Risk Factors for Peripartum and Postpartum Stroke and Intracranial Venous Thrombosis

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Background and Purpose—The study goal was to identify potential risk factors for peripartum or postpartum stroke and intracranial venous thrombosis.

Methods—Data from the Healthcare Cost and Utilization Project were analyzed for the years 1993 and 1994. Observed values were weighted with poststratification discharge weights to project to the universe of all discharges from community hospitals located in the United States. Nationally representative estimates of risk were calculated on the basis of age, race, mode of delivery, income, third-party payer, hospital size, hospital ownership, hospital location (rural versus urban), hospital teaching status, census region, and presence of specific complications. Multivariate models were developed with the use of logistic regression.

Results—Among 1 408 015 sampled deliveries, there were 183 observed cases of peripartum stroke and 170 cases of peripartum intracranial venous thrombosis in 17 states in the United States in 1993 and 1994. There were an estimated 975 cases of stroke and 864 cases of intracranial venous thrombosis during pregnancy and the puerperium in the United States among 7 463 712 deliveries during 1993 and 1994, for estimated risks of 13.1 cases of peripartum stroke and 11.6 cases of peripartum intracranial venous thrombosis per 100 000 deliveries. Multivariate analysis showed that the following were strongly and significantly associated with both peripartum and postpartum stroke: cesarean delivery; fluid, electrolyte, and acid-base disorders; and hypertension. Covariates that were strongly and significantly associated with both peripartum and postpartum intracranial venous thrombosis included cesarean delivery, hypertension, and infections other than pneumonia and influenza.

Conclusions—Pregnancy-related hypertension and cesarean delivery are important risk factors for both stroke or intracranial venous thrombosis. **(*Stroke*. 2000;31:1274-1282.)**

Key Words: cerebrovascular disorders ■ epidemiology ■ pregnancy ■ puerperium ■ risk factors

With few exceptions,[1–4] most previous suggestions of potential risk factors for peripartum stroke and intracranial venous thrombosis (IVT) have come from tabulations of covariates among uncontrolled case series.[5,6] Potential risk factors for peripartum stroke and IVT were evaluated in an analysis of US National Hospital Discharge Survey data for the period of 1979 to 1991.[2] The study identified an increased risk of peripartum stroke in nonwhite women, in women with cesarean delivery, in women with pregnancy-related hypertension, and in women who delivered in large and proprietary hospitals.[2] The study also identified an increased risk of peripartum IVT in younger women and in women with cesarean delivery.[2] In multivariate models adjusted for age and race, hypertension remained a strong and significant predictor of peripartum stroke, and cesarean delivery remained strongly associated with both peripartum stroke and IVT.[2] This study, however, sampled only a small number of patients, spanned a large period of time, and did not separately evaluate postpartum events, so it was not clear whether the association of the cerebrovascular events with cesarean delivery was due to an increased risk of such events after cesarean delivery or instead due to an increased cesarean delivery rate in those who had an antepartum stroke or IVT.[2]

In a subsequent study, the analysis of the US National Hospital Discharge Survey data was expanded to include the entire period of pregnancy and the puerperium for the period of 1979 to 1991.[3] Collectively, rates for stroke and IVT were approximately 50% greater for the entire period of pregnancy and the puerperium than for the immediate peripartum period.[3] This study confirmed an increased risk of peripartum stroke in women with pregnancy-related hypertension and in women who delivered in large and proprietary hospitals[3]; in addition, it confirmed an increased risk of peripartum IVT in younger women.[3] Further exploratory analyses[7] identified an association between excessive vomiting in pregnancy and IVT during pregnancy and the puerperium and identified several other comorbid conditions associated with stroke during pregnancy and the puerperium, including infections, cardiomyopathy, and congestive heart failure. It was not possible to evaluate the association of cesarean delivery and

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cerebrovascular events in this study,[3] because data on the mode of delivery were not available for cerebrovascular events that occurred during pregnancy or puerperium but separate from the hospitalization for delivery.

The present report provides nationally representative estimates of the incidence of peripartum stroke and IVT in the United States for the period of 1993 to 1994 with the use of data from the Healthcare Cost and Utilization Project (HCUP-3). In addition, we present univariate and multivariate analyses of associations between stroke or IVT and various covariates during the peripartum and early postpartum periods.

Materials and Methods

HCUP-3 is a federal, state, and industry partnership to assemble health care data for use in health services research and health policy analysis. The information presented here is based on data from the HCUP-3 Nationwide Inpatient Sample (NIS) Releases 2 and 3, which are based on all discharges from a 20% sample of US community hospitals in 17 states for 1993 and 1994, respectively. NIS Releases 2 and 3 include all discharge records from hospitals selected through a stratified, single-stage cluster design. Collectively, they contain data from 12 923 987 inpatient records and 1 408 015 deliveries from 900 hospitals for the states Arizona, California, Colorado, Connecticut, Florida, Illinois, Iowa, Kansas, Maryland, Massachusetts, New Jersey, New York, Oregon, Pennsylvania, South Carolina, Washington, and Wisconsin. The NIS is the largest source of discharge-level information for hospital inpatients, regardless of payer, in the United States, and unlike other commonly used databases, it includes all payers and all age groups.

