Secular Increases in Spontaneous Subarachnoid Hemorrhage during Pregnancy: A Nationwide Sample Analysis

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Importance: Understanding of the epidemiology, outcomes, and management of spontaneous subarachnoid hemorrhage (sSAH) during pregnancy is limited. Small, single center series suggest a slight increase in morbidity and mortality. *Objective:* To determine if incidence of sSAH in pregnancy is increasing nationally and also to study the outcomes for this patient population. *Design, Setting, and Participants:* A retrospective analysis was performed utilizing the Nationwide Inpatient Sample (NIS) and Healthcare Cost and Utilization Project for the years 2002-2014 for sSAH hospitalizations. The NIS is a large administrative database designed to produce nationally weighted estimates. Female patients age 15-49 with sSAH were identified using the International Classification of Diseases, 9th Revision, Clinical Modification code 430. Pregnancy and maternal diagnosis were identified using pregnancy related ICD codes validated by previous studies. The Cochran-Armitage trend test and parametric tests were utilized to analyze temporal trends and group comparisons. *Main Outcomes and Measures:* National trend for incidence of sSAH in pregnancy, age, and race/ethnicity as well as associated risk factors and outcomes. *Results:* During the time period, there were 73,692 admissions for sSAH in women age 15-49 years, of which 3978 (5.4%) occurred during pregnancy. The proportion of sSAH during pregnancy hospitalizations increased from 4.16 % to 6.33% (P-$_{\text{Trend}}$ < .001) during the 12 years of the study. African-American women (8.19%) and Hispanic (7.11%) had higher rates of sSAH during pregnancy than whites (3.83%). In the NIS data, the incidence of sSAH increased from 5.4/100,000 deliveries (2002) to 8.5/100,000 deliveries (2014; P-$_{\text{Trend}}$ < .0001). The greatest increase in sSAH was noted to be among pregnant African-American women from (13.4 [2002]) to (16.39 [2014]/100,000 births). Mortality was lower in pregnant women (7.69% versus 17.37%, P < .0001). Pregnant women had a higher likelihood of being discharged to

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home (69.78% versus 53.66%, $P < .0001$) and lower likelihood of discharge to long term facility (22.4% versus 28.7%, $P < .0001$) than nonpregnant women after sSAH hospitalization. *Conclusions and Relevance:* There is an upward trend in the incidence of sSAH occurring during pregnancy. There was disproportionate increase in incidence of sSAH in the African American and younger mothers. Outcomes were better for both pregnant and nonpregnant women treated at teaching hospitals and in pregnant women in general as compared to nonpregnant women.
Key Words: Subarachnoid hemorrhage—pregnancy—intracranial hemorrhage—aneurysm—health care disparity.

Introduction

Spontaneous subarachnoid hemorrhage (sSAH) is a neurological emergency; timely diagnosis and treatment may reduce the morbidity and mortality in this life-threatening and life-changing disease. The incidence of sSAH in western populations is estimated to be approximately 10-15/100,000 persons.[1,2] The same studies show a higher incidence in women. The reported frequency of sSAH in pregnant women ranges from 8 to 31/100,000 deliveries.[3] It is estimated that sSAH causes up to 1 in 10 of all maternal deaths.[4-7] Some studies suggest that the risk of sSAH during pregnancy is higher than other time periods.[8,9] Potential etiologies for sSAH include: ruptured saccular aneurysm, ruptured arteriovenous malformation (AVM), arterial dissections, peripartum vasculopathies, hypertension/eclampsia (posterior reversible encephalopathy syndrome), and cerebral venous sinus thrombosis.[8-13] Because of the lack of large population studies, the estimates about risk factors, morbidity, and mortality of sSAH in pregnancy may be erroneous. The purpose of this study is to assess the risk of sSAH among pregnant women in comparison to a nonpregnant age-matched cohort. In addition, we also tested the hypothesis that sSAH has higher morbidity and mortality among women who are pregnant than among similar aged women who are not pregnant.

