated strokes (PAS),[1-4] but may have poor positive predictive value (PPV).[5] We previously validated the sensitivity of these codes at 92%,[6] based on an internal stroke registry. However, this registry includes only cases adjudicated as strokes by a panel of vascular neurologists, and is not based on administrative data.

Methods: We queried the electronic medical record system at Columbia University Medical Center for ICD-9 codes 671.5, 674.01, 674.02, 674.03, and 674.04 for any diagnosis from January 1, 2010 through December 31, 2015. IRB approval was obtained to review the individual medical records of the patients identified. PAS was defined as any confirmed cerebrovascular event, including TIA, ischemic stroke, SAH, ICH, cerebral venous thrombosis, or clinically and radiologically confirmed reversible cerebral vasoconstriction syndrome (with or without hemorrhage or infarct).

Results: A total of 56 individual patients were identified with codes 674.0x. There were no patients with the code 671.5. Of the 56 identified patients, 45 (80.4%) had confirmed PAS. The clinical diagnoses among the 11 false positives included: brain tumor (1), chronic hypertension (1), unruptured aneurysm (2), asymptomatic moyamoya disease (1), delivery admissions for women with prior non-pregnancy related ischemic or hemorrhagic stroke (4), complicated migraine(1), and remote gunshot wound to the head (1).

Conclusions: In our sample at a tertiary care center, pregnancy-specific stroke codes had a PPV of 80.4%.

Case#	ICD-9 code (code position)	PAS (yes/no)	Timing	Clinical diagnosis
1	674.04 (5)	yes	Postpartum	Venous sinus thrombosis with ICH
2	674.04 (1)	yes	Postpartum	cardioembolic stroke
3	674.04 (1)	yes	Postpartum	RCVS with SAH
4	674.03 (1)	yes	Antepartum	cryptogenic stroke
5	674.03 (1)	yes	Antepartum	cerebellar ICH
6	674.04 (1)	yes	Postpartum	RCVS with SAH/ICH
7	674.04 (5)	yes	Postpartum	RCVS with SAH
8	674.03 (1)	yes	Antepartum	TIA
9	674.04 (1)	yes	Postpartum	RCVS
10	674.04 (1)	yes	Postpartum	RCVS
11	674.04 (5)	yes	Postpartum	SAH, possible RCVS
12	674.04 (1)	yes	Postpartum	RCVS with SAH
13	674.04 (1)	yes	Postpartum	RCVS with SAH
14	674.01 (3)	no	Delivery admission	Remote AVM bleed
15	674.04 (1)	yes	Postpartum	Cortical vein thrombosis with SAH
16	674.03 (1)	no	Antepartum	Meningioma
17	674.04 (1)	yes	Postpartum	Cortical vein thrombosis, venous infarct
18	674.02 (8)	yes	Postpartum	ICH/SAH
19	674.04 (1)	yes	Postpartum	Basilar occlusion
20	674.04 (1)	yes	Postpartum	ICA occlusion
21	674.03 (1)	yes	Antepartum	AVM rupture, ICH
22	674.03 (5)	yes	Antepartum	R MCA cryptogenic stroke
23	674.03 (1)	yes	Antepartum	AVM rupture, ICH
24	674.04 (1)	yes	Antepartum	AVM rupture, ICH
25	674.04 (1)	yes	Postpartum	RCVS with SAH
26	674.01 (2)	no	Delivery admission	Chronic hypertension
27	674.04 (1)	yes	Postpartum	Cardioembolic stroke

28	674.01 (2)	no	Delivery admission	Remote ICH from cavernous malformation
29	674.01 (1)	no	Delivery admission	Remote aneurysmal SAH
30	674.04 (1)	yes	Postpartum	ICH
31	674.04 (1)	yes	Postpartum	RCVS with ICH
32	674.04 (1)	yes	Postpartum	RCVS
33	674.01 (2)	yes	Postpartum	Recurrent RCVS
34	674.03 (1)	no	Antepartum	Unruptured aneurysm
35	674.04 (1)	yes	Postpartum	RCVS with TIA
36	674.03 (1)	no	Antepartum	Complicated migraine
37	674.02 (5)	yes	Postpartum	RCVS with ICH
38	674.01 (2)	yes	Antepartum	AVM rupture, ICH
39	674.01 (1)	yes	Antepartum	Cryptogenic stroke
40	674.02 (5)	yes	During delivery	Cardioembolic stroke
41	674.04 (1)	yes	Postpartum	RCVS with SAH
42	674.03 (1)	yes	Antepartum	Cryptogenic strokes
43	674.01 (8)	no	Delivery admission	Known moyamoya
44	674.02 (7)	yes	Postpartum	RCVS with SAH
45	674.01 (1)	no	Delivery admission	Unruptured aneurysm
46	674.01 (1)	no	Delivery admission	Unruptured AVM
47	674.03 (1)	yes	Antepartum	RCVS
48	674.02 (5)	yes	Postpartum	RCVS
49	674.01 (1)	yes	Antepartum	AVM rupture, ICH
50	674.01 (1)	yes	Postpartum	TIA
51	674.04 (1)	yes	Postpartum	RCVS with SAH
52	674.03 (1)	yes	Antepartum	AVM rupture, ICH
53	674.03 (9)	no	Postpartum	Old gunshot wound, hemiparesis
54	674.04 (1)	yes	Postpartum	ICH
55	674.01 (1)	yes	Antepartum	Cardioembolic strokes
56	674.03 (1)	yes	Antepartum	Aneurysmal SAH

