Peripartum Subarachnoid Hemorrhage

Nationwide Data and Institutional Experience

Brian T. Bateman, M.D.,* Vanessa A. Olbrecht, M.D.,† Mitchell F. Berman M.D., M.P.H.,‡ Rebecca D. Minehart, M.D.,§ Lee H. Schwamm, M.D.,# Lisa R. Leffert, M.D.‖

ABSTRACT

Background: Subarachnoid hemorrhage (SAH) in pregnancy occurs because of a variety of etiologies, which range from ruptured aneurysms to benign venous bleeding. The more malignant etiologies represent an important cause of maternal morbidity and mortality. We sought to investigate the epidemiology and mechanisms of pregnancy-related SAH.

Methods: Using the Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality, we extracted pregnancy-related admissions for women ages 15–44 from 1995–2008 and identified admissions complicated by SAH. Logistic regression identified independent predictors of SAH. Outcomes and risk factors were then compared with age-matched, nonpregnant women with SAH. We also analyzed our institution's experience with pregnancy-related SAH.

Results: There were 639 cases (5.8 per 100,000 deliveries) of pregnancy-related SAH in the cohort during the study period; SAH was associated with 4.1% of all pregnancy-related in-hospital deaths. More than half of the SAH cases occurred postpartum. Advancing age, African-American race, Hispanic ethnicity, hypertensive disorders, coagulopathy, tobacco, drug or alcohol abuse, intracranial venous thrombosis, sickle cell disease, and hypercoagulability were independent risk factors for pregnancy-related SAH. Compared with SAH in nonpregnant controls, pregnancy-related SAH had lower clipping/coiling rates (12.7% *vs.* 44.5%, $P < 0.001$). We identified 12 cases of pregnancy-related SAH in our hospital, the majority of which presented postpartum and with severe headache.

Conclusion: SAH during pregnancy results from a range of etiologies, and is less likely to be because of a cerebral aneurysm than SAH occurring in the nonpregnant patient. Peripartum SAH frequently occurs in the setting of hypertensive disorders.

What We Already Know about This Topic

- Subarachnoid hemorrhage (SAH) in pregnancy occurs because of a variety of etiologies, which range from ruptured aneurysms to benign venous bleeding

What This Article Tells Us That Is New

- SAH during pregnancy results from a range of etiologies, and is less likely to be because of a cerebral aneurysm than SAH occurring in the nonpregnant patient
- Peripartum SAH frequently occurs in the setting of hypertensive disorders

SUBARACHNOID hemorrhage (SAH) is one of several intracranial hemorrhagic syndromes that include bleeding inside of the skull, but outside of the brain itself (so-called "extra-axial bleeding," which includes SAH, subdural hemorrhage, epidural hemorrhage) and parenchymal bleeding (intracerebral hemorrhage, or ICH, contusions, petechial hemorrhage, duret hemorrhages). SAH and ICH are the two most common forms of spontaneously occurring hemorrhagic stroke. In the general population, SAH is associated with different predisposing factors than ICH, and is most often associated with an intracerebral aneurysm. The etiologies of SAH in pregnancy are diverse and include ruptured saccular[1–4] and mycotic[5] aneurysms, ruptured arteriovenous malformations,[3,4] intracranial venous thrombosis,[6] pregnancy-induced hypertension leading to pial vessel rupture,[7] in-

* Assistant Professor, † Resident, § Instructor, ‖ Assistant Professor, Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts. ‡ Professor of Clinical Anesthesiology, Department of Anesthesiology, Columbia University College of Physicians and Surgeons, New York, New York. # Professor, Department of Neurology, Massachusetts General Hospital, Harvard Medical School.

Received from the Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts. Submitted for publication November 2, 2010. Accepted for publication August 11, 2011. Support was provided solely from institutional and/or departmental sources. Presented in part at the annual meeting of Society for Obstetric Anesthesia, May 12, 2010, San Antonio, Texas, and the annual meeting of American Academy of Neurology, May 3, 2007, Boston, Massachusetts.

Address correspondence to Dr. Bateman: Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Boston, Massachusetts 02114. bbateman@partners.org. Anesthesiology 2012; 116:324–33

◇ This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

◆ This article is accompanied by an Editorial View. Please see: Flood P, Li G: A terrible headache in obstetric anesthesia. ANESTHESIOLOGY 2012; 116:242–3.

tracranial vertebral artery dissection,[8] Moyamoya disease,[9] posterior reversible encephalopathy syndrome,[10] and postpartum angiopathy, which is a form of the reversible cerebral vasoconstriction syndrome.[11–13]

Population-based data from Sweden suggest that the incidence of SAH is increased in the period around delivery.[14] However, a recent study from the Netherlands using a case-crossover study design demonstrated that the risk of aneurysmal SAH is not increased during pregnancy, labor, or the puerperium.[15] This apparent paradox, which has significant bearing on how women with known intracranial aneurysms are counseled, suggests the need for further investigation into the etiology and outcomes of SAH in pregnancy.

Also suggesting the need for further study, SAH was shown to be a leading cause of indirect maternal mortality in the triennial Confidential Enquiry into Maternal and Child Health in the United Kingdom; it was second only to cardiac disease and accounted for 11 indirect maternal deaths in 2003–2005.[16] Understanding the risk factors that predispose peripartum patients to SAH, the clinical presentation, and the distinction from more benign forms of headache (*e.g.*, postdural puncture headache) may help clinicians identify these patients so that appropriate work-up and therapy can be performed. In this study, we sought to further define this entity by retrospectively reviewing the epidemiology of pregnancy-related SAH using a nationwide administrative database, and by identifying the clinical presentation and hospital course among women with peripartum SAH admitted to our tertiary care institution.

Materials and Methods

Nationwide Data

To analyze the epidemiology of pregnancy-related SAH in the United States, we used the Nationwide Inpatient Sample (NIS), an administrative dataset that includes information on approximately 20% of all of the discharges from nonfederal, acute-care hospitals in the United States. The database is maintained by the Agency for Healthcare Research and Quality as part of the Healthcare Utilization Project. Hospitals are selected for inclusion in the NIS based on five characteristics: geographic region, ownership (public, investor-owned, and not-for-profit), location (urban or rural), teaching status, and number of in-patient beds, in order to create a sample that is maximally representative of all U.S. hospitalizations. For each year in our study period, discharges from approximately 1,000 hospitals from between 19 and 42 states were included in the NIS. A list of states that contributed to the NIS is available online.** For each of the hospital admissions, multiple data elements are reported, including patient age, race, gender, discharge destination, length of stay, and up to 15 diagnoses and procedures coded using the *International Classification of Disease—Clinical Modification,* ninth revision (ICD-9 CM).

