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Risk Factors for Pregnancy-Associated Stroke in Women with Preeclampsia

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Abstract

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

Methods—Using billing data from the 2003–2012 New York State Department of Health inpatient database, we matched women with PEC 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 and 95% confidence intervals (OR, 95% CI) for independent risk factors for PAS.

Results—Among women aged 12–55 years admitted to New York State hospitals for any reason during the study period (n= 3,373,114), 88,857 had PEC, 197 of whom (0.2%) had PAS. In multivariable analysis, women with PEC and stroke were more likely than controls to have severe PEC or eclampsia (OR 7.2, 95% 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 PEC confirmed these results.

Conclusions—Infections, chronic hypertension, coagulopathies, and underlying prothrombotic conditions increase PAS risk in women with PEC. These women may warrant closer monitoring.

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INTRODUCTION

Preeclampsia (PEC) 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 (PAS) have comorbid PEC,² and PEC increases stroke risk during the puerperium up to 6-fold.³ Among women with PAS, women with PEC are at increased risk of complications and death.^{4,5}

Although PEC affects 3–8% 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 PEC,^{4,8} and increased PEC severity is associated with an increased risk of cardiovascular events.⁹ The rarity of PAS makes it difficult to predict which PEC patients are at highest risk for cerebrovascular complications. The American Heart Association/American Stroke Association found insufficient evidence to make recommendations regarding prevention of stroke in pregnancy complicated by hypertensive disorders.¹⁰

We sought to identify modifiable risk factors that put women with PEC 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 (ICD-9), from the 2003–2012 New York State Department of Health Statewide Planning and Research Cooperative System (SPARCS) inpatient database. We identified all women aged 12–55 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 PEC were not included in the study, regardless of whether they had strokes during or after pregnancy. Cases were defined as women with PEC and PAS, including diagnosis codes for transient ischemic attack (TIA) or ischemic stroke, intracerebral hemorrhage (ICH), cerebral venous thrombosis, and codes specific for non-specified PAS. Pregnancy-specific stroke codes were validated using internal datasets (Supplemental Table I). In women with more than one 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 postpartum time frame was chosen due to limitations of ICD-9 coding.¹² Traumatic ICH 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 PEC without PAS.

Pre-defined exposures of interest, selected based on previously described associations with PEC and/or 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 SPARCS-specific indicator.^{13,14} Infections

acquired during the stroke hospitalization were not included. Coding details are in Supplemental Table II.

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

Statistical analysis

We conducted univariable analyses comparing risk factors among cases and controls using chi square tests. Including only those PAS risk factors with $p < 0.2$ from the univariable analysis,¹⁷ we calculated unadjusted and adjusted odds ratios and 95% confidence intervals (OR, 95% CI) using multivariable conditional logistic regression. Prespecified subgroup analyses included a sensitivity analysis excluding all cases and controls with eclampsia (642.6x), and a subgroup analysis of postpartum strokes. All analyses were completed with SAS version 9.3 (SAS Institute, Cary, NC). A p -value of < 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 due to the public, de-identified nature of the data.

RESULTS

Baseline characteristics of women with PEC, with and without PAS

Among women aged 12–55 years admitted for any reason during the study period ($n = 3,373,114$), 88,857 had PEC, including eclampsia. Of these, 197 (0.2%) had PAS and were identified as cases, giving a cumulative incidence of PAS in women with PEC of 222/100,000 during the study period. In the unmatched sample, compared to the 88,660 women with PEC who did not have PAS, women with PEC 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 PEC, and 57 (28.9%) had eclampsia. The 197 stroke cases were matched with 591 non-stroke controls of the same age, race/ethnicity and insurance status (Figure 2).

Timing and characteristics of strokes in women with PEC 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 postpartum; and 3 (1.5%) occurred during an admission without

delivery, with no further characterization of timing. Of 131 postpartum strokes, 82(62.6%) occurred after discharge (Figure 2). Stroke types included 92(46.7%) hemorrhagic strokes, 26(13.1%) ischemic, 8(4.1%) TIA, 5(2.5%) cerebral venous thromboses, and 70(35.5%) non-specific PAS; 9 women had multiple subtypes (Supplemental Figure I). In-hospital mortality was 13.2% among cases, compared to 0.2% among controls. Details of discharge disposition/mortality are in Supplemental Table III.