Supplemental Table II. ICD-9 Codes Used in Identifying Patients and Patient Characteristics

Patient characteristics	CODES (ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification)
IDENTIFICATION OF DELIVERIES AND PREGNANCY CHARACTERISTICS	
Antepartum admission	Admissions with pregnancy code (630-648) with no delivery code;[7] fifth digit of 3 in codes for pregnancy-related primary or secondary diagnosis; V22, V23, V28, or 792.3 for any listed diagnosis; antenatal DRG codes 378–384 [8]
Delivery admission	Admissions with delivery code (vaginal or cesarean delivery, see below)[7]
Postpartum admission	Admissions with postpartum code (660-677) with no delivery code OR APR/DRG 561;[7] fifth digit of 2 or 4 in pregnancy-related codes for primary or secondary diagnosis; code V24 for any listed diagnosis; or postpartum DRG codes 376–377[8]
Postpartum stroke during delivery admission	Admissions with delivery code AND pregnancy-associated stroke code with suffix .x2 (fifth digit "2")[9]
Vaginal delivery	V27, 72.x, 73.x, 650–659, APR/DRG 541, 560[10]
Cesarean delivery	74.0x-74.2x, 74.4, 74.9x, 669.70, 669.71, 762.1, 763.4 or APR/DRG 540[11]
Peripartum hemorrhage	666[4]
Gestational hypertension	642.3x, 642.9x[12]
Mild or unspecified preeclampsia[a]	642.4x, 642.7x[13]
Severe preeclampsia[a]	642.5x[13]
Eclampsia[a,b]	642.6x[13]
Multiple gestation	V27.2-V27.8, 651.x[11]
Proteinuria/nephrotic syndrome	791.0, 581.81[9]
Gestational diabetes	648.8x[11]
Small for gestational age	656.5x[10]
Assisted reproductive technology	V23.85[9]
History of previous cesarean section	654.2x[12]
Primagravida	V22.0, V23.81, V23.83[9]
Multigravida	V22.1, V23.82, V23.84[9]
Grand multiparity (5 or more deliveries)	V23.3, 659.40, 659.41, 659.43[9]
Stillbirth	656.4x, V27.1, V27.3, V27.4, V27.6, V27.7[11]

[a]These codes were shown to have PPV of 94.5% when applied to inpatient hospitalizations[13]	
[b]For the severity-stratified analysis, "eclampsia" was included in the "severe" group due to a validation study showing that more than half of women given this code did not meet criteria for eclampsia; all the women in the validation study misclassified as "eclampsia" met criteria for "severe preeclampsia" as defined until the 2013 update by the American College of Obstetricians and Gynecologists.[14,15]	
VASCULAR RISK FACTORS	
Sickle cell disease	282.4x, 282.6x[11,12]
Systemic lupus erythematosus	710.0x[11,12]
Coagulopathy	286.0-286.9, 287.1, 287.3-287.5, 289.81-289.82[16]
Hypercoagulable state	289.81, 289.82,[17] 649.3x[9]
DVT/PE (acute, chronic, or history of prior)	415.1x, 453.4x, 453.5x, 453.72, 453.74, 453.75, 453.76, 453.77, 453.82, 453.84, 453.85, 453.86, 453.87, 671.3x, 671.4x, 673.0x, 673.1x, 673.2x, 673.3x, 673.8x, V12.51, V12.55[9]
Chronic renal disease	581.x-583.x, 585.x, 587.x, 588.x, 646.2x[11,12]
Active smoking	305.1.x, 649.0x[12]
Preexisting hypertension	401.x-405.x, 642.0x-642.2x, 642.7x[11]
Diabetes mellitus (excluding gestational diabetes)	250.x, 648.0x[11,12]
Obesity	278.0x, 649.1x ,V85.3, V85.4[12]
Migraine	346.x[7]
Malignancy	140.x-208.x[11]
Pulmonary hypertension	416.0, 416.8, 416.9[11,12]
Chronic ischemic heart disease	412.x-414.x[11,12]
Congenital heart disease	745.0x-747.4x, 648.5x[11,12]
Valvular heart disease	394.x-397.x, 424.x[11,12]
Congestive heart failure	428.22, 428.23, 428.32, 428.33, 428.42, 428.43[12]
Drug abuse or dependence	304.x-305.0x, 305.2x-305.9x, 648.3x[11,12]
Alcohol abuse	291.xx, 303.xx, 305.0x[12]
INFECTIONS[9]	
Pregnancy-related (includes the following):	
Postpartum infection	670x, 672x[4]
Chorioamnionitis	658.4x[11]
Infectious and parasitic conditions in the mother classifiable elsewhere but complicating pregnancy childbirth or the puerperium	647.xx