Using the NIS for the years 1995–2008, we identified all admissions for women between the ages of 15 and 44 with a primary or secondary diagnosis of SAH (ICD-9 CM 430). We excluded those patients with a diagnosis code indicating traumatic brain injury (ICD 9 CM 800–804, 850–854) or a primary diagnosis suggesting an admission for rehabilitation (ICD 9 CM V 57).[17] Within the remaining group, we identified admissions with ICD-9 CM codes for antepartum and postpartum conditions or delivery (ICD-9 CM: 640.x-677.x, V22.x-V24.x, V27.x,-V28.x). These admissions were designated as being pregnancy-related SAH.

Some of the admissions for pregnancy-related SAH had a specific code for "cerebrovascular disorders of the puerperium" (ICD 9 CM 674.0×). There is a modifier for this diagnostic code that identifies whether the complication was antepartum or postpartum, and whether it occurred during the admission for delivery. There is not a specific modifier that denotes whether the cerebrovascular disorder occurred during the labor or delivery itself; it is therefore likely that SAH that occurred during labor or delivery would be coded as "postpartum," along with those that actually occurred postpartum.

To estimate the incidence of antepartum and postpartum SAH, we first determined the at-risk person-years in the antepartum and postpartum period. The overall number of pregnancies in the cohort was determined by searching the database for the ICD-9 codes for livebirth (ICD-9 V27.0, V27.2, V27.5, 650) and stillbirths (ICD-9 V27.1, V27.3, V27.4, V27.6, V27.7, or delivery codes with 656.4). As gestational age at time of delivery is not recorded in the NIS, gestational length was imputed as described by Kittner *et al.*[18] and as used in other studies of stroke in pregnancy.[19] Live births were assumed to occur at 38 weeks gestation, and stillbirths were assumed to occur at 28 weeks, followed by a 6-week postpartum period for both livebirths and stillbirths. Total antepartum at-risk person-years were calculated by multiplying the total number of livebirths by 38/52 yr and the total number of stillbirths by 28/52 yr, and then adding these two figures. Postpartum at-risk person-years were calculated by multiplying the sum of the number of livebirths and stillbirths by 6/52 yr. For estimates of the incidence of antepartum and postpartum SAH events, the calculated relative proportion for each age group (determined using the cases coded with 674.0×) was applied to all cases of peripartum SAH in that age group. The incidence of antepartum and postpartum SAH was then calculated by dividing the estimated number of antepartum and postpartum SAH cases, by age group, by the relevant at-risk person years.

We then calculated the rate of peripartum SAH per 100,000 obstetric admissions for each year over the 14-yr study period, and tested for linear trend using logistic regression. We also tested for trend adjusting for changes in ma-

** Available at: http://www.hcup-us.ahrq.gov/partners.jsp?NIS. Accessed August 26, 2011.

ternal age and race, as well as for changes in the prevalence of hypertensive diseases.

Potential risk factors for pregnancy-related SAH were identified by a survey of the published literature; the prevalence of these comorbid conditions and demographic characteristics were then compared in patients with pregnancy-related SAH and a control group containing all delivery admissions that were not complicated by SAH. Comorbid conditions were identified using appropriate ICD-9 CM codes and included hypertensive diseases (ICD 9 CM 401–405, 642.x), coagulopathy (ICD 9 CM 286, 641.3, 649.3, 666.3), thrombocytopenia (ICD 9 CM 287.3–287.5), tobacco abuse (ICD 9 CM 305.1, 649.0), drug abuse (ICD 9 CM 304, 305.2–305.9, 648.3), intracranial venous thrombosis (ICD 9 CM 325, 671.5, 437.6), sickle cell thalassemia/disease (ICD 9 CM 282.4, 282.6), hypercoagulability (ICD 9 CM 289.81, 289.82), alcohol abuse (ICD 9 CM 291, 303, 305.0), obesity (ICD 9 CM 278.0), and multiple gestations (ICD 9 CM V27.2-V27.7, 651). Demographic factors included age and race, as reported in the NIS. The univariate association of each of the aforementioned demographic variables and comorbidities were tested. A logistic regression model was then constructed using all variables with a significant univariate association with peripartum SAH ($P < 0.05$) to identify independent predictors of pregnancy-related SAH. Collinearity diagnostics were performed for the variables included in the multivariate logistic regression model; variance inflation factors were 1.00–1.22 (mean 1.09) and the condition number was 4.4; multicollinearity was therefore not an issue for the planned analysis.

We estimated the morbidity and in-hospital mortality for pregnancy-related SAH using the disposition of the identified cases (either routine, in-hospital death, discharge with home health care, transfer to long-term and intermediate care facilities, and transfer to another short-term hospital) and length of hospitalization. We also examined rates of treatment by craniotomy (ICD 9 CM 39.51, 39.52) or endovascular coiling (ICD 9 CM 39.72, 39.79). We compared the rates of each of these outcomes in the pregnancy-related SAH group with a control group that included all admissions for nontraumatic SAH in women aged 15–44 yr, who did not have a pregnancy-related code. We also compared the prevalence of the risk factors found to have a significant, independent association with peripartum SAH with the prevalence in the control group with nonpregnancy-related SAH.