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 PEC 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 to 2% of controls ($p<0.0001$). After adjusting for other risk factors, significant risk factors for stroke were severe preeclampsia or eclampsia (OR7.2, 95% CI 4.6–11.3); infections POA (OR3.0, 95% CI 1.6–5.8); chronic hypertension (OR3.2, 95% CI 1.8–5.5); prothrombotic states (OR3.5, 95% CI 1.3–9.2); and coagulopathies (OR3.1, 95% CI 1.3–7.1) (Table 2).

Demographics and risk factors in severity-matched cohort

When cases were matched to controls by PEC severity, similar risk factors emerged: infections POA (OR2.6, 95% CI 1.4–4.6); prothrombotic states (OR2.9, 95% CI 1.3–6.4); and chronic hypertension (OR4.2, 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 (OR3.0, 95% CI 1.4–6.3) and infection POA (OR4.5, 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 (OR8.4, 95% CI 3.1–22.5) and prothrombotic states (OR6.6, 95% CI 2.5–17.5) increased stroke risk; the association of infection POA did not reach statistical significance after adjusting for other risk factors (OR1.9, 95% CI 0.9–4.0; Supplemental Table IV). Demographics of mild versus severe cases and controls are shown in Supplemental Table V.

Subgroup analyses

In the subgroup analysis excluding women with eclampsia (ICD-9 642.6x), results were similar: women with chronic hypertension (adjusted OR4.2, 95% CI 2.2–7.8), infection POA (adjusted OR3.7, 95% CI 1.8–7.7), and prothrombotic states (adjusted OR2.6, 95% CI 1.1–6.3), had higher risk of stroke (Supplemental Table VI). In the subgroup analysis including only postpartum 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 delivery and stroke risk (adjusted OR0.7, 95% CI 0.4–1.1). Otherwise, similar risk factors were found in women with postpartum stroke (Supplemental Tables VII–VIII).

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 population was 222/100,000, over six 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 postpartum, consistent with prior research.⁷ More than 1 in 10 women with PEC 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 one study, infections tripled the odds of peripartum cerebral venous thrombosis.²³ The pathophysiology of PEC remains incompletely understood,¹ although imbalance of pro- and anti-angiogenic factors and an increase in pro-inflammatory cytokines appear to play roles.²⁴ Animal models of PEC have demonstrated impaired cerebral autoregulation, increased blood-brain barrier permeability, and neuronal hyperexcitability, mediated by elevated levels of tumor necrosis factor-*alpha*.^{25–28} In the setting of PEC-associated inflammation and puerperal hypercoagulability, superimposed infection could trigger stroke by exacerbating inflammation and coagulopathy.¹¹

While we included only infections present on admission 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 PEC-associated PAS has important clinical implications, as 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 postpartum women, since similar symptoms may occur with normal postpartum recovery. Women with preeclampsia undergo postpartum 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 PEC-associated stroke is poorly characterized. Chronic hypertension shifts the cerebral autoregulatory curve,²⁹ but is not associated with loss of dynamic cerebral autoregulatory capacity due to 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 autoreactivity³² leading to hyperemia, hypertensive leukoencephalopathy, and/or the reversible cerebral vasoconstriction syndrome (RCVS),³³ all of which can be associated with stroke.³⁴ RCVS is highly associated with postpartum stroke.³⁵

Unfortunately, we were unable to assess investigate the role of RCVS and stroke in our population, since RCVS is not reliably captured by ICD-9 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 PEC.^{4,36} Only 2.5% of strokes in our cohort were due to 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 ICH/SAH risk. Patients with PEC and a history of coagulopathy likely warrant increased vigilance in the peripartum period.

Other vascular risk factors

Heart disease has been identified as a risk factor for PAS in women with PEC.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, since other studies have found otherwise; alternatively, the pathophysiology of PAS in women with PEC may bear little relation to traditional vascular risk factors.