Mastitis	675.xx
Puerperial infections	670.0x, .1x, .8x
Sexually transmitted (includes the following):	
HIV	HIV-specific flag in SPARCS database
Syphilis	647.0x
Gonorrhea	647.1x
Other venereal	647.2x
Trichomoniasis	131.xx
Sexually transmitted infections	091.xx - 099.xx
Herpes simplex	054.xx
Respiratory (includes the following):	
Acute nasopharyngitis	460
Acute sinusitis	461.x
Acute pharyngitis	462
Acute laryngitis and tracheitis	464.xx
Acute upper respiratory infections of multiple or unspecified sites	465.x
Chronic sinusitis	473.x
Postnasal drip	784.91
Viral pneumonia	480.x
Pneumococcal pneumonia	481
Other bacterial pneumonia	482.xx
Pneumonia due to other specified organism	483.x
Pneumonia in infectious diseases classified elsewhere	484.x
Bronchopneumonia, organism unspecified	485
Pneumonia, organism unspecified	486
Streptococcal sore throat	034.0
Whooping cough	033.xx
Abscess of lung	513.0
Tuberculosis, pulmonary	011, 012

Rheumatic pneumonia	517.1
Pulmonary coccidioidomycosis, unspecified	114.5
Primary coccidioidomycosis (pulmonary)	114.0
Infection by Histoplasma, pneumonia	115.x5
Pneumonitis due to toxoplasmosis	130.4
Pneumocystosis	136.3
Candidiasis of lung	112.4
Ornithosis with pneumonia	073.0
Postmeasles pneumonia	055.1
Varicella (hemorrhagic) pneumonitis	052.1
Pulmonary actinomycotic infection	039.1
Pulmonary tularemia	021.2
Pulmonary anthrax	022.1
Diphtheria	032.0 - 032.3, 032.84
Genitourinary (includes the following):	
Infections of kidney	590.xx
Cystitis	595.xx
Urethritis not sexually transmitted and urethral syndrome	597.xx
Urethral stricture due to infection	598.0x
Urinary tract infection	599.0
Gastrointestinal (includes the following):	
Gastrointestinal infections	001.xx - 009.xx
Sepsis (includes the following):	
Bacteremia	790.7
Sepsis	995.91
Severe sepsis	995.92
Septic shock	785.52
Septicemia	038.0, 038.1x-0.38.9x

Sepsis in pregnancy	670.2x, 670.3x
Anthrax septicemia	022.3
Meningococcemia	036.2
Herpetic septicemia	054.5
Septic arterial embolism	449
Other (includes the following):	
Cellulitis	681.xx, 682.xx, 686.xx
Lyme disease	088.81
Plague	020.2, 020.3, 020.4, 020.5
Diseases due to other mycobacteria	031.0
Q fever	083.0
Primary extrapulmonary coccidioidomycosis	114.1
ACUTE CEREBROVASCULAR DISEASE CODES (not pregnancy-specific)[1]	
Ischemic stroke	433.01, 433.10, 433.11, 433.21, 433.31, 433.81, 433.91, 434.00, 434.01, 434.11, 434.91, and 436[1]
Transient ischemic attack	435[1]
Intracerebral hemorrhage	431[1]
Subarachnoid hemorrhage	430[1]
Epidural/subdural intracranial hemorrhage	432[3]
Pituitary apoplexy	253.2[3]
Carotid/vertebral artery dissection	443.21, 443.24[3]
Cerebral venous thrombosis	325[18]
Other acute cerebrovascular disorders	437.x[19]
Iatrogenic stroke	997.02[1]
Trauma (excluded from analysis)	800-804, 850-854[3]
Acute rehabilitation admission (excluded from analysis)	V57.x
PREGNANCY-SPECIFIC STROKE CODES	
Peripartum phlebitis and thrombosis, cerebral venous thrombosis, and thrombosis of intracranial venous sinus	671.5[3,4]
Cerebrovascular disorders in the puerperium, unspecified	674[1]