Institutional Data

To further elucidate the etiology, presentation, and clinical course of pregnancy-related SAH, we performed a retrospective review of women identified with this complication at our tertiary care institution. After obtaining Partners Hospitals'

Table 1. Patient Characteristics, Comparing Pregnant or Postpartum Patients with Subarachnoid Hemorrhage and Patients Hospitalized for Delivery without Subarachnoid Hemorrhage, Nationwide Inpatient Sample, 1995–2008

	Pregnancy-related Admissions with Subarachnoid Hemorrhage, n (%) (n = 639)	Delivery Admissions without Subarachnoid Hemorrhage, n (%) (n = 11,069,923)	Univariate Odds Ratio (95% CI)	*P* Value
Age, years				
<25	140 (21.9)	3,941,640 (35.6)	Referent	—
25–34	328 (51.3)	5,609,935 (50.7)	1.65 (1.35–2.01)	<0.01
35–44	171 (26.8)	1,518,348 (13.7)	3.17 (2.54–3.96)	<0.01
Race				
Caucasian	194 (30.4)	4,567,284 (41.3)	Referent	—
African-American	159 (24.9)	1,120,099 (10.1)	3.34 (2.71–4.12)	<0.01
Hispanic	91 (14.2)	1,847,567 (16.7)	1.16 (0.90–1.49)	0.24
Asian/Pacific Islander	14 (2.2)	369,686 (3.3)	0.89 (0.52–1.53)	0.68
American Indians	*	46,019 (0.4)	*	0.5
Other	21 (3.3)	362,787 (3.3)	1.36 (0.87–2.14)	0.18
Missing	159 (24.9)	2,756,481 (24.9)	1.36 (1.1–1.67)	<0.01
Hypertensive disorders	256 (40.1)	840,454 (7.6)	8.14 (6.94–9.53)	<0.01
Coagulopathy	27 (4.2)	33,379 (0.3)	14.59 (9.92–21.45)	<0.01
Thrombocytopenia	12 (1.9)	52,061 (0.5)	4.05 (2.29–7.17)	<0.01
Tobacco abuse	41 (6.4)	318,711 (2.9)	2.31 (1.69–3.17)	<0.01
Drug abuse	21 (3.3)	115,066 (1)	3.24 (2.09–5)	<0.01
Intracranial venous thrombosis	19 (3)	1,224 (0)	277.13 (174.97–438.94)	<0.01
Sickle cell disease	*	11,693 (0.1)	*	<0.01
Hypercoagulability	*	8,214 (0.1)	*	<0.01
Alcohol abuse	*	11,339 (0.1)	*	<0.01
Obesity	*	113,849 (1.0)	*	0.34
Multiple gestation	*	180,409 (1.6)	*	0.29

* Data cannot be disclosed in accordance with Healthcare and Utilization Project restrictions on small cell size, prohibiting disclosure of cells with 10 or fewer observations.

Institutional Review Board (Boston, Massachusetts, United States) approval, we used an electronic query tool to identify women who had a discharge diagnosis of SAH, and an additional pregnancy-related diagnosis. Electronic patient records, including patient notes, laboratory values, and radiology images and reports, were used to obtain patient histories. The pertinent abstracted data were reviewed by both a board-certified vascular neurologist and a board-certified anesthesiologist to determine if the identified patients had experienced a SAH in the peripartum period. The peripartum period was defined as the time between conception and 1 yr postdelivery (the period that defines pregnancy-related deaths by the Center for Disease Control and the American Congress of Obstetricians and Gynecologists).[20] Patients were included only if subarachnoid hemorrhage was their primary pathology; patients with intraparenchymal hemorrhage with subarachnoid extension were excluded.

We then calculated an incidence of peripartum SAH per 100,000 deliveries by dividing the number of patients admitted with peripartum SAH at Massachusetts General Hospital (excluding transfers) by the estimated total number of deliveries. Because of the limited number of cases, we were unable to estimate antepartum and postpartum incidence rates based on the Massachusetts General Hospital sample.

Statistical Analysis

NIS data are reported using the unweighted dataset. For our analysis of trend, we utilized the sampling weights to generate national estimates. In accordance with NIS restrictions, data cells containing 10 or fewer observations were not shown. Categorical variables were compared with chi-square test. Length of stay, which was not normally distributed, was compared with the Mann–Whitney U test. Statistical analyses were performed using SPSS (SPSS, Inc. Version 11.5, Chicago, IL) and STATA (StataCorp LP, Version 10.0, College Station, TX). Statistical significance was judged as $P < 0.05$.

Results

There were 639 cases of pregnancy-related SAH among women age 15 to 44 yr old in the NIS during the study period, 1995–2008. During this time, there were 11,070,014 deliveries and 12,855,405 pregnancy-related admissions, resulting in a pregnancy-related SAH prevalence of 5.8 (95% CI, 5.3–6.2) per 100,000 deliveries and 5.0 (95% CI, 4.6–5.4) per 100,000 pregnancy-related admissions. Of the pregnancy-related SAH, 535 (83.7%) had a code specifying whether the SAH was antepartum or postpartum, and 357 (66.7%) occurred in the postpartum period. The source of the patient admission was recorded in 581 (90.9%) of the cases of pregnancy-related SAH: 288 (49.6%) were admitted from the emergency department, 114 (19.6%) from another hospital, 12 (2.1%) from another healthcare facility (including long-term care facility), and 167 (28.7%) were coded as routine admissions. Of the women with pregnancy-related SAH, 66 (10.3%) died; thus SAH was associated with 4.1% of all pregnancy-related in-hospital deaths in the NIS.

Table 1 compares the prevalence of various demographic and medical conditions for women with pregnancy-related SAH and women hospitalized for delivery that did not have pregnancy-related SAH. In our univariate analysis, women with pregnancy-related SAH were significantly older than the general delivering population and were more likely to be African-American. In addition, women with pregnancy-related SAH had significantly higher rates of hypertensive disorders, coagulopathy, thrombocytopenia, tobacco, drug, and alcohol abuse, intracranial venous thrombosis, sickle cell disease, and hypercoagulability. In 14 cases (2.2%) of pregnancy-related SAH, patients were coded with ICD 9 CM 747.81, used to denote cerebrovascular malformations including arteriovenous malformations, cavernous malformations, unruptured cerebral aneurysms, dural arteriovenous fistulae, and venous malformations.[21] Because it is unlikely that this diagnostic code would be used in the delivery admissions for patients with asymptomatic disease, we did not include this entity in our analysis of risk factors for peripartum SAH.

