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Acute Stroke During Pregnancy and Puerperium

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ABSTRACT

BACKGROUND Acute stroke during pregnancy or within 6 weeks of childbirth is devastating for the mother and her family, yet data regarding incidence and contemporary trends are very limited.

OBJECTIVES This study sought to investigate the incidence and outcomes of acute stroke and transient ischemic attack during pregnancy or within 6 weeks of childbirth in a large database.

METHODS The National Inpatient Sample was queried to identify women age ≥18 years in the United States with pregnancy-related hospitalizations from January 1, 2007, to September 30, 2015. Temporal trends in acute stroke (ischemic and hemorrhagic)/transient ischemic attack incidence and in-hospital mortality were extracted.

RESULTS Among 37,360,772 pregnancy-related hospitalizations, 16,694 (0.045%) women had an acute stroke. The rates of acute stroke did not change (42.8 per 100,000 hospitalizations in 2007 vs. 42.2 per 100,000 hospitalizations in 2015; $p_{trends} = 0.10$). Among those with acute stroke, there were increases in prevalence of obesity, smoking, hyperlipidemia, migraine, and gestational hypertension. Importantly, in-hospital mortality rates were almost 385-fold higher among those who had a stroke (42.1 per 1,000 pregnancy-related hospitalizations vs. 0.11 per 1,000 pregnancy-related hospitalizations; $p < 0.0001$). The rates of in-hospital mortality among pregnant women with acute stroke decreased (5.5% in 2007 vs. 2.7% in 2015; $p_{trends} < 0.001$).

CONCLUSIONS In this contemporary analysis of pregnancy-related hospitalizations, acute stroke occurred in 1 of every 2,222 hospitalizations, and these rates did not decrease over approximately 9 years. The prevalence of most stroke risk factors has increased. Acute stroke during pregnancy and puerperium was associated with high maternal mortality, although it appears to be trending downward. Future studies to better identify mechanisms and approaches to prevention and management of acute stroke during pregnancy and puerperium are warranted.
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Acute stroke remains a major cause of disability and mortality worldwide (1). In recent years, the incidence of stroke has been rising among the younger population, including pregnant women (2). Acute stroke during pregnancy is an infrequent but potentially devastating event for both the mother and her family. During pregnancy, hemodynamic changes, the hypercoagulable state, and other factors that have yet to be identified likely contribute to the increased risk of cardiovascular events (3). The increasing prevalence of traditional cardiovascular risk factors such as hypertension, diabetes, and obesity among younger adults (4), as well as the advancing maternal age at the time of birth (5), may contribute to increase the risk of acute stroke during pregnancy. A previous analysis suggested that the incidence of acute stroke during pregnancy and puerperium has been slowly rising from 1994 to 2007 (6). However, there are few studies evaluating these trends and the prevalence of risk factors in more recent years. To address this important knowledge gap, we evaluated trends in the incidence and

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outcomes of acute stroke during pregnancy and puerperium, as well as the trends in the prevalence of risk factors for acute stroke, using a large contemporary nationwide database.

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METHODS

DATA SOURCE. The Nationwide Inpatient Sample (NIS) database was queried for data detailing hospital admissions between January 2007 and September 2015. The NIS is made publicly available by the Agency for Healthcare Research and Quality for the Healthcare Cost and Utilization Project (7). The NIS represents the largest publicly available all-payer database and contains discharge-level administrative data on inpatient diagnoses and procedures from a stratified sample of approximately 20% of U.S. hospitals through 2012. Starting from 2012, the NIS represents a sample of 20% of discharges from all hospitals. The NIS provides a weight variable for establishing an estimate of national statistics.

STUDY POPULATION. Women (age ≥18 years) who were hospitalized during pregnancy, labor, and the post-partum period due to pregnancy-related conditions (i.e., primary or secondary diagnoses) were identified by using the corresponding International Classification of Diseases-9th Revision-Clinical Modification (ICD-9-CM) diagnostic and procedure codes (Online Table 1). Stroke was identified using ICD-9-CM diagnosis codes for hemorrhagic stroke (subarachnoid hemorrhage [430.xx] and intracerebral hemorrhage [431.xx]), ischemic stroke (433.xx and 434.xx), and transient ischemic attack (TIA) (435.xx) (8,9). Studies have shown that ischemic and hemorrhagic stroke identification from administrative use of ICD-9-CM codes have a high specificity (99%) and positive predictive value (approximately 87%) (8). Because our analysis was related to pregnant and post-partum women, we also used ICD-9-CM codes 674.0 and 997.02, which are specific codes for cerebrovascular disorders in puerperium and cesarean birth, respectively. All available discharge diagnoses (i.e., primary or secondary) for stroke or TIA were included.