Cerebrovascular disorders in the puerperium, delivered, with or without mention of antepartum condition	674.01[1]
Cerebrovascular disorders in the puerperium, delivered, with mention of postpartum complication	674.02[1]
Cerebrovascular disorders in the puerperium, antepartum condition or complication	674.03[1]
Cerebrovascular disorders in the puerperium, postpartum condition or complication	674.04[1]
References for codes are noted in table and included in Reference list at end of Supplementary Appendix. ICD-9: International Classification of Diseases, 9th edition. APR: All patient refined. DRG: diagnosis related group. PPV: positive predictive value. DVT: deep vein thrombosis. PE: pulmonary embolism. HIV: human immunodeficiency virus. SPARCS: Statewide Planning and Research Cooperative System.	

Supplemental Table III. Discharge disposition in women with preeclampsia, with and without pregnancy-associated stroke (control group matched on age, race/ethnicity, and severity of preeclampsia).

Disposition	Cases (PEC and PAS) n = 197 (%)	Controls (PEC and no PAS) n = 591 (%)
Home	89 (45.2)	540 (91.4)
Home with home services	30 (15.2)	39 (6.6)
Left against medical advice	1 (0.5)	7 (1.2)
Acute inpatient rehabilitation	23 (11.7)	1 (0.2)
Other acute care hospital	22 (11.2)	2 (0.3)
Skilled nursing facility	6 (3.0)	1 (0.2)
Death (in hospital)*	26 (13.2)	1 (0.2)

*There was no significant difference in mortality between stroke cases with mild and severe PEC; 7 of 57 (12.3%) of mild cases died, and 19 of 140 (13.6%) severe cases died (p=0.81). The majority of women who died had hemorrhagic strokes (21 of 26, 80.1%). More deaths were due to hemorrhagic stroke in the severe group than in the mild group (89.5% vs 57.1%, p=0.06), although the difference did not reach statistical significance.

Supplemental Table IV. Subgroup analysis, mild and severe cases/controls, univariable analysis