Table 2 shows the results of our logistic regression analysis identifying independent predictors of pregnancy-related SAH. Advancing age, African-American race and Hispanic ethnicity (compared with Caucasian race), hypertensive disorders, coagulopathy, tobacco, drug, and alcohol abuse, intracranial venous thrombosis, sickle cell disease, and hypercoagulability were all independent predictors of preg-

Table 2. Independent Predictors of Peripartum Subarachnoid Hemorrhage from Multivariate Logistic Regression Model, Nationwide Inpatient Sample, 1995–2008

	Odds Ratio (95% CI)	*P* Value
Age, years		
<25	Referent	—
25–34	1.87 (1.53–2.28)	<0.01
35–44	3.29 (2.62–4.12)	<0.01
Race		
Caucasian	Referent	—
African-American	3.28 (2.65–4.07)	<0.01
Hispanic	1.44 (1.12–1.86)	<0.01
Asian/Pacific Islander	0.94 (0.55–1.62)	0.83
American Indians	0.53 (0.07–3.77)	0.52
Other	1.54 (0.98–2.43)	0.06
Missing	1.45 (1.17–1.79)	<0.01
Hypertensive disorders	7.02 (5.97–8.24)	<0.01
Coagulopathy	7.88 (4.96–12.52)	<0.01
Thrombocytopenia	0.66 (0.34–1.29)	0.23
Tobacco abuse	2.39 (1.71–3.33)	<0.01
Drug abuse	1.76 (1.09–2.85)	0.02
Intracranial venous thrombosis	179.39 (110.81–290.42)	<0.01
Sickle cell disease	7.98 (3.93–16.2)	<0.01
Hypercoagulability	4.06 (1.75–9.43)	<0.01
Alcohol abuse	2.68 (1.04–6.93)	0.04

Table 3. Discharge Destination, Procedures, and Risk Factors among Female Patients with Subarachnoid Hemorrhage Ages 15–44, Comparing Peripartum and Nonpregnancy-related Subarachnoid Hemorrhage, Nationwide Inpatient Sample, 1995–2008

	Pregnancy-related Subarachnoid Hemorrhage (n = 639)	Nonpregnancy-related Subarachnoid Hemorrhage (n = 10,114)	*P* Value
Discharge destination*	—	—	—
In-hospital death	66 (10.3)	1,853 (18.3)	<0.01
Routine, home healthcare or against medical advice, alive (destination unknown)	420 (65.7)	5,361 (53)	<0.01
Short-term hospital	80 (12.5)	1,205 (11.9)	0.647
Transfer other: includes skilled nursing Facility, intermediate care facility, another type of facility	73 (11.4)	1,684 (16.7)	<0.01
Procedure	—	—	—
Treatment with aneurysm coiling/clipping	81 (12.7)	4,501 (44.5)	<0.01
Length of stay, days	6 (3–12)	9 (3–16)	<0.01
Risk factors	—	—	—
Hypertensive disorders	256 (40.1)	2,982 (29.5)	<0.01
Coagulopathy	27 (4.2)	166 (1.6)	<0.01
Tobacco abuse	41 (6.4)	1,649 (16.3)	<0.01
Drug abuse	21 (3.3)	809 (8)	<0.01
Intracranial venous thrombosis	19 (3)	65 (0.6)	<0.01
Sickle cell disease	†	59 (0.6)	0.06
Hypercoagulability	†	17 (0.2)	<0.01
Alcohol abuse	†	372 (3.7)	<0.01
Cerebrovascular anomaly	14 (2.2)	177 (1.8)	0.41

Shown as N (%), except length of stay, which is reported as median and interquartile range.

* Missing n = 11. † Data cannot be disclosed in accordance with Healthcare and Utilization Project restrictions on small cell size, prohibiting disclosure of cells with 10 or fewer observations.

nancy-related SAH. Hypertensive diseases were particularly important independent risk factors and were present in 256 (40.1%) of the cases. Of note, because the diagnosis of intracranial venous thrombosis is sometimes made in retrospect once a patient is imaged because of concern for SAH, we performed a second logistic regression model excluding intracranial venous thrombosis as a predictor. This had very little effect on the model; both the significance and the magnitude of risk associated with the other predictors were essential unchanged (data not shown). We also performed separate logistic regression analyses to identify independent predictors of antepartum and postpartum SAH. Each of the independent predictors for peripartum SAH (table 2) was also significant for antepartum SAH except for age 25–34 yr, Hispanic ethnicity, tobacco and alcohol abuse, and hypercoagulability. For postpartum SAH, all predictors were the same as in peripartum SAH except Hispanic ethnicity, drug and alcohol abuse (data not shown).

To better understand how pregnancy-related SAH might differ from nonpregnancy-related SAH, we identified a control group consisting of 10,114 cases of nonpregnancy-related SAH

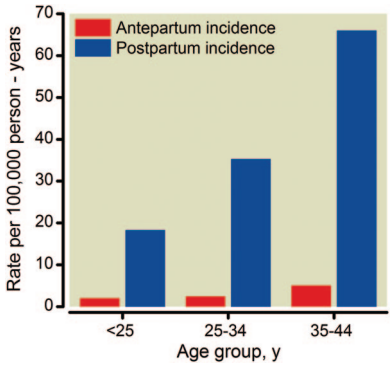

Fig. 1. Estimated incidence of antepartum and postpartum subarachnoid hemorrhage, Nationwide Inpatient Sample, 1995–2008.

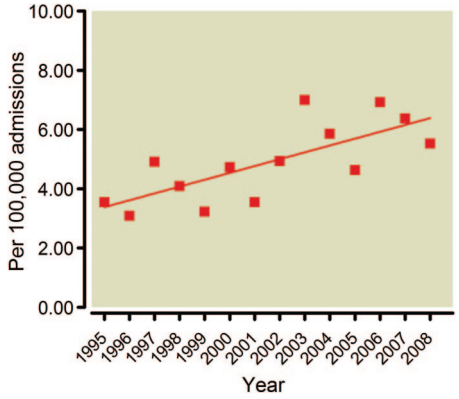

Fig. 2. Trends in the rate of peripartum subarachnoid hemorrhage per 100,000 obstetric admissions, Nationwide Inpatient Sample, 1995–2008.

in women aged 15 to 44. As shown in table 3, the in-hospital mortality for pregnancy-related SAH compared with these controls was significantly lower (10.3% *vs.* 18.3%, $P < 0.001$), as was the rate of discharge to a skilled nursing or intermediate care facility (11.4% *vs.* 16.7%, $P < 0.001$). The aneurysm clipping/coiling rate was four times lower (12.7% *vs.* 44.5%, $P < 0.001$). Of note, in the postpartum SAH cases, the clipping/coiling rate was only 6.2%. The median length of hospital stay was also substantially lower (6 *vs.* 9 days, $P < 0.001$). In our analysis of risk factors, patients with pregnancy-related SAH had higher rates of hypertensive diseases, coagulopathy, and intracranial venous thrombosis, and lower rates of drug, tobacco, and alcohol abuse when compared with patients with nonpregnancy-related SAH. There was not a significant difference in coded rates of cerebrovascular anomalies.

