Original Research

Hypertensive Disorders and Pregnancy-Related Stroke

Frequency, Trends, Risk Factors, and Outcomes

Lisa R. Leffert, MD, Caitlin R. Clancy, BA, Brian T. Bateman, MD, MSc, Allison S. Bryant, MD, MPH, and Elena V. Kuklina, MD, PhD

OBJECTIVE: To evaluate trends and associations of hypertensive disorders of pregnancy with stroke risk and test the hypothesis that hypertensive disorders of pregnancy-associated stroke results in higher rates of stroke-related complications than pregnancy-associated stroke without hypertensive disorders.

METHODS: A cross-sectional study was performed using 81,983,216 pregnancy hospitalizations from the 1994–2011 Nationwide Inpatient Sample. Rates of stroke hospitalizations with and without these hypertensive disorders were reported per 10,000 pregnancy hospitalizations. Using logistic regression, adjusted odds ratios (OR) with 95% confidence intervals were obtained.

RESULTS: Between 1994–1995 and 2010–2011, the nationwide rate of stroke with hypertensive disorders of pregnancy increased from 0.8 to 1.6 per 10,000 pregnancy hospitalizations (103%), whereas the rate without these disorders increased from 2.2 to 3.2 per 10,000 pregnancy hospitalizations (47%). Women with hypertensive disorders of pregnancy were 5.2 times more likely to have a stroke than those without. Having traditional stroke risk factors (eg, congenital heart disease, atrial fibrillation, sickle cell anemia, congenital coagulation defects) substantially increased the stroke risk among hypertensive disorders of pregnancy hospitalizations: from adjusted OR 2.68 for congenital coagulation defects to adjusted OR 13.1 for congenital heart disease. Stroke-related complications were increased in stroke with hypertensive disorders of pregnancy compared with without (from adjusted OR 1.23 for nonroutine discharge to adjusted OR 1.93 for mechanical ventilation).

CONCLUSION: Having traditional stroke risk factors substantially increased the stroke risk among hypertensive disorders of pregnancy hospitalizations. Stroke with hypertensive disorders in pregnancy had two distinctive characteristics: a greater increase in frequency since the mid-1990s and significantly higher stroke-related complication rates.

(Obstet Gynecol 2015;125:124–31)

DOI: 10.1097/AOG.0000000000000590

LEVEL OF EVIDENCE: III

Despite the fact that hypertensive disorders of pregnancy are prevalent and a strong risk factor for pregnancy-associated stroke, there is a dearth of literature examining its trends, etiologies, risk factors, and outcomes.[1,2] Several previous analyses have showed a temporal increase in the number of pregnancy hospitalizations with stroke during 1994–2007 in the United States: 47% for antenatal hospitalizations and 83% for postpartum hospitalizations.[2] The frequency of preeclampsia has also increased by approximately 25%,[3] worsening in severity over the time period.[4] In this study, we elucidate pregnancy-associated stroke using the Nationwide Inpatient Sample by 1) estimating the changes in overall pregnancy associated stroke as well as stroke with and without hypertensive disorders of pregnancy from 1994–1995 to 2010–2011; 2) demonstrating how traditional stroke risk factors affect the relationship between

From the Obstetric Anesthesia Division, Department of Anesthesia, and Department of Anesthesia, Critical Care & Pain Medicine, and the Department of Obstetrics and Gynecology, Massachusetts General Hospital, Boston, Massachusetts; and the Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Support was provided solely from institutional and/or departmental resources.

Presented at the Society for Obstetric Anesthesia and Perinatology 46th Annual Meeting, May 14–18, 2014, Toronto, Ontario, Canada.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Corresponding author: Lisa R. Leffert, MD, Chief, Division of Obstetric Anesthesia, Department of Anesthesia, Critical Care & Pain Medicine, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114; e-mail: lleffert@partners.org.

Financial Disclosure

The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/15

these hypertensive disorders of pregnancy and stroke; and 3) assessing whether stroke with hypertensive disorders of pregnancy has higher stroke-related complications rates than stroke without them.