The sampling frame is limited to community hospitals, as defined by the American Hospital Association Annual Survey of Hospitals, from states participating in HCUP-3. Hospital sampling probabilities are proportional to the number of US community hospitals in each stratum, with strata based on a combination of 5 characteristics: region (ie, northeast, south, midwest, and west), location (urban or rural), teaching status, ownership/control (ie, government, nonfederal, and private, not for profit; private, investor owned), and bed size (ie, small, medium, and large, varying by location and teaching status).

Inpatient stay records include clinical and resource use information typically available from discharge abstracts. NIS Releases 2 and 3 contain information on >100 variables, including patient demographic characteristics, median income for patient's area of residence, expected source of payment, diagnoses and procedures, admission and discharge status, length of stay, and hospital characteristics.

NIS Releases 2 and 3 also provide discharge weights, which were calculated through poststratification to project to the universe of all discharges from community hospitals located in the United States. Hospitals were stratified on the same variables that were used for sampling: geographic region, urban/rural location, teaching status, bed size, and ownership. The final weight of each discharge is equal to the number of universe discharges represented in the corresponding stratum during the calendar year. Weighing the sample data by the final discharge weights produces national estimates. More detailed data on the design of the survey and the magnitude of sampling errors associated with the estimates are available in the technical documentation.[8,9]

Case Selection

Cases were identified from the abstracted discharge diagnoses when 1 of the 7 possible discharge diagnoses codes was either (1) *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM)[10] rubric 674.0 ("cerebrovascular disorders in the puerperium"), which includes any condition classifiable to "cerebrovascular disorders" (rubrics 430 to 434, 436 to 437), but occurring during pregnancy, childbirth, or the puerperium, or (2) ICD-9-CM rubric 671.5 ("other phlebitis and thrombosis" as complications of the puerperium), which includes cerebral venous thrombosis and thrombosis of intracranial venous sinuses.

In this report, cases coded to rubric 674.0 are designated "stroke," and cases coded to rubric 671.5 are designated "intracranial venous thrombosis." Stroke includes subarachnoid and intracerebral hemorrhage and ischemic stroke. No further breakdown into stroke types is possible because of limitations of the ICD-9-CM disease classification system: in ICD-9-CM, rubric 674.0 is not further categorized, and the general cerebrovascular rubrics (430 to 438) exclude conditions occurring during pregnancy, childbirth, or the puerperium.

Deliveries were identified if either (1) 1 of the discharge diagnoses was coded to ICD-9-CM rubric category V27 ("outcome of delivery"), which codes the outcome of delivery on the mother's record and serves as an indicator that the hospitalization was the hospitalization of delivery and not a separate prenatal or postnatal hospitalization, or (2) 1 of the 4 possible procedure codes was 1 of the ICD-9-CM rubrics from 72.x to 74.0, which collectively code various delivery procedures.

Because the HCUP-3 database excludes unique person identifiers, it is not possible to link medical records over time. Thus, information from the hospitalization of delivery, including mode of delivery (cesarean or vaginal delivery), could not be linked with events that occurred either before or after the delivery hospitalization. Because an evaluation of mode of delivery was a major interest based on previous results,[2] we restricted case selection to the hospitalization of delivery for this study. The peripartum period for purposes of this study was the period of the hospitalization of delivery, and the early postpartum period was the period from delivery to hospital discharge. Postpartum events were identified by the fifth digit subclassification of complications related to pregnancy in the ICD-9-CM classification system.

Cases and deliveries were restricted to the age range of 15 to 44 years.

Demographics, Comorbidities, and Surgical Complications

Data elements available in the NIS include age, sex, race, median household income of patient's zip code, expected source of payment, hospital size and characteristics, disposition of patient, and diagnosis and procedure codes. Information on selected comorbid conditions[3,7] was derived from diagnosis codes as follows, with ICD-9-CM rubrics in parentheses: diabetes mellitus (250, 648.0), disorders of fluid, electrolyte, and acid-base balance (276), rheumatic fever and valvular heart disease (390 to 398, 421, 424), hypertension (401 to 405, 642), cardiomyopathy (425), heart failure (428), pneumonia and influenza (480 to 487), other infections (001 to 139, 320 to 324, 382 to 383, 421, 460 to 466, 475, 478.12, 478.22, 478.24, 479.29, 499.0, 522.0, 522.4 to 522.7, 523.0, 523.3 to 523.4, 526.4, 526.6, 527.2 to 527.3, 528.0 to 528.3), and excessive vomiting in pregnancy (643).