Methods

Data Source

We used data collected by the National Inpatient Sample (NIS) and Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality for the years 2002-2014. These publicly available data are sponsored by the Agency for Healthcare Research and Quality of the US Department of Health and Human Services.[14,15] The NIS is the largest publicly available all-payer inpatient database in the United States, yielding national estimates of hospital inpatient stays. Prior to 2012, the NIS approximated a 20% stratified sample of all community hospitals in the United States and included all inpatient hospitalizations from those hospitals. Beginning in 2012, the NIS approximates a 20% stratified sample of discharges from the US community hospitals, excluding rehabilitation and long-term acute care hospitals. It also provides proportional weights to calculate national estimates of the entire hospitalized US population. Each individual hospitalization is deidentified and maintained in the NIS as a unique entry with 1 primary discharge diagnosis and up to 24 secondary diagnoses. Each entry also contains information about demographics, hospital characteristics, insurance status, comorbidities, inpatient procedures, disposition status, length of hospital stay (LOS), and costs of hospitalization. The use of this database has been validated by multiple studies including those in stroke and sSAH.[16-19] We calculated and reported variances according to the NIS guidelines.[20]

As this study used publicly available administrative dataset with non-identifiable information local ethics and IRB approval is not necessary at the participating institutes.

Study Population and Design

We identified all female patients age 15-49 with a diagnosis of sSAH by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code 430 (Supplemental Table V). We excluded patients with traumatic brain injury by using the diagnosis ICD-9-CM code 800-804,850-854. This method has been previously validated for using administrative data like NIS and has higher specificity and sensitivity to identify SAH cases.[16] The pregnancy and maternal diagnosis were identified using the variable ‘neomat’, which identifies discharges with neonatal and/or maternal diagnoses and procedures using pregnancy related ICD-9-CM codes validated by previous studies. Proportional weights provided by the NIS were used to obtain a weighted sample of the study population that is representative of the whole U.S. population.

Outcomes studied include: incidence, basic demographic features including age and ethnicity, mortality, LOS, and hospital costs. To estimate the incidence of pregnancy related SAH, we should first determine the at-risk population. The ideal at-risk population should be pregnant women each year. As no such data available for yearly basis we decided to use only live births as a denominator for incidence calculation. We derived live births data from the US census for the duration of study.[21] We estimated baseline characteristics for both pregnancy related SAH and nonpregnancy related SAH. Univariate association of each of the demographic variables and risk factors was tested. A logistic regression model was constructed using all variables having a significant association with sSAH ($P < .05$) to identify independent predictors of pregnancy-related sSAH.

Estimation of the morbidity and in-hospital mortality was based on disposition data identified in NIS. In addition, we analyzed the available data on patient management which included endovascular coiling (ICD 9CM 39.72, 39.79) or craniotomy and clipping (ICD 9CM 39.51, 39.52) identified by ICD 9 CM data codes. We compared those results with the proportion of risk factors, morbidity, in hospital-mortality, and management differences among nonpregnant women of reproductive age group with SAH.

Definition of Variables

We analyzed patient and hospital level characteristics of the study population by hospital region. Hospital regions were categorized as Northeast, Midwest, South, and West.[14,15] Patient level characteristics included age, race, median household income by zip code (<$36,000; $36,000-$45,000; >$45 000), primary insurance payer (Medicare/Medicaid versus private insurance versus self-pay, or no charge). Hospital level characteristics included hospital bed size (small versus medium versus large), hospital location/teaching status (urban teaching versus urban nonteaching and rural). In order to better calculate the hospitalization costs, the NIS data were merged with cost-to-charge ratios available from the HCUP.[14,15] Adjusted cost for each year was calculated in terms of the 2014 cost, after adjusting for inflation according to the latest consumer price index data released by the US government. This enabled us to standardize the cost over the study period. LOS and cost were only calculated among survivors.

Statistical Analysis

To assess the difference between baseline characteristics of the study population, we used the chi-square test, student's t test and the nonparametric Kruskal-Wallis test. To analyze secular trends in the incidence of SAH, we used Cochrane-Armitage test for trend. Two-level regression models (patient-level variables nested within hospital-level variables) were constructed to determine whether hospital bed size, payer's status, and hospital location/teaching status were significant predictors of outcomes after adjusting for potential confounders. A P value of <.05 was considered statistically significant for all analyses. Standard errors and variances of population estimates were calculated as recommended by HCUP. NIS restrictions with data cells containing less than 10 or less notations were adhered to in the data report.[14-17] Proportional weights provided by the NIS were used to obtain a weighted sample of the study population that is representative of the whole US population. Previous studies on sSAH using NIS have validated the use of this dataset in this select population.[18,19] The analyses were completed using SAS 9.4, SAS Institute Inc, Cary NC.