	Mild Group			Severe group			Matched on Severity		
Prevalence of risk factors	Cases (PAS)	Controls (without PAS)	p-value	Cases (PAS)	Controls (without PAS)	p-value	Cases (PEC and PAS)	Controls (PEC without PAS)	p-value
	n=57 (%)	n=171 (%)		n=140 (%)	n=420 (%)		N = 197 (%)	N (591)	
Pre-existing hypertension	25 (44)	35 (20)	p=0.001	19 (14)	9 (2)	p<0.0001	44 (22)	44 (7)	<.0001
Prothrombotic states	1 (2)	9 (5)	p=0.5	25 (18)	13 (3)	p<0.0001	26 (13)	22 (4)	<.0001
Hypercoagulable state	*1 (2)*	*6 (4)*	*p=0.7*	*14 (10)*	*10 (2)*	*p<0.0001*	*15 (8)*	*16(3)*	*0.002*
Sickle cell	*0 (0)*	*1 (1)*	*p=1.0*	*5 (4)*	*0 (0)*	*p<0.0001*	*5 (3)*	*1 (0)*	*0.005*
Lupus	*0 (0)*	*2 (1)*	*p=1.0*	*2 (1)*	*0 (0)*	*p=0.1*	*2 (1)*	*2 (0)*	*0.3*
DVT/PE (acute, chronic, or history of prior)	*0 (0)*	*0 (0)*		*10 (7)*	*3 (1)*	*p<0.0001*	*10 (5)*	*3 (1)*	*<.0001*
Any infection present on admission	12 (21)	9 (5)	p=0.001	16 (11)	25 (6)	p=0.04	28 (14)	34 (6)	p<0.001
Genitourinary infection	*10 (18)*	*4 (2)*	*p=0.002*	*10 (7)*	*6 (1)*	*p=0.001*	*20 (10)*	*10 (2)*	*p<0.001*
Chorioamnionitis	*0 (0)*	*4 (2)*	*p=0.6*	*4 (3)*	*8 (2)*	*p=0.5*	*4 (2)*	*12 (2)*	*p=1.0*
Non-specified pregnancy related infection	*3 (5)*	*4 (2)*	*p=0.4*	*3 (2)*	*16 (4)*	*p=0.4*	*6 (3)*	*20 (3)*	*p=1.0*
Respiratory infection	*0 (0)*	*0 (0)*		*0 (0)*	*2 (0)*	*p=1.0*	*0 (0)*	*2 (0)*	*p=1.0*
Gastrointestinal infection	*0 (0)*	*0 (0)*		*1 (1)*	*1 (0)*	*p=0.4*	*1 (1)*	*1 (0)*	*p=0.4*
Sexually transmitted infection (includes HIV)	*1 (2)*	*0 (0)*	*p=0.3*	*0 (0)*	*6 (1)*	*p=0.3*	*1 (1)*	*6 (1)*	*p=0.7*
Sepsis	*1 (2)*	*1 (1)*	*p=0.4*	*2 (1)*	*0 (0)*	*p=0.1*	*3 (2)*	*1 (0)*	*p=0.1*
Other infection	*3 (5)*	*0 (0)*	*p=0.02*	*1 (1)*	*11 (3)*	*p=0.3*	*4 (2)*	*11 (2)*	*p=1.0*
Coagulopathy	5 (9)	7 (4)	p=0.2	24 (17)	26 (6)	p<0.0001	29 (15)	33 (6)	<.0001
Migraine	3 (5)	0 (0)	p=0.02	3 (2)	5 (1)	p=0.4	6 (3)	5 (1)	0.03
Any heart disease	1 (2)	0 (0)	p=0.3	5 (4)	4 (1)	p=0.05	6 (3)	4 (1)	0.02
Congestive heart failure	*0 (0)*	*0 (0)*		*1 (1)*	*0 (0)*	*p=0.3*	*1 (1)*	*0 (0)*	*0.3*
Chronic ischemic heart disease	*0 (0)*	*0 (0)*		*1 (1)*	*0 (0)*	*p=0.3*	*1 (1)*	*0 (0)*	*0.3*
Congenital heart disease	*0 (0)*	*0 (0)*		*1 (1)*	*1 (0)*	*p=0.3*	*1 (1)*	*0 (0)*	*0.3*
Valvular heart disease	*1 (2)*	*0 (0)*	*p=0.3*	*2 (1)*	*4 (1)*	*p=0.6*	*3 (2)*	*4*	*0.4*
Chronic renal disease	0 (0)	3 (2)	p=0.6	1 (1)	2 (0)	p=1.0	1 (1)	5	1.0
Proteinuria/nephrotic syndrome	0 (0)	0 (0)		1 (1)	0 (0)	p=0.3	1 (1)	*0 (0)*	0.3
Drug abuse or dependence	1 (2)	3 (2)	p=1.0	3 (2)	7 (2)	p=0.7	4 (2)	10 (2)	0.8
Alcohol abuse	1 (2)	4 (2)	p=1.0	3 (2)	9 (2)	p=1.0	4 (2)	13 (2)	1.0
HIV/AIDS (SPARCS Indicator)	0 (0)	0 (0)		0 (0)	3 (1)	p=0.6	0 (0)	3 (1)	0.6
Diabetes	4 (7)	6 (4)	p=0.3	3 (2)	8 (2)	p=1.0	7 (4)	14 (2)	0.4
Active smoking	2 (4)	6 (4)	p=1.0	2 (1)	7 (2)	p=1.0	4 (2)	13 (2)	1.0
Obesity	6 (11)	2 (1)	p=0.004	2 (1)	13 (3)	p=0.4	8 (4)	15 (3)	0.3
Pulmonary hypertension	0 (0)	0 (0)		0 (0)	2 (0)	p=1.0	0 (0)	2 (0)	1
Gestational diabetes	0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	*0 (0)*	
Gestational hypertension	2 (4)	4 (2)	p=0.6	5 (4)	16 (4)	p=0.9	7 (4)	20 (3)	1.0
Multiple gestation	1 (2)	10 (6)	p=0.3	3 (2)	31 (7)	p=0.02	4 (2)	41 (7)	0.008
Multigravida	0 (0)	0 (0)		17 (12)	134 (32)	p<0.0001	35 (18)	182	0.0004

Supplemental Table V: Demographics and risk factors: Comparing mild vs severe controls, mild vs severe cases