Statistical Analyses

Risks of each type of event were calculated as the estimated number of discharges with each condition among the estimated number of deliveries at the sampled hospitals. The estimation procedure involved an inflation of counts of sampled patient abstracts by the poststratification weight, with adjustments for nonresponding hospitals and missing abstracts and adjustments for oversampling or undersampling of discharges reported in the sampling frame for each data year. Standard errors and 95% CI values were computed for the estimated risks. CIs for incidence rates were based on an asymptotic normal approximation to the binomial applied to the weighted case counts. CIs for the case fatality rates were based on a large-sample Taylor's series approximation for a ratio of 2 proportions, with each based on weighted counts. In the case of a zero case fatality, one half was added to the zero frequency to apply this approximation.

Statistical significance for univariate analyses was assessed using the χ^2 statistic with the weighted counts normalized to the total sample size for each year. Weighted counts normalized to the total sample size means that each weight was first divided by the sum of the weights across the sample and then multiplied by the total sample size. Basing the analysis on the original weights would have created an artificially large sample size (equal to the sum of the weights) in which all effects, no matter how trivially small, would be improperly determined to be statistically significant. When cell frequencies were <5, probability values were based on Fisher's exact test applied to the unweighted counts.

The log odds of each of the types of events were regressed on all independent variables with the use of a series of logistic regression models. All independent variables were treated as categorical variates with appropriate dummy variables used to contrast the different levels of these variables. The base level for a categorical variable was chosen to demonstrate the significant comparisons among the levels of that variable. To account for the sampling design, observations in the logistic regression models were weighted by the number of universe discharges represented by the corresponding stratum.

All computations were made with the frequency, logistic, and generalized linear model procedures in PC-SAS version 6.12 for Windows (SAS Institute Inc). Robustness of reported standard errors was determined with the Surveymeans procedure in the not yet officially released version 8.0 of PC-SAS (SAS Institute Inc). Statistical significance for all univariate and multivariate analyses was determined at the $P<0.01$ level. When reporting significance levels, $\ll$ is used to indicate "much less than."

Results

There were 183 observed cases of peripartum stroke and 170 cases of peripartum IVT in the sample from among 1 408 015 sampled deliveries, for observed risks of 13.0 cases of stroke, 12.1 cases of IVT, and 25.1 cases of either outcome per 100 000 deliveries. Based on the sampling scheme of the HCUP-3, we estimate that during the 2 years from 1993 to 1994, there were 975 cases of peripartum stroke and 864 cases of peripartum IVT during pregnancy and the puerperium among 7 463 712 deliveries in the United States. This yielded nationally representative risks (expressed as cases per 100 000 deliveries) of 13.1 for stroke (95% CI 11.2 to 15.0), 11.6 for IVT (95% CI 9.8 to 13.4), and 24.6 for either outcome (95% CI 22.0 to 27.2).

Among the 183 patients with stroke, 133 (72.7%) were discharged routinely; 8 (4.4%) were discharged to another short-term hospital; 10 (5.5%) were discharged to skilled nursing, intermediate care, or other facility; 2 (1.1%) were discharged to home health care; 1 (0.5%) left against medical advice; and 29 (15.8%) died. Among the 170 patients with IVT, 159 (93.5%) were discharged routinely; none were discharged to another short-term hospital; 1 (0.6%) was discharged to skilled nursing, intermediate care, or other facility; 9 (5.3%) were discharged to home health care; 1 (0.6%) left against medical advice; and none died. Estimated nationally representative in-hospital case fatality rates were 14.7% for stroke (95% CI 11.8% to 17.6%), 0.0% for IVT (95% CI 0.0% to 0.9%), and 7.8% overall (95% CI 6.1% to 9.5%).

Of the 353 observed cases of peripartum stroke or IVT, 2 (0.6%) occurred antepartum, 152 (43.1%) occurred postpartum, and 199 (56.4%) were not specified as to the time of delivery. For the 183 observed cases of peripartum stroke, 2 (1.1%) occurred antepartum, 65 (35.5%) occurred postpartum, and 116 (63.4%) were not specified as to the time of delivery. For the 170 observed cases of peripartum IVT, none occurred antepartum, 87 (51.2%) occurred postpartum, and 83 (48.8%) were not specified as to the time of delivery. The differences in the proportions of antepartum, postpartum, and unspecified cases for stroke and cerebral venous thrombosis were significant ($P=0.003$).