Figure 1 shows the estimated incidence of antepartum and postpartum SAH per 100,000 at-risk person years. The estimated antepartum incidence rose from 2.0 per 100,000 person-years in women less than 25 yr old to 5.0 in women 35–44 yr old. The risk in the postpartum period was markedly higher: 18.3 per 100,000 person-years in women less than 25 yr to 66.0 in women 35–44 yr.

Figure 2 shows the prevalence of peripartum SAH per 100,000 obstetric admissions by year from 1995–2008. Test for linear trend revealed a significant increase ($P <$ than 0.001); this trend persisted after adjustment for changes in age and race ($P < 0.001$) and the prevalence of hypertensive disorders ($P < 0.001$).

Because administrative claims data are do not capture detailed clinical information, we also retrospectively reviewed our institutional experience to learn more about the etiology and clinical course of peripartum SAH. We identified 12 cases of pregnancy-related SAH from 1996–2010 (table 4); six of these women (50%) were transferred from an outside facility for neurocritical care or neurosurgical evaluation. Of the 12, six were Caucasian (50%), three were African American (25%), and three were Hispanic (25%). These patients presented with SAH most commonly in the postpartum period (range postpartum day 0–12, mean day 7); only five of the 12 (41.7%) developed SAH before delivery. The most common presenting symptom was severe headache. Four of the 12 cases were aneurysmal or because of an arteriovenous malformation (33.3%), and two were associated with venous sinus thrombosis (16.7%). One patient died (8.3%), and two were discharged with neurologic deficits (16.7%). As there have been approximately 35,000 deliveries at our institution since 1995 and six of the patients with SAH presented to our center (*i.e.*, not transferred from outside hospitals for neurosurgical or neurocritical care), this corresponds to a peripartum SAH rate of 17.1 (95% CI, 6.3–37.3) per 100,000 deliveries.

Discussion

In this study, we analyze pregnancy-related SAH using the NIS dataset (approximately 20% of all U.S. hospital admissions) and our tertiary care institutional experience. Our three principal findings were: the etiology of peripartum SAH is varied and is likely less often related to cerebral aneurysms than SAH in the general population, the risk of peripartum SAH is greatest in the peri-delivery/postpartum period, and many peripartum SAH cases occur in patients with pregnancy-related hypertension.

Incidence of SAH

In the NIS and in our institutional series, the incidence of SAH was 5.8 and 17.1 per 100,000 deliveries, respectively; these rates are similar to the those reported in previous studies (6.3–13.8 per 100,000 deliveries).[4,22,23] Most pregnancy-related SAHs occurred in the delivery/postpartum period (67% in the NIS and 58% in our institutional data). Our estimated antepartum SAH incidence was similar, albeit slightly lower, than published SAH rates for age-matched subjects from the general population.[24] The postpartum incidence was substantially greater than that observed in the antepartum period. Given the low craniotomy rate (6.2%) associated with postpartum SAH in the NIS sample, this increase is likely driven by nonaneurysmal causes. Although the precise etiology of this increase is unknown, the marked hemodynamic, coagulation, and hormonal fluctuations[18] accompanying the delivery/postpartum period may be important contributors.

We found a slight rise in the rates of peripartum SAH in obstetric patients in the United States during the study period (fig. 2); this trend was not explained by changes in patients' age, race, or the prevalence of hypertensive disorders. Whether the underlying cause is better diagnosis through increased use of neuroimaging, improved SAH coding, or changes in the prevalence of relevant obstetric and/or medical conditions deserves future study.

Etiology of SAH in Pregnancy

Our data suggest that peripartum SAH is less frequently aneurysmal than SAH occurring without pregnancy. Although the ICD 9 CM code that identifies SAH does not distinguish aneurysmal from nonaneurysmal SAH, clipping/coiling procedures are a useful surrogate for aneurysmal cases, as most patients with aneurysmal SAH who survive the initial bleed will be clipped or coiled to prevent rebleeding. In the NIS dataset, the rate of these procedures in patients with pregnancy-related SAH was 12.7%, *versus* 44.5% for age-matched nonpregnant women with SAH. The clipping/coiling treatment rate in postpartum women with subarachnoid hemorrhage was even lower, at 6.2%. Nonaneurysmal SAH is typically associated with lower mortality rates than aneurysmal SAH; the lower mortality rate for pregnancy *versus* nonpregnancy-related SAH (10.3% *vs.* 18.3%) also indicates that pregnancy-related SAH is more often nonaneurysmal. Furthermore, in our institutional series, only three of the 12 patients had aneurysmal SAH.