MATERIALS AND METHODS

Data for the study were derived from the Nationwide Inpatient Sample, which is maintained by the Agency for Healthcare Research and Quality as part of the Healthcare Cost and Utilization Project. A sample of nonfederal community hospitals is selected based on geographic region, teaching status, ownership, rural or urban location, and number of beds to create a sample that is maximally representative of all U.S. hospital admissions. For each hospital admission, demographic and discharge destination data elements and up to 15 diagnoses and procedures coded using the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes are recorded based on billing data. Because the data are public and deidentified, this study was exempt from review by the institutional review board for the Centers for Disease Control and Prevention as well as for the Massachusetts General Hospital. We identified pregnancy-related admissions from 1994 to 2011 for women ages 15–44 years (Table 1). Pregnancy stage was denoted using the fifth digit modifiers on ICD-9-CM codes. Antenatal hospitalizations were defined as nondelivery admissions during pregnancy, and postpartum hospitalizations were defined as separate from delivery hospitalizations up to 6 weeks postpartum with details described elsewhere.[5,6] Our study used the list of ICD-9-CM codes proposed by the Joint Commission to identify hospitalizations with stroke in administrative databases.[7] The following ICD-9-CM codes listed at any position were used to identify diagnoses of 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), subarachnoid hemorrhage (430), intracerebral hemorrhage (431), and transient ischemic attack (435). International Classification of Diseases, 9th Revision, Clinical Modification codes for unspecified stroke during pregnancy or iatrogenic stroke (674.0 and 997.02, respectively) were included in our analysis for completeness. These diagnoses were then combined into three groups for analysis based on stroke subtype: hemorrhagic stroke (subarachnoid hemorrhage and intracerebral hemorrhage), ischemic stroke, and other (transient ischemic attack and unspecified stroke). International Classification of Diseases, 9th Revision, Clinical Modification codes for nonpyogenic thrombosis of intracranial venous sinus (437.6), phlebitis and thrombophlebitis of intracranial venous sinuses (325) and peripartum phlebitis and thrombosis, cerebral venous thrombosis, and thrombosis of intracranial venous sinus (671.5) were excluded because these conditions do not necessarily result in a stroke.

Hospitalizations with hypertensive disorders of pregnancy were identified by using ICD-9-CM codes: 642.0x, 642.1x, 642.2x, 642.3x, 642.4x, 642.5x, 642.6x, 642.7x, 642.9x, and 401.x-405.xx. The ICD-9-CM code 780.39 was used to indicate stroke-associated seizure and code 642.6 for seizure indicating eclampsia.

As required by the Nationwide Inpatient Sample data user agreement to protect individual identity, data cells containing 10 or fewer observations were eliminated.[8] The unit of analysis was a hospitalization, not an individual. All analyses were weighted to take into account complex survey methodology and to generate national estimates. These analyses were performed using SAS-callable 9.3 Sudaan 11.

For the trend analysis, rates per 10,000 pregnancy hospitalizations and tests for linear trend were calculated for overall pregnancy-related stroke and hypertensive and nonhypertensive disorders of pregnancy-associated stroke (Fig. 1). Orthogonal polynomial coefficients were calculated recursively by the method of Fisher and Yates for linear trend testing.[9] The significance level used to test linear trends was set at 99% (ie, $P=.01$ threshold) given our very large data set. As recommended by the Agency for Healthcare Research and Quality, the Nationwide Inpatient Sample Trends Supplemental Files (NIS-Trends) for trend analysis were used to account for temporal changes in sampling and weighting strategy.[10] Odds ratios (ORs) and their 95% confidence intervals (CIs) were obtained from multivariable logistic regression analysis to assess changes in stroke prevalence from 1994–1995 to 2010–2011. Other study intervals (1996–1997, 1998–1999, and so on) were also included in the models as categorical variables. This analysis was adjusted for changes in the distribution of maternal age, insurance coverage (payer), race–ethnicity, delivery mode, multiple gestation, hospitalizations with hypertensive disorders of pregnancy, hemorrhage during pregnancy, and known stroke-related maternal comorbid conditions (congenital heart disease, atrial fibrillation, primary thrombocytopenia, migraine, systemic lupus erythematosus, sickle cell anemia, valve disorders, congenital coagulation defects, and preexisting diabetes). Hypertensive disorders of pregnancy admissions ORs and their 95% CI were analyzed by multivariable logistic regression to assess the effect of hypertensive disorders of

Table 1. Patient Demographic Information: Pregnancy Hospitalizations, Nationwide Inpatient Sample, 1994–2011