Risks of stroke and IVT on the basis of various covariates are given in Table 1 for peripartum events. The risk of peripartum stroke increased with increasing maternal age ($P<0.001$), cesarean delivery ($P\ll0.001$), and urban hospital location ($P=0.002$) and in the presence of several comorbid conditions: fluid, electrolyte, and acid-base disorders ($P\ll0.001$); rheumatic fever and valvular heart disease ($P\ll0.001$); hypertension ($P\ll0.001$); cardiomyopathy ($P=0.03$); heart failure ($P\ll0.001$); pneumonia and influenza ($P<0.001$); and excessive vomiting in pregnancy ($P=0.009$). The risk of peripartum IVT increased with increasing maternal age ($P\ll0.001$), increasing hospital size ($P=0.006$), northeast census region hospitals ($P=0.002$), cesarean delivery ($P\ll0.001$), and in the presence of several comorbid conditions: hypertension ($P\ll0.001$), infections other than pneumonia and influenza ($P\ll0.001$), and excessive vomiting in pregnancy ($P=0.008$).

Significant univariate risk factors in early postpartum women (ie, occurring postpartum but during the hospitalization of delivery) were similar to those for all peripartum women (not shown). The risk of postpartum stroke was increased in blacks ($P<0.001$), with cesarean delivery ($P\ll0.001$), and in the presence of several comorbid conditions: fluid, electrolyte, and acid-base disorders ($P\ll0.001$); hypertension ($P\ll0.001$); heart failure ($P=0.01$); and pneumonia and influenza ($P=0.002$). The risk of postpartum IVT increased with increasing maternal age ($P\ll0.001$), in northeast census region hospitals ($P<0.001$), with cesarean delivery ($P\ll0.001$), and in the presence of comorbid conditions: hypertension ($P\ll0.001$) and infections other than pneumonia and influenza ($P\ll0.001$).

The results of the multivariate logistic regression modeling for peripartum stroke and IVT are summarized in Table 2. Covariates that were both strongly and significantly associated with peripartum stroke included cesarean delivery; fluid, electrolyte, and acid-base disorders; valvular heart disease; hypertension; and excessive vomiting in pregnancy. Covariates that were both strongly and significantly associated with peripartum IVT included older age, cesarean delivery, hypertension, infections other than pneumonia and influenza, and excessive vomiting in pregnancy.

The results of the multivariate logistic regression modeling for postpartum stroke and IVT were similar (not shown). Covariates that were both strongly and significantly associated with postpartum stroke included cesarean delivery; fluid, electrolyte, and acid-base disorders; and hypertension. Covariates that were both strongly and significantly associated with peripartum IVT included cesarean delivery, hypertension, and infections other than pneumonia and influenza. The use of unweighted logistic regression produced results almost identical to those reported earlier with weighted logistic regression. Because of the smaller sample sizes, some covari-

TABLE 1. Risk of Peripartum Cerebrovascular Events per 100 000 Deliveries in the United States as Estimated From the US Healthcare Cost and Utilization Project, 1993–1994

Factor	Stroke*	Intracranial Venous Thrombosis*	Total*
All	13.1 (183)	11.6 (170)	24.6 (353)
Age group, y			
15–24	11.4 (59)	7.9 (43)	19.3 (102)
25–34	10.7 (85)	11.2 (85)	22.9 (170)
35–44	24.4 (39)	24.9 (42)	49.3 (81)
	$P<0.001$	$P\ll0.001$	$P<0.001$
Race			
White	12.3 (81)	10.8 (75)	23.1 (156)
Black	20.7 (38)	12.2 (23)	32.9 (61)
Hispanic	14.2 (23)	10.7 (19)	24.9 (42)
Other	13.6 (10)	21.7 (16)	35.4 (26)
	$P=0.06$	$P=0.10$	$P=0.05$
Income by zip code			
<$25 000	13.7 (60)	11.4 (52)	25.1 (112)
$25 001–30 000	14.8 (40)	9.0 (25)	23.8 (65)
$30 001–35 000	12.0 (25)	13.8 (31)	25.8 (56)
>$35 000	10.7 (47)	12.7 (58)	23.4 (105)
	$P=0.43$	$P=0.40$	$P=0.92$
Payer			
Government	14.2 (75)	10.3 (58)	24.5 (133)
Insurance	12.9 (96)	13.2 (102)	26.0 (198)
Other	9.5 (11)	7.3 (9)	16.8 (15)
	$P=0.44$	$P=0.13$	$P=0.18$
Cesarean delivery			
No	7.1 (79)	7.4 (86)	14.5 (165)
Yes	34.3 (104)	26.6 (84)	60.9 (188)
	$P\ll0.001$	$P\ll0.001$	$P\ll0.001$
Diabetes mellitus			
No	13.1 (182)	11.6 (169)	24.6 (351)
Yes	13.5 (1)	11.4 (1)	24.9 (2)
	$P=0.97$	$P=0.99$	$P=0.99$
Fluid, electrolyte, and acid-base disorders			
No	12.1 (170)	11.6 (169)	23.7 (339)
Yes	346.3 (13)	11.3 (1)	357.5 (14)
	$P\ll0.001$	$P=0.98$	$P\ll0.001$
Rheumatic fever and valvular heart disease			
No	12.4 (173)	11.6 (168)	24.0 (341)
Yes	98.3 (10)	12.7 (2)	111.0 (12)
	$P\ll0.001$	$P=0.91$	$P<0.001$
Hypertension			
No	8.7 (114)	10.6 (147)	19.3 (261)
Yes	80.0 (69)	27.1 (23)	107.1 (92)
	$P\ll0.001$	$P\ll0.001$	$P\ll0.001$