PATIENT AND HOSPITAL CHARACTERISTICS. Baseline characteristics included demographics (age, race, length of hospital stay, elective admission to the hospital, patient disposition, primary payer information, and percentile of home income by residential zip code) and medical comorbidities (e.g., hypertension, hyperlipidemia, diabetes mellitus, coronary artery disease, cardiomyopathy, atrial fibrillation, heart failure, valvular heart disease, atrial septal defects, obesity, smoking history, chronic kidney disease, prior stroke/TIA, malignancy, benign tumors, obstructive sleep apnea, alcohol abuse, illicit drug abuse, depression, rheumatoid arthritis, anemia, migraine, preeclampsia/eclampsia, gestational hypertension, gestational diabetes, and systemic lupus erythematosus [SLE]) were identified with the corresponding ICD-9-CM codes. The hospital-related characteristics included bed size (small, medium, and large), location (urban vs. rural), hospital region (Northeast, Midwest, South, and West), and teaching status.

OUTCOMES MEASURED. The primary hypothesis that we tested was that the incidence of acute stroke/TIA during pregnancy and puerperium is increasing. The primary pre-specified outcome for this analysis was the incidence trend over time (years) for acute stroke during pregnancy and the puerperium. The secondary pre-specified outcomes included: 1) the trends of risk factors for acute stroke during pregnancy; and 2) the rates and trends of in-hospital mortality among women with acute stroke.

STATISTICAL ANALYSIS. The patient baseline characteristics and demographics as well as hospital-related outcomes were compared between those who had a stroke or TIA and those who did not. Categorical variables were compared with the Mantel-Haenszel chi-square test, and continuous variables were compared with analysis of variance testing. To evaluate incidence and mortality trends (10), the linear chi-square test was used, and the rates were expressed as a percentage, per 1,000 hospitalizations, or per 100,000 pregnancy-related hospitalizations, as appropriate. The independent predictors of acute stroke in pregnant women, as well as predictors of mortality in pregnant women with stroke, were examined with a hierarchical multivariable regression model to account for a between-hospitals clustering effect. Variables included in the multivariable model were statistically significant on univariate analyses and were shown to affect outcomes based on previous research. All statistical analyses were performed by using the weighted values of observations as provided by the NIS to measure national estimates. Statistical analyses were conducted using RStudio software (RStudio, Boston, Massachusetts) or SPSS software, version 25 (IBM SPSS Statistics, IBM, Armonk, New York). A 2-sided value of $p < 0.05$ was set for statistical significance. Odds ratios and the 95% confidence intervals were used to report the results of the regression analysis.

ABBREVIATIONS AND ACRONYMS

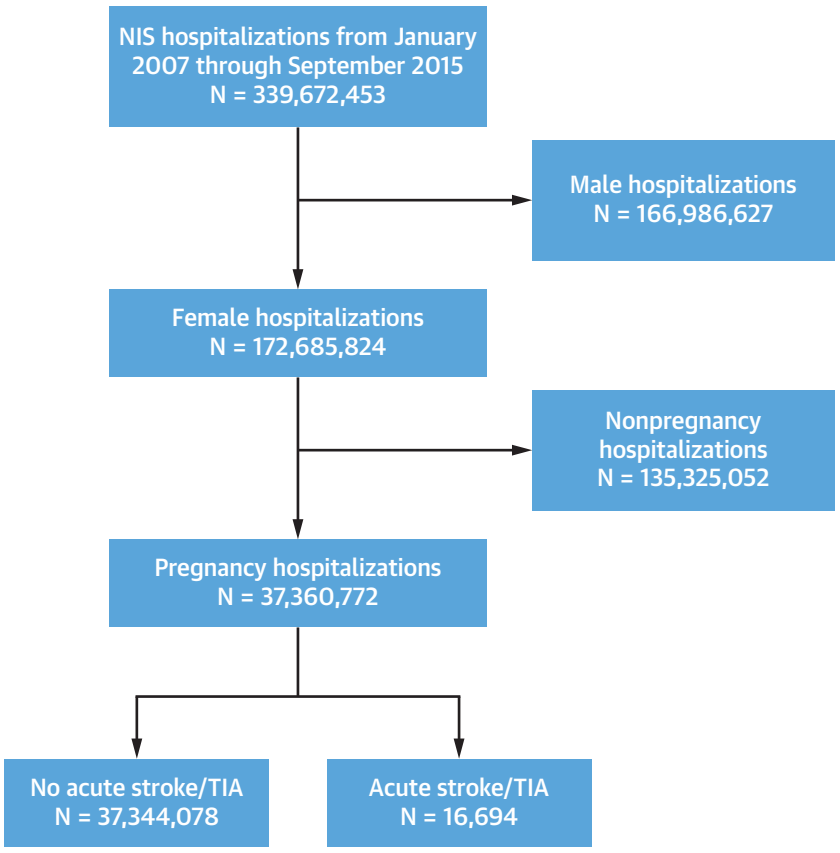
ICD-9-CM = International Classification of Diseases-9th Revision-Clinical Modification

NIS = National Inpatient Sample

SLE = systemic lupus erythematosus

TIA = transient ischemic attack

FIGURE 1 Study Flow Diagram



Flow diagram to identify how the study cohort was identified. NIS = National Inpatient Sample; TIA = transient ischemic attack.