Preeclampsia severity

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

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 PEC 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 (Supplemental Figure I). While the proportion of each of the “prothrombotic conditions” individually (hypercoagulable states, history of thromboembolic events, systemic lupus erythematosus 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 present on admission 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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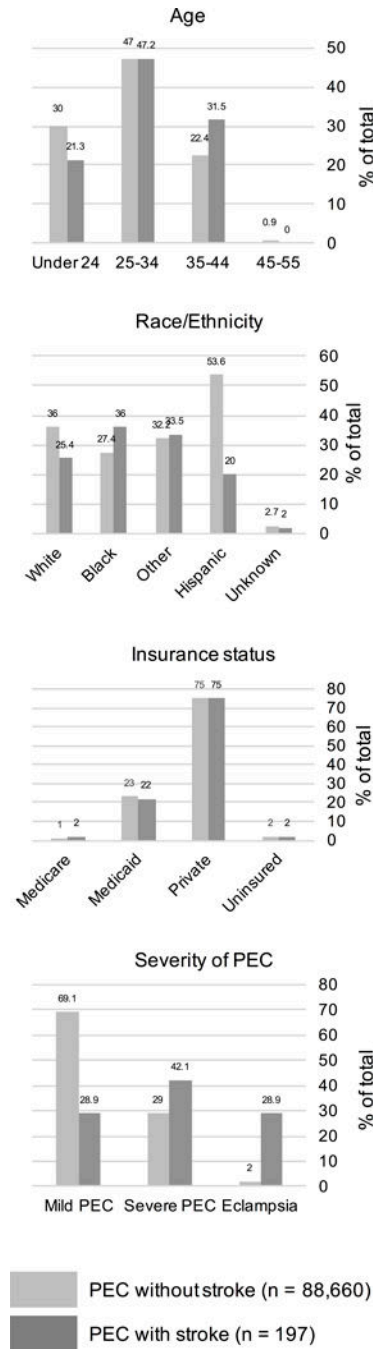


Figure 1. Baseline demographics of all women hospitalized with preeclampsia in New York State 2003-2012, with and without pregnancy-associated stroke. Cases (women with PEC and stroke, n=197) are represented in dark gray. The unmatched sample of all women with PEC and without stroke (n=88,660) is represented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

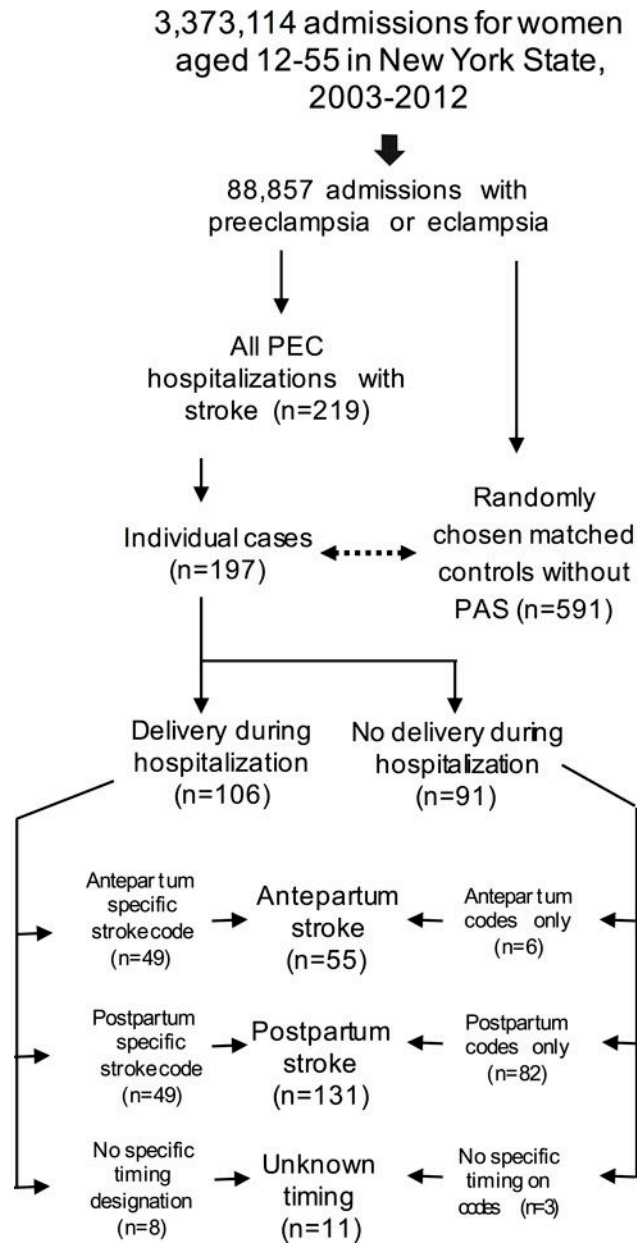


Figure 2.
Patient selection, flow diagram

88,857 patients were admitted to hospitals in New York State between 2003 and 2012 with preeclampsia. Of these, 197 individual women had preeclampsia and stroke. Strokes were classified as postpartum if they occurred either during a postpartum admission, or during a delivery admission that included a pregnancy-specific stroke code with a fifth digit of 2 or 4 indicating a postpartum complication, in accordance with ICD-9 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. PEC: preeclampsia.

Table 1

Demographics and baseline characteristics in New York State women with pre-eclampsia, with and without pregnancy-associated stroke, 2003–2012.