TABLE 1, continued

Factor	Stroke*	Intracranial Venous Thrombosis*	Total*
Cardiomyopathy			
No	13.0 (217)	11.6 (170)	24.6 (352)
Yes	378.7 (1)	0.0 (0)	378.7 (1)
	$P=0.001$	$P=0.87$	$P=0.001$
Heart failure			
No	12.9 (180)	11.6 (170)	24.5 (280)
Yes	916.7 (3)	0.0 (0)	916.7 (3)
	$P\ll0.001$	$P=0.86$	$P\ll0.001$
Pneumonia and influenza			
No	12.9 (180)	11.5 (169)	24.4 (349)
Yes	214.4 (3)	79.4 (1)	293.8 (4)
	$P\ll0.001$	$P=0.021$	$P<0.001$
Other infections			
No	13.1 (179)	10.8 (152)	23.9 (331)
Yes	10.1 (4)	39.4 (18)	49.5 (22)
	$P=0.60$	$P\ll0.001$	$P=0.001$
Excessive vomiting			
No	12.9 (181)	11.5 (168)	24.4 (349)
Yes	200.0 (2)	165.8 (2)	365.8 (4)
	$P\ll0.001$	$P\ll0.001$	$P\ll0.001$
Hospital size			
Small	8.6 (13)	4.7 (8)	13.3 (21)
Medium	11.5 (52)	10.4 (50)	21.9 (102)
Large	14.8 (118)	13.7 (112)	28.5 (230)
	$P=0.08$	$P=0.006$	$P<0.001$
Hospital ownership			
Government	12.2 (27)	13.4 (35)	25.6 (62)
Not for profit	13.4 (144)	11.9 (130)	25.2 (274)
Private	12.6 (12)	5.0 (5)	17.6 (17)
	$P=0.88$	$P=0.12$	$P=0.35$
Hospital location			
Rural	5.6 (7)	8.4 (15)	14.0 (22)
Urban	14.3 (176)	12.1 (155)	26.4 (331)
	$P=0.002$	$P=0.17$	$P=0.002$
Teaching status			
Nonteaching	11.3 (103)	10.5 (100)	21.8 (203)
Teaching	16.5 (80)	13.7 (70)	30.2 (150)
	$P=0.01$	$P=0.09$	$P=0.003$
Region			
Northeast	13.0 (36)	18.0 (53)	30.9 (89)
Midwest	9.8 (34)	11.4 (39)	21.2 (73)
South	16.4 (73)	11.3 (53)	27.7 (126)
West	12.0 (40)	7.2 (25)	19.2 (65)
	$P=0.069$	$P=0.002$	$P=0.008$

*The number of unweighted cases in the sample is given in parentheses after the estimates of risk determined with weighted frequencies.

TABLE 2. Summary of the Multivariate Logistic Models for Peripartum Cerebrovascular Events as Estimated From the US Healthcare Cost and Utilization Project, 1993–1994

	Stroke		Intracranial Venous Thrombosis		Combined Events	
Regressor	OR	95% CI	OR	95% CI	OR	95% CI
Age group, y						
15–24 vs 35–44	0.61*	0.39, 0.94	0.40†	0.25, 0.63	0.50‡	0.36, 0.69
25–34 vs 35–44	0.60†	0.41, 0.88	0.50‡	0.34, 0.73	0.55‡	0.42, 0.72
Payer						
Government vs other	1.54	0.81, 2.92	1.62	0.78, 3.38	1.59	0.98, 2.58
Insurance vs other	1.17	0.62, 2.22	1.65	0.81, 3.37	1.38	0.86, 2.23
Cesarean delivery						
Yes vs no	3.56‡	2.62, 4.83	3.10‡	2.26, 4.24	3.33‡	2.67, 4.15
Fluid, electrolyte, and acid-base disorders						
Yes vs no	7.39‡	4.01, 13.62	0.35	0.02, 7.06	4.58‡	2.56, 8.18
Rheumatic fever and valvular heart disease						
Yes vs no	5.67‡	2.96, 10.86	0.80	0.15, 4.38	3.32‡	1.83, 6.00
Hypertension						
Yes vs no	6.08†	4.44, 8.32	1.93†	1.23, 3.01	3.87‡	3.02, 4.96
Heart failure						
Yes vs no	3.76	0.86, 16.43	. . .	. . ., . . .	3.19	0.77, 13.29
Pneumonia and influenza						
Yes vs no	3.08	0.87, 10.90	3.45	0.51, 23.40	3.20*	1.12, 9.16
Other infections						
Yes vs no	0.52	0.19, 1.41	3.10‡	1.83, 5.24	1.55	0.98, 2.45
Excessive vomiting						
Yes vs no	8.60†	2.15, 34.47	14.25‡	3.19, 63.68	9.55‡	3.41, 26.77
Hospital size						
Small vs large	0.64	0.36, 1.13	0.39*	0.19, 0.83	0.53*	0.33, 0.83
Medium vs large	0.78	0.55, 1.10	0.78	0.54, 1.11	0.78	0.60, 1.00
Hospital owner						
Government vs private	0.90	0.44, 1.83	2.59	0.97, 6.92	1.39	0.79, 2.44
Nonprofit vs private	1.09	0.59, 2.02	1.79	0.70, 4.54	1.29	0.78, 2.16
Hospital location						
Urban vs rural	2.25*	1.17, 4.34	1.34	0.77, 2.35	1.71*	1.12, 2.61
Teaching hospital						
Yes vs no	1.31	0.94, 1.82	1.11	0.78, 1.57	1.22	0.95, 1.53
Region						
Northeast vs west	1.20	0.74, 1.94	0.49†	0.30, 0.83	0.78	0.56, 1.11
Midwest vs west	0.96	0.59, 1.56	0.78	0.51, 1.20	0.86	0.63, 1.19
South vs west	1.45	0.94, 2.23	0.67	0.43, 1.03	1.00	0.74, 1.34