RESULTS

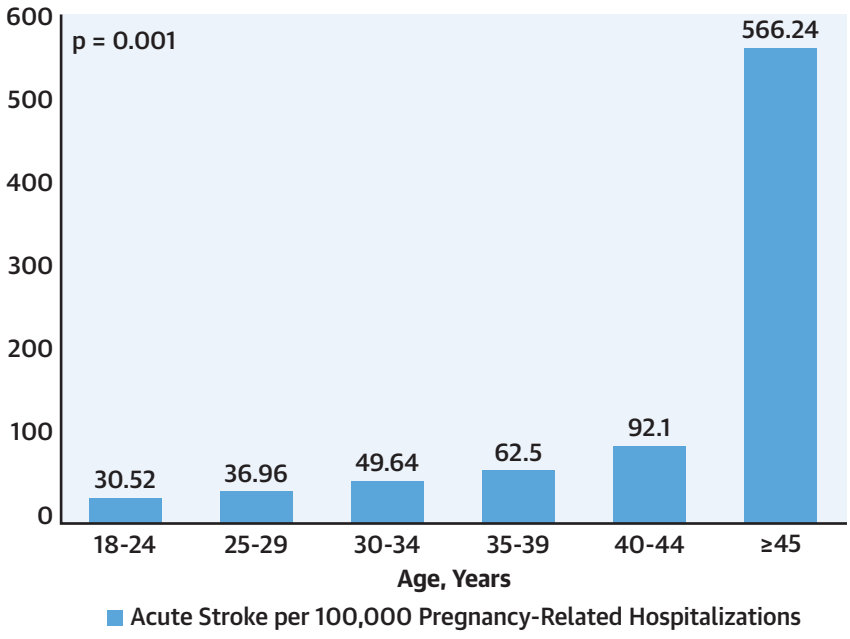
INCLUDED POPULATION. Among 37,360,772 hospitalizations for pregnancy and puerperium from January 2007 through September 2015, 16,694 (0.045%) involved acute stroke/TIA: 7,872 (47.2%) involved ischemic stroke/TIA, 5,169 (31.0%) involved hemorrhagic stroke, and 3,652 (21.8%) involved unspecified stroke (Figure 1). In a secondary analysis in which diagnostic codes for TIA and pregnancy-specific codes were excluded, the incidence of acute stroke was 0.035% (13,041/37,360,772). The incidence of acute stroke/TIA per 100,000 pregnancy-related hospitalizations increased with advancing maternal age (Figure 2).

Compared with those who did not have acute stroke/TIA, those with acute stroke/TIA were older; were more likely to be black, obese, and smokers; and had a higher proportion of hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, coronary artery disease, atrial septal defect, migraine, and rheumatologic diseases (i.e., rheumatoid arthritis and SLE). Pregnant women with acute stroke/TIA also had a higher proportion of pre-eclampsia/eclampsia but a lower proportion of gestational hypertension and gestational diabetes. Table 1 summarizes pertinent baseline patient and hospital-related characteristics.

On multivariable analysis, the following predictors were independently associated with acute stroke during pregnancy: advancing maternal age, black race, prior history of stroke/TIA, pre-eclampsia/eclampsia, migraine, atrial septal defects, hyperlipidemia, hypertension, diabetes mellitus, smoking, atrial fibrillation, valvular heart disease, coronary artery disease, heart failure, cardiomyopathy, malignancy, rheumatoid arthritis, SLE, anemia, and depression.

PRIMARY OUTCOME. During the study period, the incidence of acute stroke/TIA per 100,000 pregnancy-related hospitalizations remained largely unchanged

FIGURE 2 **Frequency of Acute Stroke/Transient Ischemic Attack per 100,000 Hospitalizations During Pregnancy and for Labor and Birth Stratified by Age Group**



The incidence of acute stroke/TIA per 100,000 pregnancy-related hospitalizations increased with advancing maternal age. TIA = transient ischemic attack.

(from 42.8 in 2007 to 49.5 in 2010, followed by a decrease to 42.2 in 2015; $p_{trends} = 0.10$). There was an increase in the rates of acute ischemic stroke/TIA (18.5 per 100,000 pregnancy-related hospitalizations in 2007 vs. 22.3 per 100,000 pregnancy-related hospitalizations in 2015; $p_{trends} < 0.0001$) and hemorrhagic stroke (12.5 per 100,000 pregnancy-related hospitalizations in 2007 vs. 14.3 per 100,000 pregnancy-related hospitalizations in 2015; $p_{trends} < 0.0001$). There was a decrease in the incidence of unspecified stroke (11.38 per 100,000 pregnancy-related hospitalizations in 2007 vs. 5.6 per 100,000 pregnancy-related hospitalizations in 2015; $p_{trends} < 0.0001$) (**Central Illustration, panel A**). In the secondary analysis, in which TIA and the pregnancy-specific codes were excluded, the incidence of acute stroke was increasing (29.8 per 100,000 pregnancy-related hospitalizations in 2007 vs. 33.0 per 100,000 pregnancy-related hospitalizations in 2015; $p_{trends} < 0.0001$) (**Figure 3**).

SECONDARY OUTCOMES. Among those with acute stroke/TIA, there was an increase in the prevalence of the following risk factors: obesity, smoking, hyperlipidemia, migraine, atrial septal defects, prior stroke, and gestational hypertension; however, the prevalence of other traditional risk factors, such as hypertension and diabetes mellitus, did not change (**Table 2**).