Characteristic	Pregnancy Hospitalizations			
	Stroke With Hypertensive Disorders of Pregnancy (n=9,890)	Stroke Without Hypertensive Disorders of Pregnancy (n=21,783)	Hypertensive Disorders of Pregnancy Without Stroke (n=6,176,848)	Without Hypertensive Disorders of Pregnancy or Stroke (n=75,774,695)
Age (y)				
15–24	2,486 (25.1)	5,740 (26.4)	2,068,206 (33.5)	27,087,409 (35.7)
25–34*	4,617 (46.7)	11,276 (51.8)	2,975,974 (48.2)	38,191,483 (50.4)
Older than 35*	2,715 (27.5)	4,736 (21.7)	1,113,919 (18.0)	10,290,055 (13.6)
Missing*	72 (0.7)	32 (0.1)	18,750 (0.3)	205,748 (0.3)
Race or ethnicity				
White*	2,877 (29.1)	8,995 (41.3)	2,551,041 (41.3)	31,645,801 (41.8)
African American*	2,641 (26.7)	3,773 (17.3)	1,032,702 (16.7)	8,723,547 (11.5)
Hispanic	1,478 (15.0)	2,776 (12.7)	842,248 (13.6)	12,599,529 (16.6)
Other	656 (6.6)	1,237 (5.7)	332,386 (5.4)	5,369,660 (7.1)
Missing	2,238 (22.6)	5,003 (23.0)	1,418,472 (23.0)	17,436,158 (23.0)
Primary payer				
Public*	4,578 (46.3)	8,616 (39.5)	2,440,210 (39.5)	30,251,779 (39.9)
Private*	4,566 (46.2)	11,362 (52.2)	3,349,159 (54.2)	40,010,509 (52.8)
Self pay, no charge, or other	747 (7.5)	1,805 (8.3)	387,480 (6.3)	5,512,408 (7.3)
Mode of delivery				
Cesarean*	2,972 (30.1)	3,530 (16.2)	2,381,491 (38.6)	17,341,295 (22.9)
Vaginal*	6,918 (69.9)	18,253 (83.8)	3,795,357 (61.4)	58,433,401 (77.1)
Multiple gestation				
Yes	138 (1.4)	203 (0.9)	245,874 (4.0)	1,322,421 (1.7)
No	9,752 (98.6)	21,580 (99.1)	5,930,974 (96.0)	74,452,274 (98.3)
Hospital region				
Northeast	1,517 (15.3)	3,921 (18.0)	960,519 (15.5)	13,303,443 (17.6)
Midwest	2,011 (20.3)	4,866 (22.3)	1,327,626 (21.5)	16,756,597 (22.1)
South	4,145 (50.0)	8,276 (38.0)	2,618,691 (42.4)	27,154,679 (35.8)
West	2,216 (22.4)	4,720 (21.7)	1,270,012 (20.6)	18,559,976 (24.5)
Hospital teaching status				
Rural	470 (4.8)	1,342 (6.2)	744,796 (12.1)	9,391,442 (12.4)
Urban nonteaching	3,120 (31.5)	6,610 (30.3)	2,231,691 (36.1)	31,403,776 (41.5)
Urban teaching	6,244 (63.1)	13,709 (62.9)	3,167,364 (51.3)	34,660,121 (45.7)
Missing	56 (0.6)	122 (0.6)	32,997 (0.5)	319,757 (0.4)

Data are n (%).

* The categories above were determined to be statistically significant ($P<.01$) in a univariate comparison between hypertensive disorders of pregnancy and nonhypertensive disorders of pregnancy-associated stroke.

pregnancy plus comorbid conditions, adjusting for age, race–ethnicity, delivery mode, payer, hospital region, hospital teaching status, and study interval. That analysis was restricted to hypertensive disorders of pregnancy admissions (Table 2). These same methods were then applied to investigate the effect of hypertensive disorders of pregnancy on stroke-related complications, including mechanical ventilation, seizure, pneumonia, prolonged hospital stay, and death during hospitalization. We used the 97th percentile (5 or more inpatient days) as our definition of prolonged hospital stay as the categorical outcome variable. Each model for stroke-related complications was also adjusted for length of stay as a continuous predictor variable, except for the models for prolonged length of stay. Analyses of temporary tracheostomy and percutaneous gastrostomy tube were limited to survivors (Table 3). Nonroutine discharge was defined as in-hospital death or discharge to any destination other than home.

Additional analyses were performed to examine the differences in risk factors and complications between hemorrhagic and ischemic stroke subtype. Both analyses are adjusted in a similar manner to the analyses described for Tables 2 and 3. The ORs for stratified stroke subtypes are available in Appendix 1 (available online at http://links.lww.com/AOG/A586) and Appendix 2 (available online at http://links.lww.com/AOG/A587).