	Mild PEC, controls (n=171)	Severe PEC, controls (n=420)	p-value	Mild PEC, cases (n=57)	Severe PEC, cases (n=140)	p-value
Age[a]			p = 0.4			p= 0.7
24 and under	30 (17.5%)	96 (22.9%)		10 (17.5%)	32 (22.9%)	
25-34	84 (49.1%)	195 (46.4%)		28 (49.1%)	65 (46.4%)	
35-44	57 (33.3%)	129 (30.7%)		19 (33.3%)	43 (30.7%)	
Race/Ethnicity[a]			p = 0.8			p= 1.0
Non-Hispanic White	42 (24.6%)	108 (25.7%)		14 (24.6%)	36 (25.7%)	
Non-Hispanic Black	63 (36.8%)	150 (35.7%)		21 (36.8%)	50 (35.7%)	
Non-Hispanic Other	33 (19.3%)	66 (15.7%)		11 (19.3%)	22 (15.7%)	
Hispanic	30 (17.5%)	87 (20.7%)		10 (17.5%)	29 (20.7%)	
Unknown	3 (1.8%)	9 (2.1%)		1 (1.8%)	3 (2.1%)	
Insurance status[a]			p = 0.5			p= 0.6
Uninsured	3 (1.8%)	3 (0.7%)		0 (0.0%)	4 (2.9%)	
Medicare	1 (0.6%)	6 (1.4%)		14 (24.6%)	29 (20.7%)	
Medicaid	35 (20.5%)	95 (22.6%)		43 (75.4%)	105 (75.0%)	
Private	132 (77.2%)	316 (75.2%)		0 (0.0%)	2 (1.4%)	
Multigravida	48 (28.1%)	134 (31.9%)	p = 0.4	18 (31.6%)	17 (12.1%)	p=0.001
Multiple gestation	10 (5.8%)	31 (7.4%)	p = 0.5	1 (1.8%)	3 (2.1%)	p=1.0
Cesarean section	92 (53.8%)	306 (72.9%)	p < 0.0001	34 (59.6%)	85 (60.7%)	p= 0.9
Any infection present on admission (includes the following)	9 (5%)	26 (6%)	p=0.8	12 (21%)	16 (11%)	p=0.1
Genitourinary infection	*4 (2)*	*6 (1%)*	*p=0.3*	*10 (6%)*	*10 (7%)*	*p=0.2*
Chorioamnionitis	*4 (2)*	*8 (2)*	*p=0.8*	*0 (0%)*	*4 (3%)*	*p=0.3*
Non-specified pregnancy related infection	*4 (2%)*	*16 (5%)*	*p=0.5*	*3 (5%)*	*3 (2%)*	*p=0.4*
Respiratory infection	*0 (0%)*	*2 (0%)*	*p=1.0*	*0 (0%)*	*0 (0%)*	
Gastrointestinal infection	*0 (0%)*	*1 (0%)*	*p=1.0*	*0 (0%)*	*1 (1%)*	*p=1.0*

Sexually transmitted infection (includes HIV)	*0 (0%)*	*6 (1%)*	*p=0.2*	*1 (2%)*	*0 (0%)*	*p=0.3*
Sepsis	*1 (1%)*	*0 (0%)*	*p=0.3*	*1 (2%)*	*2 (1%)*	*p=1.0*
Other infection	*0 (0%)*	*11 (3%)*	*p=0.04*	*3 (5%)*	*1 (1%)*	*p=0.1*
Diabetes	6 (3.5%)	8 (1.9%)	p = 0.2	4 (7.0%)	3 (2.1%)	p=0.1
Pre-existing hypertension	35 (20.5%)	9 (2.1%)	p < 0.0001	25 (43.9%)	19 (13.6%)	P<0.0001
Any heart disease[b]	0 (0%)	4 (1.0%)	p = 0.3	1 (1.8%)	5 (3.6%)	p=0.7
Migraine	0 (0%)	5 (1.2%)	p = 0.3	3 (5.3%)	3 (2.1%)	p=0.4
Obesity	2 (1.2%)	13 (3.1%)	p = 0.3	6 (10.5%)	2 (1.4%)	p=0.01
Chronic renal disease	3 (1.8%)	2 (0.5%)	p = 0.1	0 (0.0%)	1 (0.7%)	p=1.0
Prothrombotic state[c]	9 (5.3%)	13 (3.1%)	p = 0.2	1 (1.8%)	25 (17.9%)	p=0.002
History of or presence of deep venous thrombosis or pulmonary embolism	0 (0%)	3 (0.7%)	p = 0.6	0 (0.0%)	10 (7.1%)	p=0.1
Lupus	2 (1.2%)	0 (0%)	p = 0.1	0 (0.0%)	2 (1.4%)	p=1.0
Primary hypercoagulable state	6 (3.5%)	10 (2.4%)	p = 0.4	1 (1.8%)	14 (10.0%)	p=0.1
Sickle cell disease	1 (0.6%)	0 (0%)	p = 0.3	0 (0.0%)	5 (3.6%)	p=0.3
Coagulopathy	7 (4.1%)	26 (6.2%)	p = 0.4	5 (8.8%)	24 (17.1%)	p=0.2
Pulmonary hypertension	0 (0%)	2 (0.5%)	p = 1.0	0 (0%)	0 (0%)	
Active smoking	6 (3.5%)	7 (1.7%)	p = 0.2	2 (3.5%)	2 (1.4%)	p=0.6
Drug abuse or dependence	3 (1.8%)	7 (1.7%)	p = 1.0	1(1.8%)	3 (2.1%)	p=1.0
Alcohol abuse	4 (2.3%)	9 (2.1%)	p = 1.0	1(1.8%)	3 (2.1%)	p=1.0
HIV/AIDS	0 (0%)	3 (0.7%)	p = 0.6	0 (0%)	0 (0%)	