*$P<0.05$.
†$P<0.01$.
‡$P<0.001$.

ates that were significantly associated with peripartum cerebrovascular events may not have been significant when only postpartum cases were considered.

Cesarean delivery was a strong and highly significant predictor ($P \ll 0.001$) of both stroke (peripartum OR 3.56, 95% CI 2.62 to 4.83; postpartum OR 2.40, 95% CI 1.45 to 3.99) and IVT (peripartum OR 3.10, 95% CI 2.26 to 4.24; postpartum OR 4.01, 95% CI 2.56 to 6.28). Hypertension was also a strong and highly significant predictor ($P \ll 0.001$) of both stroke (peripartum OR 6.08, 95% CI 4.44 to 8.32; postpartum OR 13.95, 95% CI 8.38 to 23.22) and IVT (peripartum OR 1.93, 95% CI 1.23 to 3.01; postpartum OR

TABLE 3. US Population-Based Epidemiological Studies of Stroke and Intracranial Venous Thrombosis in Pregnancy and Puerperium: Risk per 100 000 Deliveries

Authors	Years of Study	Pregnancies, n	Stroke	Intracranial Venous Thrombosis	Total
Wiebers and Whisnant, 1985	1955–1979	26 099	3.8 (1)	0.0 (0)	3.8 (1)
Simolke et al, 1991	1984–1990	89 913	13.3 (12)*	2.2 (2)	15.5 (14)
Kittner et al, 1996	1988–1991	141 243	21.2 (30)	0.7 (1)	21.9 (31)
Lanska and Kryscio, 1997	1979–1991	280 096†	10.3 (28)‡	8.9 (21)‡	19.2 (49)‡
Witlin et al, 1997	1985–1995	79 301	13.9 (11)	11.3 (9)	25.2 (20)
Lanska and Kryscio, 1998	1979–1991	281 116§	17.7 (54)‖	11.4 (31)‖	29.1 (85)‖
Lanska and Kryscio, 1999	1993–1994	1 408 015§	13.1 (187)‡	11.6 (170)‡	24.6 (357)‡

*Cases include 2 with subarachnoid hemorrhage and 4 with other intracranial hemorrhage.

One case of retinal infarction was not included here. Reported risk includes 3 cases that occurred outside the hospitalization of delivery.

†Deliveries determined by discharge diagnosis code ICD-9 CM V27, outcome of delivery.

‡Patients based on hospitalization of delivery and represent peripartum events only.

§Deliveries determined by discharge diagnosis code ICD-9 CM V27 or procedure codes ICD-9 CM 72.x to 74.x.

‖Patients based on all antepartum, peripartum, and postpartum events.

2.42, 95% CI 1.37 to 4.29). Among the 69 hypertensive peripartum stroke patients, 4 had essential hypertension, 1 had renovascular hypertension, 7 had gestational hypertension, 36 had preeclampsia, 14 had eclampsia, and 7 had eclampsia or preeclampsia superimposed on preexisting hypertension; among the 23 hypertensive peripartum IVT patients, 2 had essential hypertension, 7 had gestational hypertension, 9 had preeclampsia, 1 had eclampsia, 1 had preeclampsia or eclampsia superimposed on preexisting hypertension, and 3 had unspecified hypertension. Thus, peripartum stroke patients were more likely to have preeclampsia or eclampsia as the reported cause of hypertension than were peripartum IVT patients (82.6% versus 47.8%, respectively; OR 5.2, 95% CI 1.9 to 14.5; $P=0.001$). Similarly, among the 36 postpartum stroke patients, 6 had gestational hypertension, 19 had preeclampsia, 9 had eclampsia, and 2 had preeclampsia or eclampsia superimposed on preexisting hypertension; among the 15 postpartum IVT patients, 1 had essential hypertension, 5 had gestational hypertension, 5 had preeclampsia, 1 had eclampsia, and 3 had unspecified hypertension. Postpartum stroke patients were more likely to have preeclampsia or eclampsia as the reported cause of hypertension than were postpartum IVT patients (83.3% versus 40.0%, respectively; OR 7.5, 95% CI 1.9 to 29.1; $P=0.005$).