A total of 703 patients (4.2%) with acute stroke/TIA died during the hospitalization. In-hospital mortality was almost 385-fold higher among pregnant women with acute stroke/TIA versus those without (42.1 per 1,000 pregnancy-related hospitalizations vs. 0.11 per 1,000 pregnancy-related hospitalizations, respectively; $p < 0.0001$). The rates of in-hospital mortality among patients with acute stroke/TIA decreased during the study period (5.5% in 2007 vs. 2.7% in 2015; $p_{trends} < 0.0001$) (**Central Illustration, panel B**). On multivariable analysis, the following predictors were independently associated with in-hospital mortality among patients with acute stroke/TIA: age ≥40 years, black and Asian race, hemorrhagic stroke (compared with ischemic stroke), anemia, heart failure, cardiomyopathy, atrial fibrillation, hypertension, pre-eclampsia/eclampsia, gestational diabetes, and cesarean delivery.

DISCUSSION

In this nationwide observational analysis of pregnancy-related hospitalizations from 2007

TABLE 1 Baseline Characteristics, Demographics, Comorbidities, and Pregnancy-Related Complications

	All Hospitalizations (N = 37,360,772)	Stroke/TIA (n = 16,694)	No Stroke/TIA (n = 37,344,078)
Age, yrs	28 (23-32)	30 (25-35)	28 (23-32)
Race			
White	52.4	45.1	52.4
Black	15.0	26.4	15.0
Hispanic	21.7	18.3	21.7
Asian or Pacific Islander	5.3	4.1	5.3
Native American	0.8	0.7	0.8
Other	4.8	5.2	4.8
Length of stay, days	2 (2-3)	4 (2-8)	2 (2-3)
Elective admission	47.5	20.4	47.5
Control/ownership of hospital			
Government, nonfederal	13.4	15.6	13.4
Private, not for profit	72.2	74.2	72.2
Private, investor owned	14.4	10.1	14.4
Bed size of hospital			
Small	11.9	6.6	11.9
Medium	27.2	21.9	27.2
Large	60.9	71.5	60.9
Location/teaching status of hospital			
Rural	10.7	4.0	10.7
Urban nonteaching	37.7	24.7	37.7
Urban teaching	51.6	71.3	51.6
Hospital U.S. census region			
Northeast	16.5	18.7	16.5
Midwest or North Central	21.2	20.4	21.2
South	38.3	40.4	38.3
West	24.0	20.4	24.0
Patient disposition			
Routine	97.2	68.6	97.3
Transfer to short-term hospital	0.4	7.0	0.4
Transfer to skilled nursing facility or intermediate care facility	0.1	12.5	0.1
Home health care	1.9	6.8	1.9
Against medical advice	0.3	1.1	0.3
Died	0.01	4.0	0.01
Primary expected payer			
Medicare	0.9	4.9	0.9
Medicaid	43.0	40.4	43.0
Private insurance	49.9	47.0	49.9
Self-pay	3.2	4.0	3.2
No charge	0.2	0.3	0.2
Other	2.9	3.3	2.9

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through 2015, we showed that acute stroke/TIA occurred in approximately 1 of every 2,222 hospitalizations. Acute stroke/TIA was independently associated with advancing maternal age, black race, prior history of stroke/TIA, pre-eclampsia/eclampsia, migraine, atrial septal defects, hyperlipidemia, hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, valvular heart disease, heart failure, malignancy, rheumatoid arthritis, SLE, anemia, and depression. The incidence of acute stroke/TIA has remained unchanged or might have increased during the study period, as observed in the secondary analysis that used the most specific codes for acute stroke (i.e., by excluding TIA and the pregnancy-specific codes). There was also an increase in the prevalence of the following risk factors among those with acute stroke/TIA: obesity, smoking, hyperlipidemia, migraine, atrial septal defects, prior stroke, and gestational hypertension. Acute stroke/TIA was associated with high maternal mortality rates, but the rates of in-hospital mortality with acute stroke/TIA have decreased.

Although the incidence of stroke has been decreasing in the United States (11), some studies have shown that this decrease is mainly driven by a reduction in the stroke incidence among men but not women (12). The findings from this study extended our knowledge by showing that although acute stroke/TIA are rare events during pregnancy and puerperium, the incidence has remained unchanged or might be increasing. The incidence of acute stroke/TIA during pregnancy and puerperium was slightly higher than that in a pooled analysis of 11 studies, which showed an incidence of 0.03% (13). That meta-analysis was composed mainly of an analysis from the NIS database years 1994 through 2011 and was restricted to young women 25 to 34 years old, along with other smaller single-center studies from several countries that enrolled patients from the 1990s until 2008 (13). Our more contemporary analysis did not apply any age restrictions. Our analysis, as well as other studies (14), showed that the cumulative incidence of acute stroke increases with advancing maternal age, and this might explain why the incidence of acute stroke/TIA was higher in our study. Our estimates are also higher than that of a recent Canadian registry (13.4 per 100,000 births) (15); however, that study did not include TIA. Our estimates remained higher than that of this Canadian registry in our secondary analysis, which excluded TIA and pregnancy-specific codes for stroke. Furthermore, black women, who are known to be at a higher risk of stroke (16), are not as largely represented in Canada as in the United States. Another possible explanation for the relatively higher incidence of acute stroke/TIA in our study compared with other studies (13,15) is our inclusion of any stroke diagnosis (rather than only a primary diagnosis of stroke). The increases in the trends in ischemic and hemorrhagic stroke noted in our study suggest that we must understand the reasons behind this rise. We also noted that the proportion of unspecified stroke has been decreasing, which likely reflects improvement in coding of stroke etiology in