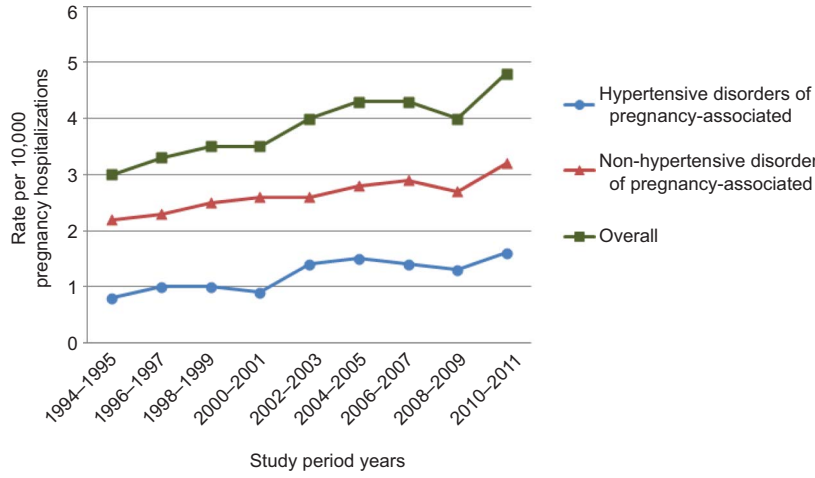

Fig. 1. Trends in stroke hospitalizations in pregnancy, with and without hypertensive disorders of pregnancy, in the United States, 1994–2011 Nationwide Inpatient Sample (n=31,673). Stroke includes intracerebral hemorrhage, subarachnoid hemorrhage, ischemic stroke, transient ischemic attack, iatrogenic stroke, and unspecified pregnancy-related stroke.

Leffert. Hypertensive Disorders of Pregnancy and Stroke. Obstet Gynecol 2015.

All other values represent simple proportions from weighted data.

RESULTS

We identified 81,983,216 pregnancy hospitalizations occurring between the years 1994 and 2011, among which there were 31,673 hospitalizations with strokes, for a frequency of 3.8 strokes per 10,000 pregnancy-related hospitalizations. Of these, 9,890 (31.2%) occurred in patients with hypertensive disorders of pregnancy and 21,783 (68.8%) were in patients without these disorders.

Table 1 compares the demographic data and clinical conditions in the pregnancy hospitalizations with and without hypertensive disorders of pregnancy: the former were more likely to occur in older age (older than 35 years) or in women of African American

Table 2. Rates and Odds Ratios* for Stroke by Selected Risk Factors Among Pregnancy Hospitalizations With Hypertensive Disorders of Pregnancy: The 1994–2011 Nationwide Inpatient Sample (n=6,186,738)

Risk Factor	Total No. of Hospitalizations With Hypertensive Disorders of Pregnancy		Rate (SE) of Stroke/10,000 Hospitalizations With Hypertensive Disorders of Pregnancy	OR (95% CI) of Having Stroke for Hospitalizations With Risk Factor*	
	Risk Factor	Risk Factor and Stroke		Unadjusted	Adjusted†
Congenital heart disease	7,535	151	200.4±0.36	12.94 (9.01–18.58)	13.10 (9.09–18.90)
Atrial fibrillation	3,058	52	170.0±0.51	10.91 (5.99–19.89)	8.13 (4.43–14.91)
Primary thrombocytopenia	7,242	62	85.6±0.26	5.46 (3.03–9.84)	5.50 (3.05–9.93)
Migraine	40,920	314	76.7±0.10	4.96 (3.79–6.49)	4.48 (3.41–5.88)
Systemic lupus erythematosus	22,859	125	54.7±0.11	3.45 (2.31–5.17)	2.89 (1.93–4.33)
Sickle cell anemia	39,307	138	35.1±0.07	2.22 (1.52–3,25)	1.58 (1.07–2.32)
Valve disorders	61,786	291	47.1±0.06	3.01 (2.31–3.93)	2.76 (2.12–3.60)
Congenital coagulation defects	36,376	146	40.1±0.07	2.54 (1.77–3.65)	2.68 (1.85–3.88)
Postpartum hemorrhage	163,629	346	21.1±0.02	1.33 (1.04–1.71)	1.33 (1.04–1.71)
Preexisting diabetes	222,485	466	20.9±0.02	1.33 (1.06–1.66)	1.09 (0.86–1.36)

SE, standard error; OR, odds ratio; CI, confidence interval.

* Referent group: hypertensive disorders of pregnancy hospitalizations without selected risk factor. For example, for hospitalizations with congenital heart disease, the referent group is hospitalizations without congenital heart disease.

† Adjusted for age, race–ethnicity, mode of delivery, study period, region, and hospital teaching status.