This helps to resolve an apparent contradiction in the literature. The population-based study from Sweden that

Table 4. Institutional Case Series of Subarachnoid Hemorrhage in Parturients

Patient	Age	Race	Transfer	Angiographically Proven Aneurysm and/or AVM	Presumed Etiology	Timing of Presentation
1	41	African-American	Yes	Yes	Ruptured saccular aneurysm	3rd trimester
2	30	Caucasian	No	No	Venous sinus thrombosis with venous hemorrhage	PPD 10
3	31	Caucasian	Yes	Yes	Ruptured saccular aneurysm	PPD 12
4	19	African-American	No	No	Benign intracranial hemorrhage from presumed venous source	PPD 8
5	29	Caucasian	Yes	No	Venous sinus thrombosis with venous hemorrhage	2 weeks following In *In vitro* fertilization implantation
6	36	Hispanic	Yes	No	Benign intracranial hemorrhage from presumed venous source	3rd trimester
7	42	Hispanic	No	No	Benign intracranial hemorrhage from presumed venous source	PPD 6
8	32	Caucasian	Yes	No	Benign intracranial hemorrhage from presumed venous source	PPD 3
9	32	African-American	No	No	RCVS	PPD 9
10	42	Caucasian	No	Yes	Likely ruptured aneurysm	PPD 0, 1 h after Cesarean delivery
11	29	Caucasian	Yes	Yes	AVM	2nd trimester
12	30	Hispanic	No	No	Benign intracranial hemorrhage from presumed venous source	2nd trimester

A-Comm = anterior communicating; AVM = arteriovenous malformation; MCA = middle cerebral artery; N/V = nausea and vomiting; P-Comm = posterior communicating; PPD = postpartum day; PRES = posterior reversible encephalopathy syndrome; RCVS = reversible cerebral vasoconstrictive syndrome; SAH = subarachnoid hemorrhage; VA = vertebral artery; XRT = radiation therapy.

reported an increased risk of peri-delivery SAH did not differentiate between aneurysmal and nonaneurysmal SAH,[14] whereas the recent Dutch study that specifically examined aneurysmal SAH did not observe excess risk associated with pregnancy.[15] As such, the increased rate of SAH observed in the Swedish study may have been secondary to higher rates of nonaneurysmal SAH in the peri-delivery period. Our study makes the point that, in order to examine the risk of aneurysmal rupture associated with pregnancy and delivery, studies need to ensure that their method of ascertainment of SAH cases makes a distinction between aneurysmal and nonaneurysmal etiologies.

Risk Factors

As in the general population,[25,26] demographic factors that influenced the risk of pregnancy-related SAH in our cohort included race and age: pregnant African-American women were 3.3 times, and Hispanic women were 1.4 times, more likely to suffer a SAH than Caucasian women, after adjusting for other risk factors. It is unclear in our study if this disparity is because of differences in access and/or quality of peripartum care or other factors. There was also marked rise in the prevalence of SAH with increasing age: from 3.6 per 100,000 deliveries for women less than 25 yr old, to 11.3 per 100,000 deliveries for

Table 4. Continued

Symptoms of Presentation	Imaging Findings	Risk Factors	Treatment	Outcome	Time of Last Known Follow-up Post-SAH
Seizure, Glasgow coma scale 3	SAH with ventricular extension and 8 × 3 mm left P-Comm aneurysm	Age, race, severe preeclampsia	Surgical clipping of aneurysm	Alive at discharge, death post discharge day 7	7 d
Bilateral, throbbing headache, 8/10 in severity extending from neck to forehead	Small left parietal SAH, incidental left vertebral artery extra-dural dissection	Smoking	Medical management (anti-coagulation for VA dissection)	Living, intact	3.3 y
Headache, 8–10/10 in severity with neck pain	SAH with multiple aneurysms, including right superior hypophyseal artery, left ophthalmic artery, and fusiform aneurysm at junction of left P1 and P2	Smoking, preeclampsia, family history of ruptured aneurysm	Surgical clipping of aneurysm	Living, mild receptive aphasia	5.7 y
Abrupt onset of severe headache	Diffuse SAH within sylvian fissures and frontotemporal sulci bilaterally	Race, smoking	Medical management (calcium channel blockers)	Living, intact	3.5 y
Severe headache, N/V, blurred vision	Venous sinus thrombosis with SAH in the cerebellar hemispheres, parietal and temporal lobes, and frontal lobe	Previous venous sinus thrombosis	Medical management (Anticoagulation)	Living, intact	2.5 y
Severe hypertension, N/V followed by seizure	SAH scattered in frontal sulci and PRES	Age, race, preeclampsia, coagulopathy	Supportive	Living, muscle weakness	1.4 y
Severe headache, blurred vision followed by seizure	Localized sulcal SAH in left middle frontal region, PRES	Age, race, postpartum onset of preeclampsia	Supportive	Living, intact	7 d
Sudden onset of severe headache, bifronal, neck pain	Small SAH in left frontal region and right quadrigeminal cistern	None	Medical management (antiepileptics, calcium channel blockers)	Living, intact	7.7 y
Rapid onset of 10/10 headache, bilateral, photophobia, neck stiffness	SAH overlying left parietal and bifrontal lobes with significant vasospasm of right MCA, left MCA and bilateral A1 segments, no PRES	Race	Medical management (calcium channel blockers)	Living, intact	4.0 y
Sudden onset of worse headache of life, photophobia	SAH over the left frontal lobe with a small broad-based aneurysm at or just distal to the left ophthalmic artery	Age	Supportive (aneurysm surveillance)	Living, intact	2.8 y
10/10 frontal headache, N/V, neck pain	Small SAH including lateral and 3rd ventricles with associated AVM and right A-Comm aneurysm	None	Delayed XRT, AVM resection, surgical clipping of aneurysm	Living, intact	3.4 y
10/10 sudden onset headache, vomiting, neck pain	SAH in the sulci, along with extension into the right occipital horn of right lateral ventricle	Race	Supportive	Living, intact	3.8 y

women 35 to 44 yr old. This effect persisted after adjusting for other risk factors. Since the number of pregnancies in women of advanced maternal age is increasing,[27] SAH may have growing public health impact.

Tobacco abuse was the leading modifiable risk factor in our cohort, as it is in nonpregnancy-related SAH,[28–30] highlighting the importance of prenatal smoking cessation efforts. Likewise, drug and alcohol abuse, present in about 3% of SAH cases, are potentially modifiable risk factors that were independently associated with SAH.

Sickle cell disease, a rare risk factor for SAH in our study, may cause endothelial damage leading to aneurysm formation.[31] Intracranial venous thrombosis also exhibited a strong association with peripartum SAH both in the NIS and our institutional series. Intracranial venous thrombosis may cause SAH either through venous congestion leading to venous rupture or because of coagulopathy, as these patients may be anticoagulated. Hypercoagulable states likely cause SAH *via* similar mechanisms.