Results

Disease Hospitalizations

From 2002 to 2014, there were 73,692 hospitalizations due to sSAH among women in the age group of 15-49. Out of 73,692 hospitalizations, 3978 (5.4%) occurred in pregnant women. Over the 12 years proportion of pregnant woman

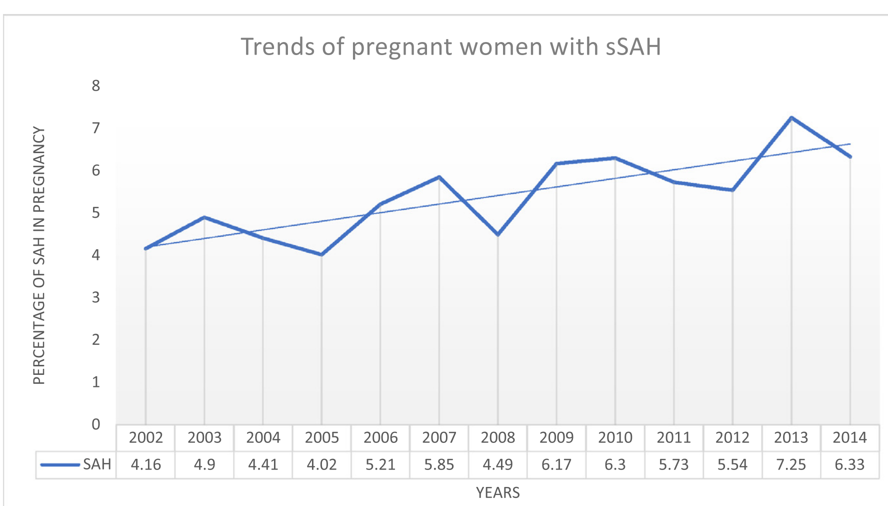

Figure 1. *Trends of pregnant women with sSAH. Abbreviation: sSAH, spontaneous subarachnoid hemorrhage.*

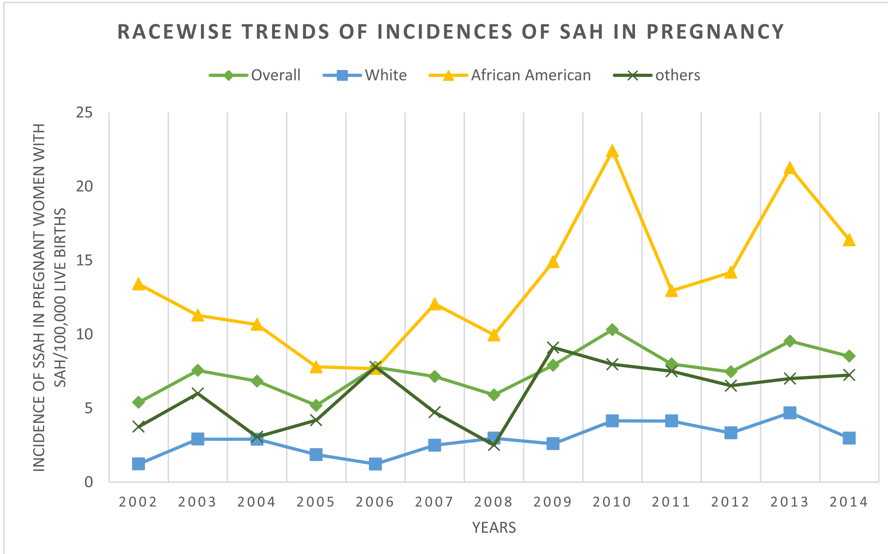

Figure 2. *Race-wise trends of sSAH incidences among pregnant women from 2002 to 2014. Abbreviation: sSAH, spontaneous subarachnoid hemorrhage.*

hospitalizations having sSAH increased from 4.16% (in 2002) to 6.33% (in 2014; $P\text{-}_{\text{Trend}} < .0001$; Fig 1).

Temporal Trends of sSAH Incidences

As shown in Figure 2, over the 12 years of study period, the overall incidence of sSAH during the pregnancy increased from from 5.4/100,000 deliveries (2002) to 8.5/100,000 deliveries (2014;$P\text{-}_{\text{Trend}} < .0001$; Fig 2).