Table 3. Rates and Odds Ratios*† for Stroke-Related Complications by Hypertensive Disorders of Pregnancy Status Among Pregnancy Hospitalizations With Stroke: The 1994–2011 Nationwide Inpatient Sample (n=31,673)

	Total No. of Stroke Hospitalizations With Complications	
Complication	Hospitalizations With Nonhypertensive Disorders of Pregnancy-Associated Stroke (n=21,783)	Hospitalizations With Hypertensive Disorders of Pregnancy-Associated Stroke (n=9,890)
Mechanical ventilation	2,366	2,246
Pneumonia	475	406
Seizure	1,897	1,199
Died during hospitalization	974	785
Prolonged hospital stay	9,071	5,903
Nonroutine discharge‡	15,563	6,268
Percutaneous gastrostomy tube§	397	190
Temporary tracheostomy§	488	198

SE, standard error; OR, odds ratio; CI, confidence interval.
* Referent group: hospitalizations with nonhypertensive disorders of pregnancy-associated stroke.
† Adjusted for age, race–ethnicity, mode of delivery, study period, length of stay, hospital characteristics, and stroke subtype. Prolonged hospital stay was not adjusted for length of stay.
‡ Nonroutine discharge was defined as in-hospital death or discharge to any destination other than home.
§ Among survivors.

race. Between 1994–1995 and 2010–2011, overall pregnancy-related stroke increased by 61.5% (from 3.0 to 4.8 per 10,000 pregnancy hospitalizations) (Fig. 1). The stroke rates with hypertensive disorders of pregnancy increased from 0.8 to 1.6 per 10,000 pregnancy hospitalizations (102.6%) compared with an increase from 2.2–3.2 per 10,000 pregnancy hospitalizations (46.6%) for those without these disorders (P for linear trend for both $<.001$). The rates of hypertensive disorders of pregnancy increased by 71% (P for linear trend $<.001$). We noted a particular increase in all three categories of pregnancy-associated stroke in the time interval from 1998–1999 to 2001–2002 without an accompanying change in coding. Adjustment for the changes in prevalence of hospitalizations with hypertensive disorders of pregnancy, payer, age, race–ethnicity, delivery mode, multiple gestation, hemorrhage during pregnancy, and maternal comorbid conditions explained most increases in the overall stroke prevalence from 1994–1995 to 2010–2011 (unadjusted OR compared with adjusted OR with 95% CI for 2010–2011 with 1994–1995 as the referent group: OR 1.61, 95% CI 1.39–1.87 compared with adjusted OR 1.19, 95% CI 1.03–1.37). The adjustments only partially explained increases in the prevalence of stroke with hypertensive disorders of pregnancy (unadjusted OR 2.02, 95% CI 1.59–2.57 compared with adjusted OR 1.69, 95% CI 1.33–2.15) and stroke without hypertensive disorders of pregnancy (unadjusted OR 1.47, 95% CI 1.24–1.73 compared with adjusted OR 1.18, 95% CI 1.00–1.39). This adjustment also only partially explained increases in the prevalence of hypertensive disorders of pregnancy (unadjusted OR 1.71, 95% CI 1.64–1.79 compared with adjusted OR 1.57, 95% CI 1.50–1.63).

The majority of pregnancy-related strokes occurred outside of the delivery period (66%): 32% antenatally and 34% postpartum. In the hypertensive group, 15% of strokes occurred antenatally and 42% occurred postpartum. In the nonhypertensive group, 40% of the strokes occurred antenatally and 30%, postpartum (Appendix 3, available online at http://links.lww.com/AOG/A588). Hospitalizations with hypertensive disorders of pregnancy were 5.2 (95% CI 4.9–5.6) times more likely to have the ICD-9-CM code for stroke (data not shown). Traditional stroke risk factors, including congenital coagulation defects, valve disorders, sickle cell anemia, systemic lupus erythematosus, migraine, primary thrombocytopenia, atrial fibrillation and congenital heart disease, conferred additional risk of pregnancy-related stroke among hospitalizations with hypertensive disorders of pregnancy (adjusted OR ranging from 1.33 [95% CI 1.04–1.71] for postpartum hemorrhage to 13.1 [95% CI 9.09–18.9] for congenital heart disease) (Table 2). Moreover, most traditional stroke risk factors had a stronger association with