more recent years rather a true decrease in the incidence of the events. Nevertheless, we showed that the incidence of acute stroke is likely increasing in the secondary analysis by using the most specific codes for acute stroke.

During pregnancy and puerperium, there is a state of hypervolemia and increased venous stasis, associated with an increase in prothrombotic factors, that contribute to the increased risk of ischemic stroke and cerebral vein thrombosis (3). Hypertension remains the most common preventable risk factor for stroke (ischemic or hemorrhagic) in the general population (16), and efforts have been directed toward reducing the burden of hypertension along with other traditional risk factors (17). Our findings showed that hypertension is a prevalent risk factor and is independently associated with acute stroke/TIA. Furthermore, the prevalence of hypertension did not decrease during the study period among pregnant women with stroke. We also found that the prevalence of other traditional cardiovascular risk factors (i.e., obesity, smoking, hyperlipidemia) has been increasing whereas the prevalence of diabetes mellitus did not change. These findings suggest that additional efforts should be directed toward reducing the burden of these risk factors among women in the childbearing period. Notably, studies have shown that traditional risk factors are less prevalent among women with pregnancy-related stroke compared with non-pregnancy-related stroke of the same group, which suggests that pregnancy-related stroke might have some unique pathophysiologic mechanisms (18).

Besides the traditional cardiovascular risk factors, we identified other independent risk factors that were associated with acute stroke/TIA. Consistent with the growing body of evidence linking migraine to the risk of ischemic and hemorrhagic stroke (19–21), we found that migraine was associated with acute stroke/TIA during pregnancy and puerperium. Migraine is not well distinguished from pre-eclampsia in pregnancy in administrative data; thus, administrative databases might introduce misclassification for the diagnosis of migraine in pregnant women (22). Atrial septal defects (which includes patent foramen ovale) were associated with acute stroke/TIA. With the emergence of randomized controlled trial data in recent years supporting the benefit of patent foramen ovale closure in patients with cryptogenic stroke (23), physicians are more likely to look for a patent foramen ovale in younger patients with stroke. Hence, the association between acute stroke/TIA observed in our study is likely due to the fact that physicians are unlikely to search for an atrial septal defect/patent foramen ovale in patients without stroke.

TABLE 1 Continued

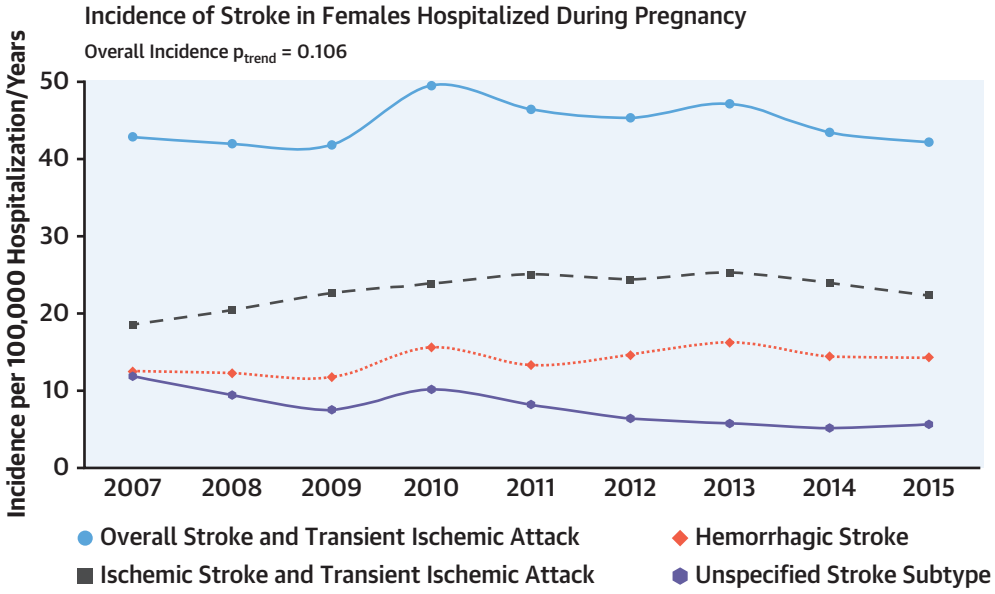
	All Hospitalizations (N = 37,360,772)	Stroke/TIA (n = 16,694)	No Stroke/TIA (n = 37,344,078)
Median household income, percentile			
<25	27.8	31.1	27.8
25–49	25.2	25.9	25.2
50–74	24.6	22.3	24.6
≥75	22.4	20.7	22.4
Comorbidities			
Hypertension	0.9	11.9	0.9
Hyperlipidemia	0.2	6.1	0.2
Diabetes mellitus	1.3	4.5	1.3
Ischemic heart disease	0.1	2.7	0.1
Cardiomyopathy	0.1	1.7	0.1
Atrial fibrillation	0.04	1.4	0.04
Heart failure	0.1	4.6	0.1
Atrial septal defects	0.0	3.0	0.0
Obesity	4.8	7.7	4.8
Smoking	2.1	7.0	2.1
Chronic kidney disease	0.1	1.6	0.1
Malignancy	0.1	1.9	0.1
Benign tumors	1.5	3.5	1.5
Obstructive sleep apnea	0.1	0.7	0.1
Alcohol abuse	0.1	0.3	0.1
Illicit drug abuse	0.5	1.0	0.5
Depression	2.1	6.0	2.1
Rheumatoid arthritis	0.1	0.4	0.1
Anemia	11.3	22.4	11.2
Migraine	0.7	9.6	0.7
Systemic lupus erythematosus	0.1	1.0	0.1
Valvular lesions	0.4	4.3	0.4
Prior stroke	0.1	4.0	0.1
Pregnancy complications			
Gestational hypertension	3.4	2.8	3.4
Pre-eclampsia/eclampsia	4.4	19.3	4.4
Gestational diabetes	7.4	6.8	7.4
Cesarean delivery	30.0	17.9	30.0