[a] p-values refer to significance of distribution across categories.
[b] "Any heart disease" includes congenital or valvular heart disease, congestive heart failure, or chronic ischemic heart disease.
[c] "Prothrombotic state" includes history of or current deep venous thrombosis or pulmonary embolism, lupus, primary hypercoagulable states, or sickle cell disease.

Supplemental Table VI. Stroke risk factors in cases and controls (matched on age, race/ethnicity, and severity), excluding cases and controls with eclampsia

Risk factors: multivariable analysis (excluding eclampsia)		Odds ratio	95% CI
Chronic hypertension	Unadjusted	4.1	2.3-7.4
	Adjusted	**4.2**	**2.2-7.8**
Infection present on admission	Unadjusted	4.2	2.2-8.1
	Adjusted	**3.7**	**1.8-7.7**
Prothrombotic states	Unadjusted	3.4	1.8-6.4
	Adjusted	**2.6**	**1.1-6.3**
Multiple gestation	Unadjusted	0.3	0.1-0.9
	Adjusted	**0.2**	**0.06-0.8**
Heart disease	Unadjusted	3.6	1.0-13.4
	Adjusted	1.4	0.3-6.6
Multigravida	Unadjusted	0.7	0.4-1.1
	Adjusted	0.8	0.5-1.3
Coagulopathy	Unadjusted	3.2	1.7-6.0
	Adjusted	1.7	0.7-4.0

Supplemental Table VII. Subgroup Analysis: Post-partum cases only

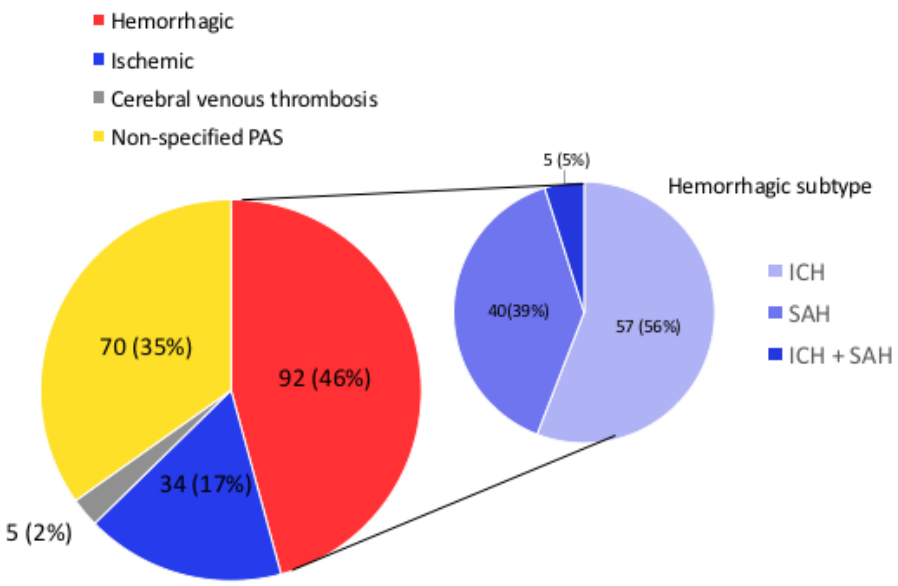
Risk factors, postpartum cases and their controls: univariate analysis	Cases (PEC and postpartum PAS)	Controls (PEC without PAS)	p-value
	n=131 (%)	n=393 (%)	
Chronic hypertension	**30 (23)**	**27 (7)**	**p<0.0001**
Prothrombotic states	**18 (14)**	**13 (3)**	**p<0.0001**
Hypercoagulable state	*9 (7)*	*10 (3)*	*p=0.03*
Sickle cell	*2 (2)*	*0 (0)*	*p=0.1*
Lupus	*1 (1)*	*1 (0)*	*p=0.4*
DVT/PE (acute, chronic, or history of prior)	*7 (5)*	*2 (1)*	*p=0.001*
Any infection present on admission	**22 (18)**	**22 (6)**	**p<0.0001**
Genitourinary infection	*18 (14)*	*4 (1)*	*p<0.0001*
Chorioamnionitis	*3 (2)*	*9 (2)*	*p=1.0*
Non-specified pregnancy related infection	*4 (3)*	*15 (4)*	*p=0.8*
Respiratory infection	*0 (0)*	*2 (1)*	*p=1.0*
Gastrointestinal infection	*0 (0)*	*1 (0)*	*p=1.0*
Sexually transmitted infection (includes HIV)	*0 (0)*	*4 (1)*	*p=0.6*
Sepsis	*2 (2)*	*1 (0)*	*p=0.2*
Other infection	*2 (2)*	*8 (2)*	*p=1.0*
Coagulopathy	**16 (12)**	**19 (5)**	**p=0.003**
Migraine	**4 (3)**	**2 (1)**	**p=0.04**
Any heart disease	**5 (4)**	**2 (1)**	**p=0.01**
Congestive heart failure	*1 (1)*	*0 (0)*	*p=0.25*
Chronic ischemic heart disease	*0 (0)*	*0 (0)*	
Congenital heart disease	*3 (2)*	*2 (1)*	*p=0.2*
Valvular heart disease	*1 (1)*	*0 (0)*	*p=0.25*
Chronic renal disease	0 (0)	3 (1)	p=0.6
Proteinuria/nephrotic syndrome	1 (1)	0 (0)	p=0.25
Drug abuse or dependence	1 (1)	6 (2)	p=0.7
Alcohol abuse	2 (2)	6 (2)	p=1.0
HIV/AIDS (SPARCS Indicator)	0 (0)	2 (1)	p=1.0
Diabetes	4 (3)	9 (2)	p=0.7
Active smoking	3 (2)	9 (2)	p=1.0
Obesity	3 (2)	11 (3)	p=1.0
Pulmonary hypertension	0 (0)	1 (0)	p=1.0
Gestational diabetes	0 (0)	0 (0)	
Gestational hypertension	4 (3)	12 (3)	p=1.0
Multiple gestation	**1 (1)**	**24 (6)**	**p=0.01**
Multigravida	**18 (14)**	**122 (31)**	**p=0.0001**
Cesarean section	**68 (52)**	**254 (65)**	**p=0.002**