Rate (SE) of Complication/10,000 Stroke Hospitalizations		OR (95% CI) of Having Complication for Hospitalizations with Hypertensive Disorders of Pregnancy*	
Hospitalizations With Nonhypertensive Disorders of Pregnancy-Associated Stroke (n=21,783)	Hospitalizations With Hypertensive Disorders of Pregnancy-Associated Stroke (n=9,890)	Unadjusted	Adjusted†
1,081.2±0.48	2,270.9±0.96	2.41 (2.09–2.79)	1.93 (1.63–2.25)
218.1±0.23	410.5±0.47	1.92 (1.41–2.61)	1.78 (1.26–2.51)
870.9±0.43	1,212.3±0.75	1.45 (1.26–1.71)	1.29 (1.08–1.55)
447.1±0.32	793.7±0.59	1.85 (1.49–2.28)	1.29 (1.02–1.64)
4,164.3±0.83	5,968.7±1.15	2.08 (1.87–2.31)	1.24 (1.08–1.42)
7,144.6±0.75	6,337.7±1.13	1.44 (1.29–1.62)	1.23 (1.08–1.40)
182.2±0.20	192.1±0.32	1.11 (0.75–1.64)	1.04 (0.64–1.68)
224.0±0.22	200.2±0.33	0.91 (0.61–1.36)	0.78 (0.45–1.34)

ischemic stroke than with hemorrhagic stroke, except for congenital coagulation defects, which had a stronger association with hemorrhagic stroke (Appendix 1, http://links.lww.com/AOG/A586).

Among pregnancy hospitalizations with stroke and hypertensive disorders of pregnancy, there were higher rates of complications (per 10,000 hospitalizations) than in hospitalizations with stroke without these hypertensive disorders, including the need for mechanical ventilation, seizure, pneumonia, prolonged hospital stay, and death during hospitalization (adjusted OR ranging from 1.23, 95% CI 1.08–1.40 for nonroutine discharge to 1.93, 95% CI 1.63–2.25 for mechanical ventilation) (Table 3). No significant differences were found for temporary tracheostomy and percutaneous gastrostomy tube placements between the two groups. Hemorrhagic stroke had higher complication rates and the direction of associations remained the same except for in-hospital mortality and nonroutine discharge for ischemic stroke (Appendix 2, http://links.lww.com/AOG/A587).

DISCUSSION

Despite a 10-year decline in overall stroke prevalence and mortality among older adults in the United States,[11] our data show that the rate of pregnancy-related stroke increased by 61.5% between 1994–1995 and 2010–2011. Rates of stroke with hypertensive disorders of pregnancy increased disproportionately. The rate of hypertensive disorders of pregnancy also increased during the study period.[2,3] Known risk factors for each such as heart disease, hypertensive disorders, maternal comorbid conditions, and advanced maternal age have been implicated.[1,12] Adjustment for the changes in these factors in our analysis partially explained the substantial observed increases in the hypertensive disorders of pregnancy-associated stroke prevalence. Our additional findings that traditional cardiac and noncardiac stroke risk factors impart independent stroke risk in women with hypertensive disorders of pregnancy are biologically and clinically plausible. Preeclampsia involves systemic endothelial dysfunction and elevated coagulation beyond that of normal pregnancy.[13,14] Hypertension is an established risk factor for both hemorrhagic and ischemic stroke.[15] Ischemic stroke can be caused by large artery atherosclerosis, small vessel occlusion, or cardioembolism, all of which could be increased in hypertensive disorders of pregnancy.[16] Whether the predisposition for stroke in hypertensive pregnant patients is genetic, acquired, or both is poorly understood. There is evidence that these women are at risk for stroke peripartum and later in life[17] and there is a heightened awareness of the need to standardize and improve their care.[18] To facilitate the timely recognition, diagnosis, and management of the disease, the American College of Obstetricians and Gynecologists Task Force on Hypertension has revised the definition of preeclampsia such that proteinuria is not an absolute requirement for diagnosis.[19] Women with a history of early-onset preeclampsia and preterm birth or preeclampsia in more than one prior pregnancy are now instructed to receive low-dose aspirin to lower the risk of preeclampsia. Our results confirmed that both the ante- and postpartum periods are times of vulnerability for stroke and preventive therapy, diagnostic tests, and treatments should be targeted accordingly. Severe hypertension (systolic blood pressure 160 mm Hg or higher or diastolic

blood pressure 110 mm Hg or higher) treatment, twice-weekly antepartum blood pressure checks, and blood pressure monitoring for a minimum of 72 hours postpartum and at 7–10 days postpartum in patients with hypertension are advocated.[19] Because nonsteroidal antiinflammatory medications can exacerbate hypertension, they should be used with discretion in hypertensive patients.[19]

The American Heart Association endorses treatment of moderate hypertension in pregnancy (systolic blood pressure between 150 and 159 mm Hg or diastolic blood pressure between 100 and 109 mm Hg) as well as severe hypertension, although they acknowledge that the maternal–fetal risk–benefit ratios are not well established.[17] Further investigation at the population level is needed to determine whether these interventions will reduce hypertensive disorders of pregnancy-associated stroke.