Values are median (interquartile range) or %.
TIA = transient ischemic attack.

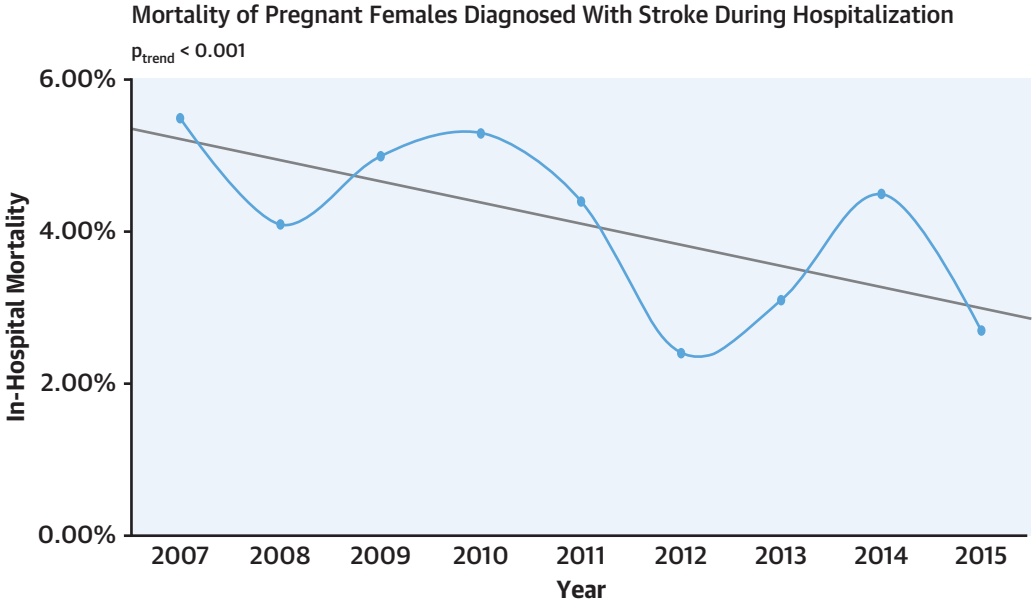
Furthermore, studies have shown that the ability of administrative databases to accurately diagnose atrial septal defects is limited (24). Thus, the strong association between atrial septal defects and acute stroke observed in our study is likely an overestimation of the true effect. Atrial fibrillation and valvular heart disease (including prosthetic valves) are known risk factors for cardioembolic ischemic events and hemorrhagic stroke (as a complication of anticoagulation therapy) (25,26). Similar to previous studies, which showed that pre-eclampsia/eclampsia is associated with both ischemic and hemorrhagic stroke (27,28), pre-eclampsia/eclampsia was associated with acute stroke/TIA in our analysis. Although data suggest that the rates of severe pre-eclampsia have been increasing in the United States (29), our data were

CENTRAL ILLUSTRATION **Stroke During Pregnancy and Puerperium**

A **Temporal Trends of Acute Stroke During Pregnancy and Puerperium in the United States**