Hypertensive diseases of pregnancy were present in 40% of SAH cases and increased the risk of SAH seven-fold, likely secondary to a combination of hypertension-induced aneurysm rupture and, more commonly, pial vessel rupture.[7] This association underscores the need for appropriate blood pressure control in vulnerable pregnant patients. Recent investigation suggests treating systolic blood pressures in excess of

155–160 mmHg in the setting of preeclampsia/eclampsia spectrum disorders to prevent stroke.[32]

Although our analysis helps clinicians identify patients most at risk for SAH, a limitation of coding in administrative data are that all SAH etiologies must be considered together. There may be some difference in the type and magnitude of risk associated with certain conditions depending on the etiology of the SAH.

Pregnancy-related ICH (*i.e.*, intraparenchymal hemorrhage) has previously been studied using administrative data.[19] The rate of pregnancy-related ICH per 100,000 deliveries (6.1) was similar to our current data for SAH (5.8)††. As with SAH, the increased risk of ICH associated with pregnancy was primarily attributable to events in the postpartum period. They also exhibit some overlap in patient characteristics and comorbidities that are independent risk factors (including African-American race, hypertensive disorders, coagulopathy, and tobacco abuse). Although in-hospital mortality rate for pregnancy-related ICH was substantially higher than that of pregnancy-related SAH (20.3% *vs.* 10.3%), the shared risk factors and markedly increased postpartum incidence suggests potentially similar etiologies. This may be particularly true for nonaneurysmal SAH. It may be that the hemodynamic, coagulation-related, and other physiologic changes occurring at delivery and immediately postpartum predispose to both types of hemorrhage.

Clinical Presentation

Patients with peripartum SAH often present with postpartum headache.[33] As anesthesiologists typically do an initial evaluation of postpartum headache to rule out those related to dural puncture, an understanding of the presentation, risk factors, and implications of this disease is of clinical importance.

The acute onset and severity of these headaches and associated symptoms in SAH (table 4) differ from the often gradual onset, positional, "spinal" headaches. Prompt recognition of the possibility of a serious underlying neurologic etiology of a headache and referral of these patients to neurologists or neurosurgeons expeditiously is critical, as early intervention may prevent disability or death. Table 5 describes headache characteristics that suggest a serious underlying etiology.[34,35]

Limitations

Our study has several limitations. Although the NIS analysis allows estimation of incidence and risk factors from a large sample, it depends on administrative data that are de-identified and collected for billing purposes. Although studies suggest that the sensitivity and specificity of the ICD-9 CM codes for SAH is high,[17] we cannot confirm the diagnosis and associated comorbidities with chart review. Sometimes ICD-9 CM code 674.0× (cerebrovascular disorders of the puerperium) is recorded in the NIS without other codes that specify the nature of the disorder, and some SAH cases could have been classified with this code rather than 430, which would lead to underascertainment. Our identification of institutional cases is also largely dependent on billing coding, so these same limitations apply. Our calculation of incidence may be affected by out-of-hospital deliveries (not captured in the NIS) and the possibility that some SAH patients may be counted more than once if they transferred from one hospital to another. An additional limitation of NIS data are that there are important potential confounders (*e.g.*, history of previous SAH, known unruptured arteriovenous malformation or aneurysm, or family history of SAH) that lack associated ICD-9 CM codes or are grossly undercoded.

Table 5. Features of Headache Suggesting Serious Underlying Disorders

Character of the Headache
Acute onset of severe headache (seconds to minutes)
Lack of similar headache in the past
Progressively worsening or persistent headache*
Associated signs or symptoms
Focal neurological findings*
Decreased level of consciousness
Vomiting at onset of headache*
Syncope at onset of headache
Fever
Meningismus
Seizure

* If occurring in migraineur, may be concerning if different from that patient's typical migraine pattern.

Conclusion

Our study suggests that peripartum SAH includes a heterogeneous mix of etiologies and occurs most frequently in the postpartum period; it is less likely aneurysmal, and thus generally associated with a better prognosis, than nonpregnancy-related SAH. Although our study cannot directly address the question of whether aneurysm rupture is more frequent in pregnancy, it does suggest that studies examining this question should not utilize administrative data, as the mixture of aneurysmal and nonaneurysmal SAH captured with ICD 9 codes will cloud interpretation. As SAH (likely of the aneurysmal type) is a leading cause of indirect maternal mortality, future multi-institutional collaboration is needed to better clarify the risks of aneurysmal rupture associated with pregnancy.

The authors thank H. Christian Schumacher, M.D., Physician, Lehigh Neurology, Allentown, Pennsylvania, and Michael Lyon-Loftus, M.D., Resident, Weill Cornell Medical College, New York, New York, for valuable discussions and ideas regarding the use of the Nationwide Inpatient Sample to study subarachnoid hemorrhage.

†† The frequency of SAH in the 1993–2002 cohort of ICH admissions analyzed for the 2006 paper was 5.6%. For the current SAH study, which includes admissions from 1995 to 2008, 7.4% also had a diagnosis of ICH. The number of case admissions included in both studies, *i.e.*, that had both SAH and ICH from 1995–2002, the period of study period overlap between the papers, is 16.