Because stroke in the young is often mistaken for more benign occurrences such as migraine or seizure,[20] these patients may miss the opportunity to benefit from deficit-sparing therapies. Tissue plasminogen activator has been classified as a pregnancy category C drug, historically excluding pregnant women from clinical trials demonstrating its effectiveness for ischemic stroke thrombolysis.[21] However, recent published case reports and expert opinions espouse the application of intraarterial and intravenous thrombolysis in eligible pregnant and postpartum patients with ischemic stroke.[21–23]

We hypothesized that patients with hypertensive disorders of pregnancy would have more severe stroke-related complications than patients without hypertensive disorders of pregnancy as a result of a higher proportion of hemorrhagic stroke and its often poorer outcomes.[24–26] However, the increased odds of severe stroke complications found in our hypertensive disorders of pregnancy cohort were independent of stroke subtype. It is possible that the patients with hemorrhagic stroke were more likely to die, and the survivors were more similar to the ischemic stroke survivors.

Our study has several limitations. Although the National Inpatient Sample allows the investigation of a large number of data points for stroke, a rare event, these data are from ICD-9-CM codes collected for billing purposes. Validation studies suggest that the codes for stroke and hypertensive disorders of pregnancy generally have high specificity but more limited sensitivity.[3,27–29] Given the high specificity of the diagnosis of the exposure and outcomes, our estimates of relative risk in the analysis of risk factors and the association with adverse outcomes should be relatively unbiased. The hospitalization rate for postpartum stroke may have been underestimated, because those occurring within 6 weeks can be misclassified as nonpregnancy hospitalizations.[2] International Classification of Diseases, 9th Revision, Clinical Modification designations do not identify hemolysis, elevated liver enzymes, and low platelet count (HELLP), which is presumably coded as severe preeclampsia. With its marked thrombocytopenia, patients with HELLP may have a different stroke risk from those with severe preeclampsia and normal platelet count.

Because our units of measure are hospitalizations, not individuals, we could not account for multiple admissions or collect clinical data such as body mass index, severity of hypertension, or use of antihypertensive therapy. These factors may have contributed to the secular trends observed. The proportion of unclassified race–ethnicity was high (20–25%), because several states do not report race–ethnicity to the Healthcare Cost and Utilization Project. Although we adjusted for missing data in the models by creating a "missing" group, our estimates may not fully account for the confounding effects of race. In addition, the ICD-9-CM code 674.0x "cerebrovascular disorders in the puerperium" is often used alone in hospital discharge records such that specific stroke subtype may not available in some cases.

Stroke in young adults has historically been underdiagnosed.[30] The introduction of magnetic resonance imaging in 1994 with widespread use by year 2000[31] greatly enhanced minor ischemic stroke detection as did refinement of stroke diagnostic criteria.[32] Although this may have contributed to the increasing rates of recognition and reported incidence of stroke from 1994–1995 to 2000–2001, there continued to be steady and robust increases beyond year 2000 in our study.

In conclusion, stroke in patients with hypertensive disorders of pregnancy had two distinctive characteristics: a faster increase in frequency since the mid-1990s likely attributable, in part, to the rise in hypertensive disorders of pregnancy and maternal comorbidities and a significantly higher rate of stroke-related complications. Also, traditional cardiac and noncardiac risk factors for stroke conferred additional independent risk of stroke in these vulnerable women. These results highlight the need for continued vigilance on the part of care providers regarding hypertensive disorders of pregnancy and stroke risk factors, presentation, and diagnosis. Continued education about the management of preeclampsia and other pregnancy-related hypertensive disorders, and preventive and postacute event therapy for pregnancy-related stroke is of paramount importance.