Demographic Variables and Risk Factors

sSAH hospitalizations with pregnancy were more likely from age group 30 to 39 (47.41% versus 24.33%, $P < .0001$). The greatest increase in sSAH was noted to be among pregnant African-American women from (13.4 [2002]) to (16.39 [2014]/100,000 births) ($P\text{-}_{\text{Trend}} < .0001$; Fig 2). A similar but less impressive increase is noted among pregnant non-Hispanic white women (1.2 [2002]-2.9 [2014]/100,000 live births; $P\text{-}_{\text{Trend}} < .001$; Fig 2).

Comparisons between pregnant and nonpregnant women with sSAH. sSAH hospitalizations with pregnancy were associated with cerebral venous sinus thrombosis (3.59% versus 1.04%, $P < .0001$), and posterior reversible encephalopathy syndrome (4.56% versus 1.14%, $P < .0001$). Smoking (7.61% versus 27.47%, $P < .0001$), chronic kidney disease (.25% versus 1%, $P < .0001$), hypertension (14.22% versus 42.16%, $P < .0001$), diabetes mellitus (3.36% versus 11.81%, $P < .0001$), and cerebral vasculitis (.65% versus 2.18%, $P < .0001$) were lower in pregnant then nonpregnant women with sSAH. There was no difference in both groups for arterio-venous malformation and other cerebral vascular malformations causing sSAH (1.3% versus 1.47%, $P = .376$; Table 1). Either aneurysm clipping or endovascular coil embolization procedures were performed in 7.61% of pregnant women (clipping—2.33%/coiling—5.28%) and in 22.8% of nonpregnant women (clipping—5.28%/coiling—18.2%).

The Primary and Secondary Outcomes

Table 2 shows outcomes of sSAH hospitalizations among pregnant and nonpregnant women. Mortality was lower in pregnant women (7.69% versus 17.37%, $P < .0001$). Pregnant women had a higher likelihood of being discharged to home (69.78% versus 53.66%, $P < .0001$) and lower likelihood of discharge to long-term facility (22.4% versus 28.7%, $P < .0001$) than nonpregnant women after sSAH hospitalization (Table 2). Almost similar trends were observed between 2 cohort when compared by hospital bed size, payer status, and hospital teaching status (Table 3, Supplemental Tables I and II)

We found no difference in the outcomes when compared by payer status (Supplemental Table II).

However outcomes varied according to hospital bed-size status and hospital location/teaching status. More pregnant and nonpregnant women with sSAH were discharged home from teaching hospitals as compared to nonteaching hospitals (65.95 % and 50.37% versus 53.51% and 37.78; $P < 0001$; Supplemental Table I). Urban teaching hospitals had higher percentages of pregnant women receiving clipping or coiling procedures as a treatment (9.06% versus 2.1%; $P < .001$) than urban nonteaching and rural hospitals (Supplemental Table I). Mortality was slightly higher (8.05% versus 7.12%; $P < .001$) for pregnant women with sSAH in teaching hospitals (Supplemental Table I). Hospitals with large bed-size had higher percentages of both pregnant and nonpregnant women undergoing clipping or coiling procedures (Table 3). Large bed-size hospitals also had higher percentages of pregnant women discharged to home and lower