References

1. Kanani N, Goldszmidt E: Postpartum rupture of an intracranial aneurysm. Obstet Gynecol 2007; 109:572–4
2. Darbhamulla SV, Reddy R: Subarachnoid haemorrhage in pregnancy. J Obstet Gynaecol 2007; 27:80–1
3. Dias MS, Sekhar LN: Intracranial hemorrhage from aneurysms and arteriovenous malformations during pregnancy and the puerperium. Neurosurgery 1990; 27:855–65; discussion 865–6
4. Jaigobin C, Silver FL: Stroke and pregnancy. Stroke 2000; 31:2948–51
5. Powell S, Rijhsinghani A: Ruptured bacterial intracranial aneurysm in pregnancy. A case report. J Reprod Med 1997; 42:455–8
6. Ko YP, Hsu CY, Yang CL, Cheng SJ, Tsai HJ, Chen CP, Hsu YW: Postcesarean subarachnoid hemorrhage as the initial presentation of cerebral venous thrombosis. Taiwan J Obstet Gynecol 2007; 46:317–9
7. Shah AK: Non-aneurysmal primary subarachnoid hemorrhage in pregnancy-induced hypertension and eclampsia. Neurology 2003; 61:117–20
8. Tuluc M, Brown D, Goldman B: Lethal vertebral artery dissection in pregnancy: A case report and review of the literature. Arch Pathol Lab Med 2006; 130:533–5
9. Matsumoto Y, Asada M, Mukubou M: Postpartum subarachnoid hemorrhage due to Moyamoya disease associated with renal artery stenosis. J Obstet Gynaecol Res 2009; 35:787–9
10. Servillo G, Striano P, Striano S, Tortora F, Boccella P, De Robertis E, Rossano F, Briganti F, Tufano R: Posterior reversible encephalopathy syndrome (PRES) in critically ill obstetric patients. Intensive Care Med 2003; 29:2323–6
11. Singhal AB: Postpartum angiopathy with reversible posterior leukoencephalopathy. Arch Neurol 2004; 61:411–6
12. Moussouttas M, Abubakr A, Grewal RP, Papamitsakis N: Eclamptic subarachnoid haemorrhage without hypertension. J Clin Neurosci 2006; 13:474–6
13. Ursell MR, Marras CL, Farb R, Rowed DW, Black SE, Perry JR: Recurrent intracranial hemorrhage due to postpartum cerebral angiopathy: Implications for management. Stroke 1998; 29:1995–8
14. Salonen Ros H, Lichtenstein P, Bellocco R, Petersson G, Cnattingius S: Increased risks of circulatory diseases in late pregnancy and puerperium. Epidemiology 2001; 12:456–60
15. Tiel Groenestege AT, Rinkel GJ, van der Bom JG, Algra A, Klijn CJ: The risk of aneurysmal subarachnoid hemorrhage during pregnancy, delivery, and the puerperium in the Utrecht population: Case-crossover study and standardized incidence ratio estimation. Stroke 2009; 40:1148–51
16. Lewis G: The Confidential Enquiry into Maternal and Child Health. Saving mothers' lives: Reviewing maternal deaths to make motherhood safer – 2003–2005. The 7th report of the Confidential Enquiries into Maternal Deaths in the UK. London, CEMACH, 2007
17. Tirschwell DL, Longstreth WT Jr: Validating administrative data in stroke research. Stroke 2002;33:2465–70
18. Kittner SJ, Stern BJ, Feeser BR, Hebel R, Nagey DA, Buchholz DW, Earley CJ, Johnson CJ, Macko RF, Sloan MA, Wityk RJ, Wozniak MA: Pregnancy and the risk of stroke. N Engl J Med 1996; 335:768–74
19. Bateman BT, Schumacher HC, Bushnell CD, Pile-Spellman J, Simpson LL, Sacco RL, Berman MF: Intracerebral hemorrhage in pregnancy: Frequency, risk factors, and outcome. Neurology 2006; 67:424–9
20. Main EK: Maternal mortality: New strategies for measurement and prevention. Curr Opin Obstet Gynecol 2010; 22:511–6
21. Berman MF, Stapf C, Sciacca RR, Young WL: Use of ICD-9 coding for estimating the occurrence of cerebrovascular malformations. AJNR Am J Neuroradiol 2002; 23:700–5
22. Witlin AG, Friedman SA, Egerman RS, Frangieh AY, Sibai BM: Cerebrovascular disorders complicating pregnancy–beyond eclampsia. Am J Obstet Gynecol 1997; 176:1139–45
23. Liang CC, Chang SD, Lai SL, Hsieh CC, Chueh HY, Lee TH: Stroke complicating pregnancy and the puerperium. Eur J Neurol 2006; 13:1256–60
24. de Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ: Incidence of subarachnoid haemorrhage: A systematic review with emphasis on region, age, gender and time trends. J Neurol Neurosurg Psychiatry 2007; 78:1365–72
25. Broderick JP, Brott T, Tomsick T, Huster G, Miller R: The risk of subarachnoid and intracerebral hemorrhages in blacks as compared with whites. N Engl J Med 1992; 326:733–6
26. Eden SV, Meurer WJ, Sánchez BN, Lisabeth LD, Smith MA, Brown DL, Morgenstern LB: Gender and ethnic differences in subarachnoid hemorrhage. Neurology 2008; 71:731–5
27. Ventura SJ, Abma JC, Mosher WD, Henshaw SK: Estimated pregnancy rates for the United States, 1990–2005: An update. Natl Vital Stat Rep 2009; 58:1–14
28. Sandvei MS, Romundstad PR, Müller TB, Vatten L, Vik A: Risk factors for aneurysmal subarachnoid hemorrhage in a prospective population study: The HUNT study in Norway. Stroke 2009; 40:1958–62
29. Feigin V, Parag V, Lawes CM, Rodgers A, Suh I, Woodward M, Jamrozik K, Ueshima H; Asia Pacific Cohort Studies Collaboration: Smoking and elevated blood pressure are the most important risk factors for subarachnoid hemorrhage in the Asia-Pacific region: An overview of 26 cohorts involving 306,620 participants. Stroke 2005; 36:1360–5
30. Anderson CS, Feigin V, Bennett D, Lin RB, Hankey G, Jamrozik K; Australasian Cooperative Research on Subarachnoid Hemorrhage Study (ACROSS) Group: Active and passive smoking and the risk of subarachnoid hemorrhage: An international population-based case-control study. Stroke 2004; 35:633–7
31. Brandão RA, de Carvalho GT, Reis BL, Bahia E, de Souza AA: Intracranial aneurysms in sickle cell patients: Report of 2 cases and review of the literature. Surg Neurol 2009; 72:296–9
32. Martin JN Jr, Thigpen BD, Moore RC, Rose CH, Cushman J, May W: Stroke and severe preeclampsia and eclampsia: A paradigm shift focusing on systolic blood pressure. Obstet Gynecol 2005; 105:246–54
33. Stella CL, Jodicke CD, How HY, Harkness UF, Sibai BM: Postpartum headache: Is your work-up complete? Am J Obstet Gynecol 2007; 196:318.e1–7
34. Ward TN, Levin M, Phillips JM: Evaluation and management of headache in the emergency department. Med Clin North Am 2001; 85:971–85
35. Friedman BW, Lipton RB: Headache in the emergency department. Curr Pain Headache Rep 2011; 15:302–07