Discussion

The overall risk of 13.1 peripartum strokes per 100 000 deliveries in the United States for 1993 to 1994 is similar to the rate of 10.3 reported in a previous study with US National Hospital Discharge Survey data for the period of 1979 to 1991.[2] Both values are within the range of 3.8 to 62.5 reported in previous studies (see Table 3 for population-based studies).[1,2,5,11,12] Some of the variability reflects different study designs (eg, not all were population based), the incorporation of different subgroups of patients, inadequate ascertainment in some cases, inadequate consideration of referral bias, and small sample sizes. Similarly, the risk of 11.6 cases of peripartum IVT per 100 000 deliveries is similar to the value of 8.9 reported in the previous study with US National Hospital Discharge Survey data for the period of 1979 to 1991.[2] Both values are within the wide range of estimates reported in the literature (see Table 3 for population-based studies).[1,2,5,11] Nevertheless, the rates for peripartum IVT should be considered tentative estimates because of the extreme variability of estimates in the literature, the wide variability in clinical presentation and application of diagnostic technologies,[13–15] the relatively high proportion of such cases among all peripartum cerebrovascular events in the present study compared with some[1,5] (but not all)[4] studies that incorporated medical record review, and the low morbidity and zero mortality rates among the present cases. In general, earlier studies (that reported any cases) reported much higher rates of IVT during pregnancy and the puerperium, but these studies used data collected before the advent of CT and MRI, and most of the cases in these studies did not have documentation by either angiography or autopsy. Studies that reported no cases of IVT generally had too few deliveries on which to base solid estimates.

Death from cerebrovascular events during pregnancy and the puerperium typically results from intracranial hemorrhage or malignant hypertension.[4,12] Maternal deaths associated with ischemic lesions are uncommon, particularly with venous thrombosis, and when they do occur, they usually result from secondary intracranial hemorrhage.[5,16] Although recent studies have demonstrated that the prognosis of IVT is far better than previously thought and better than that for arterial stroke,[16–24] in the present study the mortality rate associated with IVT was still lower than would be anticipated. In recent studies, the rate of death from all causes of IVT has generally been from 2% to 10%,[16–24] although some of these studies incorporated cases collected over a large time span.[17,24] The mortality rate is significantly less for IVT related to pregnancy and the puerperium than for IVT from other causes.[17] In series of recent cases, there have been almost no deaths among cases related to pregnancy and puerperium[4,5,16,19,23,25] (J. Stamm, personal communication, January 2000). Nevertheless, in the present study, the absence of deaths among such a large series suggests that other factors may be contributing to the low observed mortality rate. Specifically, because hemorrhagic infarction is the predominant cause of brain injury and death in patients with IVT, such cases may have been coded instead as intracranial hemorrhage, which is a dramatic sequela and a more proximate cause of complications and death.

The associations of both peripartum stroke and IVT with cesarean delivery may in part reflect a higher likelihood of cesarean delivery among women who have had a stroke during pregnancy, particularly in the presence of hypertension, or if the event was an intracranial hemorrhage. Early authors particularly advocated cesarean delivery after intracranial hemorrhage during pregnancy to avoid the presumed increased risk of bleeding associated with the hemodynamic changes of labor and vaginal delivery. In contrast, the association of postpartum stroke and IVT with cesarean delivery suggests that cesarean delivery may increase the risk of these events. First, on the basis of temporal considerations alone, the choice of method of delivery cannot be made on the basis of postpartum cerebrovascular events. Second, surgery has long been associated with and apparently precipitates venous thrombosis.[26,27] Third, although some misclassification errors between stroke and IVT in this study with administrative hospital data cannot be excluded, the strong associations between cesarean delivery and either type of cerebrovascular event (and the strong association between cesarean delivery and the combination of both types of events) argue strongly against an artifact of misclassification as an explanation for the association. Similarly, misclassification errors between antepartum and postpartum events are possible but are unlikely to account for the observed associations with postpartum events, because studies that incorporate medical record review[1] confirm that overall a majority (almost two thirds) of cerebrovascular events associated with pregnancy occur postpartum, and, moreover if only antepartum events were associated with adverse outcomes, one would not expect comparable or greater associations with postpartum events than with all peripartum events. Levels of protein C decrease after surgery, presumably because surgically induced tissue damage induces the activation of blood clotting with increased thrombin generation, which in turn both activates protein C and accelerates its clearance from plasma.[28,29] Postsurgical decreases in protein C may compound a hereditary[30,31] or pregnancy-associated[30,32] resistance to activated protein C and thereby contribute to an increased incidence of thrombosis in postsurgical patients.[27] Another less likely possibility is that underlying conditions that lead to cesarean delivery also precipitate postpartum cerebrovascular events.