Prevalence of characteristics	Cases (PEC and PAS) n=197 (%)	Controls (PEC without PAS) n=591 (%)	p-value
Age			n/a (matched)
<i>24 and under</i>	42 (21)	126 (21)	
<i>25-34</i>	93 (47)	279 (47)	
<i>35-44</i>	62 (31)	186 (31)	
Race/ethnicity			n/a (matched)
<i>Non-Hispanic White</i>	50 (25)	150 (25)	
<i>Non-Hispanic Black</i>	71 (36)	213 (36)	
<i>Non-Hispanic Other</i>	33 (17)	99 (17)	
<i>Hispanic</i>	39 (20)	117 (20)	
<i>Unknown</i>	4 (2)	12 (2)	
Insurance status			n/a (matched)
<i>Uninsured</i>	4 (2)	12 (2)	
<i>Medicare</i>	43 (22)	129 (22)	
<i>Medicaid</i>	148 (75)	444 (75)	
<i>Private</i>	2 (1)	6 (1)	
Severity of preeclampsia			p<0.0001
<i>Mild preeclampsia</i>	73 (37)	435 (74)	p<0.0001
<i>Severe preeclampsia</i>	90 (46)	157 (27)	p<0.0001
<i>Eclampsia</i>	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
<i>Hypercoagulable state</i>	15 (8)	7 (1)	p<0.0001
<i>Sickle cell disease</i>	5 (3)	1 (0)	p=0.005
<i>Systemic lupus erythematosus</i>	2 (1)	0 (0)	p=0.06
<i>DVT/PE (acute, chronic, or history of prior)</i>	10 (5)	7 (1)	p=0.003
Infection present on admission (includes following)	28 (14)	33 (6)	p<0.0001
<i>Genitourinary infection</i>	20 (10)	13 (2)	p<0.0001
<i>Chorioamnionitis</i>	4 (2)	7 (1)	p=0.5
<i>Non-specified pregnancy related infection</i>	6 (3)	17 (3)	p=1.0
<i>Respiratory infection</i>	0 (0)	2 (0)	p=1.0
<i>Gastrointestinal infection</i>	1 (1)	1 (0)	p=0.4
<i>Sexually transmitted infection (includes HIV)</i>	1 (1)	7 (1)	p=0.7
<i>Sepsis</i>	3 (2)	2 (0)	p=0.1
<i>Other infection</i>	4 (2)	12 (2)	p=1.0
Coagulopathy	29 (15)	16 (3)	p<0.0001

Prevalence of characteristics	Cases (PEC and PAS)	Controls (PEC without PAS)	p-value
Migraine	6 (3)	1 (0)	p=0.001
Heart disease (includes following)	6 (3)	5 (1)	p=0.02
<i>Congestive heart failure</i>	<i>1 (1)</i>	<i>0 (0)</i>	<i>p=0.3</i>
<i>Chronic ischemic heart disease</i>	<i>1 (1)</i>	<i>0 (0)</i>	<i>p=0.3</i>
<i>Congenital heart disease</i>	<i>1 (1)</i>	<i>1 (0)</i>	<i>p=0.4</i>
<i>Valvular heart disease</i>	<i>3 (2)</i>	<i>4 (1)</i>	<i>p=0.4</i>
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	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. PEC: preeclampsia. PAS: pregnancy-associated stroke. DVT: deep vein thrombosis. PE: pulmonary embolism.

See Supplemental Table II for complete details of diagnostic codes.

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 ^a	Unadjusted	7.5 (3.5–16.1)
	Adjusted	3.5 (1.3–9.2)
Coagulopathy ^b	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 ^c	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)

^a Includes primary hypercoagulable state, history of deep vein thrombosis or pulmonary embolism, systemic lupus erythematosus, sickle cell disease.

^b Includes bleeding diatheses and thrombocytopenia.

^c Includes congenital, valvular, and ischemic heart disease, and congestive heart failure.

See Supplemental Table II for complete details of diagnostic codes.

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	Mild cases only	Severe cases only
		Odds ratio (95% CI)	Odds ratio (95% CI)	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 ^a	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 ^b	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 ^c	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)

^aIncludes primary hypercoagulable state, history of deep vein thrombosis or pulmonary embolism, systemic lupus erythematosus, sickle cell disease.

^bIncludes bleeding diatheses and thrombocytopenia.

^cIncludes congenital, valvular, and ischemic heart disease, and congestive heart failure.

See Supplemental Table II for complete details of diagnostic codes.