REFERENCES

1. Grear KE, Bushnell CD. Stroke and pregnancy: clinical presentation, evaluation, treatment, and epidemiology. Clin Obstet Gynecol 2013;56:350–9.
2. Kuklina EV, Tong X, Bansil P, George MG, Callaghan WM. Trends in pregnancy hospitalizations that included a stroke in the United States from 1994 to 2007: reasons for concern? Stroke 2011;42:2564–70.
3. Kuklina EV, Ayala C, Callaghan WM. Hypertensive disorders and severe obstetric morbidity in the United States. Obstet Gynecol 2009;113:1299–306.
4. Ananth C, Keyes K, Wapner R. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. BMJ 2013;347:f6564.
5. Kuklina EV, Callaghan WM. Cardiomyopathy and other myocardial disorders among hospitalizations for pregnancy in the United States: 2004-2006. Obstet Gynecol 2010;115:93–100.
6. Kuklina EV, Whiteman MK, Hillis SD, Jamieson DJ, Meikle SF, Posner SF, et al. An enhanced method for identifying obstetric deliveries: Implications for estimating maternal morbidity. Matern Child Health J 2008;12:469–77.
7. Joint Commission on Disease-Specific Care Certification Program. Stroke performance measurement implementation guide, 2nd edition, version 2.a. 2008. Available at: http://www.jointcommission.org/assets/1/18/stroke_pm_implementation_guide_ver_2a.pdf. Retrieved September 2014.
8. HCUP Nationwide Inpatient Sample (NIS). Healthcare cost and utilization project (HCUP). Rockville (MD): Agency for Healthcare Research and Quality; 1994–2011.
9. SUDAAN Example Manual. Research Triangle Park (NC): Research Triangle Institute; 2012.
10. Houchens R, Elixhauser A. Using the HCUP nationwide inpatient sample to estimate trends (updated for 1988–2004). Vol 5. Rockville (MD): Agency for Healthcare Research and Quality; 2006. p. 1–53.
11. Russo CA, Andrews RM. Statistical briefs No. 51: hospital stays for stroke and other cerebrovascular diseases, 2005. Rockville (MD): Agency for Health Care Policy and Research; 2008.
12. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA 2012;307:491–7.
13. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. Science 2005;308:1592–4.
14. Sibai B, Dekker G, Kupferminc M. Pre eclampsia. Lancet 2005; 365:785–99.
15. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet 2010;376:112–23.
16. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35–41.
17. Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:1545–88.
18. van Dillen J, Mesman J, Zwart JJ, Bloemenkamp KW, van Roosmalen J. Introducing maternal morbidity audit in the Netherlands. BJOG 2010;117:416–21.
19. American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122:1122–31.
20. Kuruvilla A, Bhattacharya P, Rajamani K, Chaturvedi S. Factors associated with misdiagnosis of acute stroke in young adults. J Stroke Cerebrovasc Dis 2011;20:523–7.
21. Tsivgoulis G, Alexandrov AV, Chang J, Sharma VK, Hoover SL, Lao AY, et al. Safety and outcomes of intravenous thrombolysis in stroke mimics: a 6-year, single-care center study and a pooled analysis of reported series. Stroke 2011; 42:1771–4.
22. Selim MH, Molina CA. The use of tissue plasminogen-activator in pregnancy: a taboo treatment or a time to think out of the box. Stroke 2013;44:868–9.
23. Demchuk AM. Yes, intravenous thrombolysis should be administered in pregnancy when other clinical and imaging factors are favorable. Stroke 2013;44:864–5.
24. Lawrence ES, Coshall C, Dundas R, Stewart J, Rudd AG, Howard R, et al. Estimates of the prevalence of acute stroke impairments and disability in a multiethnic population. Stroke 2001;32:1279–84.
25. Sharshar T, Lamy C, Mas JL. Incidence and causes of strokes associated with pregnancy and puerperium. A study in public hospitals of Ile de France. Stroke in Pregnancy Study Group. Stroke 1995;26:930–6.
26. Paolucci S, Antonucci G, Grasso MG, Bragoni M, Coiro P, De Angelis D, et al. Functional outcome of ischemic and hemorrhagic stroke patients after inpatient rehabilitation: a matched comparison. Stroke 2003;34:2861–5.
27. Tirschwell DL, Longstreth WT Jr. Validating administrative data in stroke research. Stroke 2002;33:2465–70.
28. Callaghan WM. Invited commentary: Identifying women with hypertension during pregnancy–is high specificity sufficient? Am J Epidemiol 2007;166:125–7.
29. Yasmeen S, Romano PS, Schembri ME, Keyzer JM, Gilbert WM. Accuracy of obstetric diagnoses and procedures in hospital discharge data. Am J Obstet Gynecol 2006;194:992–1001.
30. Singhal AB, Biller J, Elkind MS, Fullerton HJ, Jauch EC, Kittner SJ, et al. Recognition and management of stroke in young adults and adolescents. Neurology 2013;81: 1089–97.
31. Burke JF, Kerber KA, Iwashyna TJ, Morgenstern LB. Wide variation and rising utilization of stroke magnetic resonance imaging: data from 11 states. Ann Neurol 2012;71:179–85.
32. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:2064–89.