The very strong association of pregnancy-related hypertension with peripartum and postpartum stroke is consistent with previous findings[2,3,12] and with the known pathophysiology of cerebrovascular complications of hypertension.[2] The weaker association between pregnancy-related hypertension and IVT was not identified in previous studies that used the US National Hospital Discharge Survey,[2,3] perhaps because of the smaller sample size of that survey, even during a 13-year study period.

Pneumonia and influenza were associated with stroke in univariate analyses and in the multivariate analyses for postpartum stroke, whereas other infections were associated with IVT in both univariate and multivariate analyses for peripartum and postpartum events. A number of studies have suggested that infections may trigger cerebral infarction, particularly in young patients,[33–38] although plausible underlying pathogenetic mechanisms remain to be determined.[38] Most of the available studies have been case reports or uncontrolled case series, but several case-control studies have supported these associations.[33–38] Most of these case-control studies indicate that infection increases the risk of stroke compared with controls in persons $<$50 years old.[33,34,38]

The associations of fluid, electrolyte, and acid-base disorders with both peripartum and postpartum stroke cannot be attributed to a single pathophysiological mechanism, because the specific ICD-9-CM rubrics included (and actually coded) in this category cover a wide range of conditions, including hyponatremia, hypernatremia, hypokalemia, hyperkalemia, acidosis, mixed acid-base disorder, and volume depletion. It is possible that fluid, electrolyte, and acid-base disorders are a nonspecific marker for medically ill stroke patients. However, such conditions were rarely coded in patients with IVT.

Several limitations of this study must be emphasized. First, the results, although highly statistically significant, are based on a relatively small number of observed events for some covariates, albeit in a very large population under study. Because of the small number of events, particularly for analyses of postpartum cases, we cannot exclude the possibility that some marginally significant results, or even some nonsignificant results, could become significant with increases in sample size. Second, the reliability and validity of the clinical diagnoses were not directly verifiable and may have varied across institutions. Compared with other diseases, however, the reliability and accuracy of clinical stroke diagnoses are generally high when stroke is considered collectively, because stroke has a distinctive clinical profile with an acute and often dramatic onset and because cerebral imaging is readily available.[39–43] However, the reliability and accuracy of diagnosis of IVT are probably less than those for other forms of cerebrovascular disease.[13–15,25,44] In addition, reported frequencies of comorbidities may be underestimates, because of bias against the recording and coding of chronic comorbid conditions on computerized discharge abstracts. Third, routine hospital discharge diagnoses may be somewhat less accurate than standard clinical diagnoses (eg, because of variation and errors in medical record abstraction and coding),[45–47] although the reliability of abstraction of cerebrovascular disease diagnoses from the medical record is fairly good for the broad category of stroke.[45–47] Despite modest imprecision of selection of the principle diagnosis for cerebrovascular disease from among all diagnoses reported, estimated rates of hospitalization for cerebrovascular disease from the original data and from reabstracted data differ by only a small amount.[46] Fourth, some important clinical data are not available in the HCUP-3 database, including the type of stroke, indices of neurological complications, results of cranial imaging or angiography if performed, and complete documentation of important comorbidities and their severity. Fifth, no specific validation studies have been performed on the accuracy of the coding of antepartum versus postpartum events. Although misclassification of events as antepartum or postpartum could bias the regression analyses of postpartum events, it is unlikely to fully account for the observed associations.

Despite some limitations, administrative databases such as the HCUP-3 data set are useful in monitoring peripartum stroke and IVT on a much broader scale than would otherwise be possible. Indeed, the number of postpartum cases in previous studies that used other approaches is small and would generally be insufficient for analytical studies of potential risk factors: in previous population-based studies with nonadministrative data (Table 3),[1,4,5,11] the number of postpartum cases of stroke or IVT ranged from 1 to 19. In the largest population-based, multicenter study by Kittner et al,[1] there were only 19 postpartum cerebrovascular events among women discharged from any of 46 hospitals in central Maryland and Washington, DC, during a 2-year period. In contrast, in the present study with national public-use administrative data from 900 hospitals across 17 states, there were 152 postpartum cerebrovascular events (ie, 65 with stroke and 87 with IVT) during a 2-year period. Identified associations in such data sets provide important insights that can be further investigated in studies with prospectively collected data aggregated from multiple institutions and during longer time periods.

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Risk Factors for Peripartum and Postpartum Stroke and Intracranial Venous Thrombosis

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