Table 1. *Baseline characteristics of SAH in pregnant and nonpregnant women*

	Pregnancy	No pregnancy	*P* value
Primary admissions of with sSAH (weighted)	3978	69,714	
Age (years)			<.0001
15-19	4.49%	1.99%	
20-29	40.22%	9.14%	
30-39	47.41%	24.33%	
40-49	7.89%	64.54%	
Race			<.0001
White	36.02%	53.62%	
African American	34.23%	22.71%	
Hispanic	18.82%	14.56%	
Others	10.93%	9.11%	
APRDRG risk mortality			<.0001
1	.38%	13.06%	
2	18.33%	27.81%	
3	40.36%	29.26%	
4	40.68%	29.09%	
Median household income for patient's ZIP code*			<.0001
0-25th percentile	26.93%	27.44%	
26-50th percentile	23.69%	23.39%	
51-75th percentile	20.1%	21.47%	
76-100th percentile	21.72%	18.19%	
Hospital characteristics			
Bed size			<.0001
Small	4.44%	4.55%	
Medium	19.95%	16.81%	
Large	74.75%	77.92%	
Hospital location/teaching status			.0006
Urban nonteaching & rural	23.14%	20.87%	
Urban teaching	76.86%	79.13%	
Hospital region			.458
Northeast	15.68%	16.15%	
Midwest	21.82%	21.51%	
South	41.09%	40.14%	
West	21.4%	22.2%	
Payment type			<.0001
Medicare/Medicaid	44.51%	28.35%	
Private insurance (including HMOs and PPOs)	48.48%	51.93%	
Self-pay/no charge/others	7.01%	19.42%	
Comorbidities			
Anomalies of cerebrovascular system	1.3%	1.47%	.376
Cerebral venous sinus thrombosis	3.59%	1.04%	<.0001
Smoking	7.61%	27.47%	<.0001
SCD	.36%	.63%	.034
Acute kidney injury	1.68%	4.06%	.139
Chronic kidney disease	.25%	1%	<.0001
Hypertension	14.22%	42.16%	<.0001
Diabetes	3.36%	11.81%	<.0001
Septicemia	3.14%	6.65%	<.0001
Heart failure	.13%	.06%	<.0001
Mechanical ventilation	19.53%	32.69%	<.0001
Cardiac procedure	.13%	.91%	<.0001
Liver disease	0%	.71%	<.0001
Cerebral vasculitis	.65%	2.18%	<.0001
PRES	4.56%	1.14%	<.0001

Abbreviations: HMO, Healthcare Maintenance Organization; ICVT, cerebral venous sinus thrombosis; PPO, Preferred Provider Organization; PRES, posterior reversible encephalopathy syndrome; SCD sickle cell disease.

*This represents a quartile classification of the estimated median household income of residents in the patient's ZIP Code. These values are derived from ZIP Code-demographic data obtained from Claritas. The quartiles are identified by values of 1-4, indicating the poorest to wealthiest populations. Because these estimates are updated annually; the value ranges vary by year. http://www.hcupus.ahrq.gov/db/vars/zipinc_qrtl/nisnote.jsp.

Table 2. *Outcomes of sSAH in pregnant and nonpregnant women*

Outcomes	Pregnancy	No pregnancy	*P* value
Discharge			
Transfer to home	69.78%	53.66%	<.0001
Transfer to long term facility	22.4%	28.7%	<.0001
Mortality	7.69%	17.37%	<.0001
Clipping	2.33%	4.68%	<.0001
Coiling	5.28%	18.2%	<.0001

Abbreviation: sSAH, spontaneous subarachnoid hemorrhage.

percentages of pregnant women discharged to long term facilities (Table 3).

Supplemental Table III shows univariate and multivariate logistic regression analysis to predict all cause in-hospital mortality in pregnant woman with sSAH and Supplemental Table IV shows univariate and multivariate logistic regression derivatives of predictors for discharge to long term facilities in pregnant woman with sSAH. There was no statistically significant difference in in-hospital mortality by Hospital bed size, payer's status, or hospital type. However pregnant woman with sSAH hospitalized in large bed size hospitals or urban teaching hospitals had significantly lower odds of discharge to long term facilities (adjusted odds ratio .31, 95% confidence interval: .17-.58, $P = .0002$) and (adjusted odds ratio .30, 95% confidence interval: .19-.48, $P \leq .0001$), respectively.

Numerically, less pregnant women who were treated with either coiling or clipping died. In the pregnant women, clipping was associated with 4.78% mortality and the deaths in the coiling arm was less than 5 (<1%) as compared to 7.19% (clipping) and 10.47% (coiling) in the nonpregnant women.

Discussion

sSAH during pregnancy is a life-threating condition for both mother and unborn child. Maternal mortality in the developed world is approximately 10/100,000 deliveries.[3,4,14] The reported incidence of sSAH during pregnancy and the puerperium is 8-31/100,000 deliveries.[4-7] The etiologies of sSAH include both aneurysmal and nonaneurysmal causes. De Rooji et al report that the incidence of aneurysmal SAH in women in general to be approximately 11.5/100,000 person years and it increases with age.[9] Some studies have reported increase in sSAH in pregnancy whereas others report no significant change in incidence.[8-12]

In this study, we report an increasing incidence of sSAH from 5.4/100,000 deliveries (2002) to 8.5/100,000 deliveries (2014), a trend that is statistically significant (*P*-trend $< .001$). These values are similar to the previously reported rates of 6.3-13.8/100,000 deliveries,[6,7,9,12] however the increasing trend was unexpected. In our study, the greatest increase in sSAH was noted to be among pregnant African-American women (Fig 2).