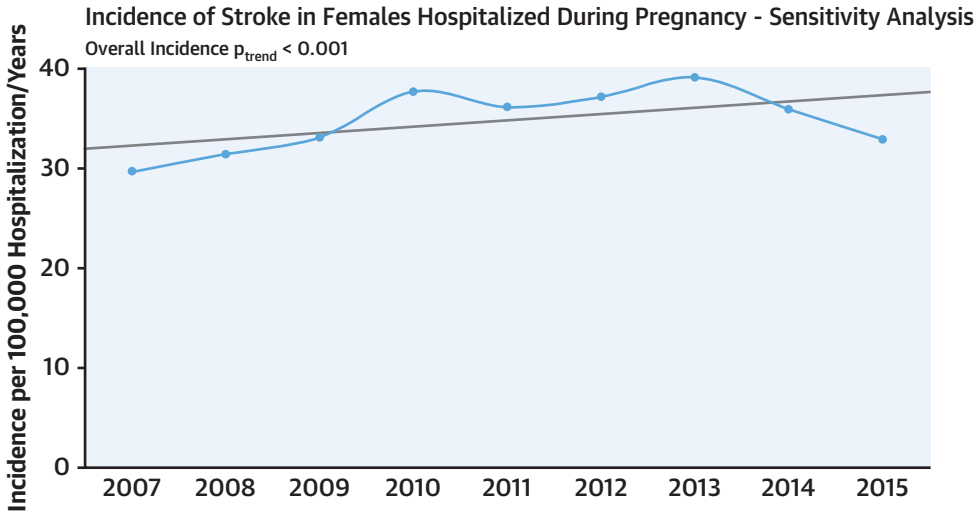
B **Temporal Trends of Mortality Related to Acute Stroke During Pregnancy in the United States**



Elgendy, I.Y. et al. J Am Coll Cardiol. 2020;75(2):180–90.

(A) Temporal trends in the incidence of acute stroke/transient ischemic attack complicating pregnancy and puerperium in the United States from 2007 through 2015. The incidence of acute stroke/transient ischemic attack per 100,000 pregnancy-related hospitalizations has remained largely unchanged: there was an increase from 42.8 in 2007 to 49.5 in 2010, followed by a decrease to 42.2 in 2015 ($p_{trends} = 0.10$). **(B)** Temporal trend of pregnancy-related stroke mortality in the United States from 2007 through 2015. The rates of in-hospital mortality among patients with acute stroke/transient ischemic attack decreased (5.5% in 2007 vs. 2.7% in 2015; $p_{trends} < 0.0001$).

FIGURE 3 **Temporal Trends in the Incidence of Acute Stroke Complicating Pregnancy and Puerperium in the United States From 2007 Through 2015 After Excluding the ICD-9-CM Codes of Transient Ischemic Stroke and Pregnancy-Related Codes**



The incidence of acute stroke has been increasing: 29.8 per 100,000 pregnancy-related hospitalizations in 2007 versus 33.0 per 100,000 pregnancy-related hospitalizations in 2015 ($p_{trends} < 0.0001$). ICD-9-CM, International Classification of Diseases-9th Revision-Clinical Modification.

restricted to those women who had a stroke/TIA, which represents a very small proportion of pregnant and postpartum women. In addition, we did not attempt to make a distinction between mild and severe pre-eclampsia. Nevertheless, early identification of pregnant women who are at high risk of pre-eclampsia and the offering of preventive measures such as low-dose aspirin might help reduce the risk of

TABLE 2 **Trends of the Prevalence of Risk Factors and Comorbidities Among Pregnant Women With Acute Stroke**

Risk Factor	2007	2008	2009	2010	2011	2012	2013	2014	2015	p Value
Hypertension	13.7	11.5	10.6	10.6	12.7	12.7	13.1	11.5	10.5	0.431
Hyperlipidemia	2.3	5.6	5.6	4.3	7.0	7.0	8.1	10.4	5.4	<0.0001
Diabetes mellitus	3.9	5.0	3.0	4.8	6.4	5.7	2.4	5.3	4.3	0.433
Coronary artery disease	3.0	2.0	2.7	3.2	3.1	1.9	2.6	2.5	3.1	0.983
Cardiomyopathy	1.9	1.5	1.9	1.2	1.2	1.6	3.1	1.4	1.6	0.445
Atrial fibrillation	1.5	0.5	2.2	0.5	2.2	0.8	2.1	1.7	1.6	0.072
Heart failure	4.7	4.7	7.3	3.9	3.8	4.1	5.8	3.9	5.1	0.319
Atrial septal defects	2.6	1.5	3.0	3.2	3.5	3.2	3.4	3.9	4.3	<0.0001
Obesity	3.6	3.7	5.8	8.0	7.8	8.1	11.0	11.2	11.7	<0.0001
Smoking	3.3	7.6	6.1	4.5	5.6	7.8	10.5	10.4	8.6	<0.0001
Chronic kidney disease	1.4	1.6	3.3	0.2	0.8	1.4	2.1	2.0	1.9	0.385
Rheumatoid arthritis	0.5	1.0	0.3	0.2	1.0	0.3	0.0	0.0	0.8	0.020
History of stroke	0.2	3.4	3.3	5.8	4.8	4.3	4.5	5.3	4.7	<0.0001
Migraine	6.2	7.7	6.2	6.9	12.7	9.7	13.9	10.4	15.6	<0.0001
Valvular disease	4.4	6.3	3.8	3.7	3.8	6.2	3.4	3.7	3.5	0.014
Systemic lupus erythematosus	0.7	1.7	0.8	1.0	1.0	0.8	0.8	1.4	0.8	0.729
Anemia	16.2	18.3	19.6	24.5	22.7	27.6	24.7	24.2	26.1	<0.0001
Gestational hypertension	1.7	1.5	3.2	1.4	4.0	2.2	3.1	4.5	4.7	<0.0001
Pre-eclampsia/eclampsia	21.7	18.0	18.9	19.6	19.1	21.6	20.2	13.2	21.8	0.066
Gestational diabetes	6.5	4.9	5.8	8.9	7.6	7.0	6.0	7.9	6.6	0.072