PEC: preeclampsia. PAS: pregnancy-associated stroke. DVT: deep vein thrombosis. PE: pulmonary embolism. Bolded characteristics were included in the multivariable model.

Supplemental Table VIII. Stroke risk factors in post-partum cases and their controls (matched on age, race/ethnicity, and severity)

Risk factors: multivariable analysis		**Odds ratio**	**95% CI**
Chronic hypertension	Unadjusted	5.6	2.8-11.0
	Adjusted	**5.0**	**2.3-10.5**
Infection present on admission	Unadjusted	3.6	1.9-6.9
	Adjusted	**3.6**	**1.8-7.3**
Prothrombotic states	Unadjusted	4.4	2.1-9.1
	Adjusted	**3.6**	**1.4-9.7**
Coagulopathy	Unadjusted	2.8	1.4-5.6
	Adjusted	1.3	0.5-3.5
Heart disease	Unadjusted	7.5	1.5-38.7
	Adjusted	3.7	0.4-33.4
Multiple gestation	Unadjusted	0.1	0.02-0.9
	Adjusted	0.1	0.01-1.0
Multigravida	Unadjusted	0.4	0.2-0.6
	Adjusted	**0.4**	**0.2-0.7**
Cesarean section	Unadjusted	0.6	0.4-0.9
	Adjusted	0.7	0.4-1.1

Supplemental Figure I: Stroke subtypes in women with preeclampsia and stroke



There were 197 women identified during the study period with preeclampsia and stroke of any type. The large circle indicates stroke types (ischemic, hemorrhagic, cerebral venous thrombosis or non-specified), with raw numbers and percentage of total cases. The smaller circle indicates the subtypes of hemorrhagic stroke in shades of blue, with raw numbers and percentages within the group of women with hemorrhagic strokes. Of the 92 women with hemorrhagic strokes, 11 (12.0%) had underlying coagulopathies and 12 (13.0%) had underlying prothrombotic states. Among women with ischemic strokes, 6 of 34 (17.6%) had coagulopathies, and another 6 of 34 (17.6%) had prothrombotic states; in non-specified PAS, 12 of 70 (17.1%) had coagulopathies, and 8 of 70 (11.4%) had prothrombotic states. PAS: pregnancy-associated stroke. ICH: intracerebral hemorrhage. SAH: subarachnoid hemorrhage.

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