The better outcomes in pregnant women in surgically treated as well as nonsurgically treated pregnant mothers as compared to nonpregnant women may be explained by the lower prevalence of traditional risk factors such as hypertension and smoking. In addition, the younger age as compared to the nonpregnant women may also explain a better prognosis. Among nonpregnant women, the higher prevalence of diabetes mellitus and chronic kidney disease also might have played a role in the worse outcome in this group. Diabetes and chronic kidney disease have been reported to be independent risk factors for in-hospital mortality.[22,23] Although this study did not assess the etiology of sSAH, we did use the surrogate of neurosurgical or endovascular procedures as an indication of the presence of a ruptured aneurysm. We found that 7.61% of pregnant women had these interventions while the frequency was 22.8% in nonpregnant women. Our

Table 3. *Outcomes of sSAH in pregnant and nonpregnant women according to hospital bed-size*

Outcomes	Small		*P* value	Medium		*P* value	Large		*P* value
	Pregnant	Nonpregnant		Pregnant	Nonpregnant		Pregnant	Nonpregnant	
Discharge									
Transfer to home	57.19%	44.1%	<.001	56.53%	43.33%	<.001	65.16%	48.92%	<.001
Transfer to long term facility	36.63%	39.78%	<.001	34.97%	35.75%	.078	27.09%	34.27%	<.001
Mortality	6.18%	16.12%	<.001	8.5%	20.93%	<.001	7.75%	16.81%	<.001
Clipping	0%	4.11%	NA	2.49%	4.67%	<.001	2.46%	4.73%	.001
Coiling	3.06%	12.94%	<.001	2.48%	13.92%	<.001	6.22%	19.39%	<.001

Abbreviation: sSAH, spontaneous subarachnoid hemorrhage.

study did not show higher risk of AVM or other cerebrovascular malformation rupture leading to sSAH in pregnant women as compared to nonpregnant cohort. This result validates the study by Liu et al showing that pregnancy does not increase risk of hemorrhage with cerebral AVM.[24]

It is also noteworthy that maternal mortality in the United States has doubled in the time period of 1990 to 2013 and was 28/100,000 live births in 2013.[20] Interestingly our study did not show difference in treatment allocations as well as outcomes on the basis of insurance status of the patients. In a study, Hobson et al reported that patients insured by Medicare had fewer surgical procedures and poor outcomes.[25] Our study found more pregnant and non-pregnant women with sSAH were discharged home from teaching hospitals as compared to non-teaching hospitals. In a study by Burke et al, major teaching hospital status was associated with lower mortality rates.[26] In another study, McDonald et al noted significantly less adverse outcomes in SAH patients who were treated at teaching hospitals.[27] Our study supports these findings. The differences may be secondary to multiple reasons including rigorous internal guidelines and training standards of house staff, availability of multidisciplinary expertise, with more specialized knowledge and usually more staffing of both nursing and physicians all of which may translate in better outcomes.

Limitations

This study has some limitations. NIS is an excellent tool for estimating national trends for uncommon conditions such as sSAH in pregnancy and helps with estimation of incidence, risk factors and outcomes. However, being an administrative database, it is limited in differentiating sSAH from aneurysmal and non-aneurysmal causes. Also, it limits us from studying the severity of sSAH by clinical parameters such as the Hunt and Hess Scale or Glasgow Coma Scale. Multiple studies have validated the use of the administrative database in research such as ours.[16-19,28]

Conclusions

We report the results for pregnant women with sSAH. We saw an increasing trend in incidence over 12 years of this study period with better outcomes for pregnant women with sSAH as compared to non-pregnant women. This study also shows disproportionate increase in incidence of sSAH in the African American and younger mothers and that sSAH in pregnancy has a diverse etiology.

This study cannot answer the questions related to aneurysmal rupture during pregnancy or delivery. Future studies may help shed more light on the predictors and outcomes of both aneurysmal and aneurysmal SAH in pregnant women.

Supplementary Materials

Supplementary data to this article can be found online at doi:10.1016/j.jstrokecerebrovasdis.2019.01.025.

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