Values are %.

acute stroke (30). Studies have also shown that the prevalence of gestational diabetes is increasing (31); however, our analysis showed that the prevalence of gestational diabetes among pregnant women with stroke/TIA did not change. We found that cesarean birth was less likely associated with acute/stroke TIA. Some studies have shown that outcomes of vaginal and cesarean delivery are probably similar after stroke (3,32); however, we found that cesarean birth was associated with increased mortality after acute stroke/TIA, suggesting that sicker women with acute stroke/TIA were likely offered cesarean delivery in our study.

In this investigation, the maternal mortality rate with acute stroke/TIA was high (approximately 4.2%). Interestingly, we also observed that the rates of in-hospital mortality were decreasing during the study period. These findings are consistent with the decrease in stroke-related mortality observed among the general population worldwide (33). Improvements in timely computed tomographic imaging, thrombolytic therapy, and the recent introduction of mechanical thrombectomy contributed to the improved outcomes among patients with stroke in recent years (34-36); however, the role of these therapies remains unclear among pregnant women with ischemic stroke because this population has been excluded from randomized trials of these therapies. Data from the Get With The Guidelines Stroke Registry suggest that reperfusion therapy (defined as intravenous tissue plasminogen activator, catheter-based thrombolysis, thrombectomy, or any combination of these) was associated with similar favorable outcomes and reperfusion rates among pregnant or postpartum women compared with nonpregnant women (37). A recent consensus document from Canada suggests that these reperfusion therapies could be offered to pregnant and postpartum women who otherwise meet criteria (38). Future studies in this area remain warranted. Consistent with the general population (39), we also found that hemorrhagic stroke was associated with higher odds of in-hospital mortality compared with ischemic stroke/TIA during pregnancy and puerperium, because hemorrhagic strokes are usually more severe and tend to result in more extensive injury (39).

STUDY LIMITATIONS. The findings of this investigation should be interpreted in the context of potential limitations. First, this is an observational, nonrandomized design. Although we adjusted for potential confounders, the risk of unmeasured confounding could not be excluded. Second, the NIS is an administrative database relying on ICD-9-CM codes and is thus subject to coding errors (i.e., miscoding and undercoding). Third, the NIS database lacks important clinical information such as the stroke severity and subtype, imaging data, and data regarding medications during the hospital encounter. Fourth, we could not comment on the outcomes beyond the index hospitalization because the NIS database is restricted to in-hospital data only. Fifth, the NIS database relies on discharge rather than admission diagnoses, so we could not determine whether stroke or TIA was the primary reason for hospital admission or developed later during that admission. Sixth, the diagnosis codes for TIA and the pregnancy-specific codes for stroke (ICD-9-CM codes 674.0 and 997.02) have not been validated in studies validating the ICD-9-CM codes of stroke from the administrative database (8,40). Thus, we performed a secondary analysis by excluding TIA and the pregnancy-specific codes. Furthermore, these validation studies were conducted by using Medicare data (8); thus, the positive predictive value for these codes is likely to be lower in a younger population with a relatively lower prevalence of stroke. Finally, although we had information regarding maternal mortality rates, newborn mortality data are not available. Despite these limitations, this study provides important data regarding the trends and outcomes of acute stroke/TIA by using a large, contemporary nationally representative sample of women during pregnancy and puerperium.

CONCLUSIONS

In this large, contemporary, nationally representative sample of pregnancy-related hospitalizations, acute stroke/TIA occurred in 1 of every 2,222 hospitalizations. The incidence of acute stroke/TIA during pregnancy and puerperium has remained unchanged or might be increasing. Among those with acute stroke/TIA, the prevalence of traditional cardiovascular risk factors and pregnancy-related conditions such as pre-eclampsia/eclampsia increased or did not change during the study period. Acute stroke during pregnancy and puerperium was associated with high maternal mortality. Future studies focusing on identification of mechanisms and novel prevention and management strategies for acute stroke during pregnancy and puerperium are warranted.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Acute stroke is rare during pregnancy and the puerperium but is associated with high maternal mortality. The incidence has changed little, if at all, over time, paralleling trends in the prevalence of cardiovascular risk factors among pregnant women with acute stroke or transient ischemic attack.

TRANSLATIONAL OUTLOOK: Future studies should focus on identifying the mechanisms responsible for acute stroke during pregnancy and the puerperium, characterizing women at risk, and developing effective methods for prevention.

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KEY WORDS hemorrhagic stroke, ischemic stroke, pregnancy, puerperium

APPENDIX For a supplemental table, please see the online version of this paper.