OBSTETRICS

Increased risk of stroke in patients who undergo cesarean section delivery: a nationwide population-based study

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OBJECTIVE: This study used a population-based dataset to determine whether (compared with vaginal deliveries), cesarean section deliveries increase the risk of postpartum stroke during the 3-, 6-, or 12-month period after delivery.

STUDY DESIGN: This study used 1998-2003 records from the Taiwan National Health Insurance Research Database for 987,010 women with singleton deliveries from 1998-2002. Cox proportional hazard regressions were carried out to compute stroke-free survival rates between the 2 delivery modes.

RESULTS: The regression model indicated that, compared with patients who delivered vaginally, the hazard ratio for postpartum stroke among those who delivered by cesarean section was 1.67 times greater within 3 months of delivery (95% CI, 1.29-2.16), was 1.61 times greater within 6 months of delivery (95% CI, 1.31-1.98), and was 1.49 times greater within 12 months of delivery (95% CI, 1.27-1.76).

CONCLUSION: Our data indicates that cesarean section delivery is an independent risk factor for stroke.

Key words: cesarean section, postpartum stroke, stroke

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The current strategy for the prevention of stroke mainly is based on controlling against the inherent risk factors in daily life, because most of these risk factors are considered widely to have a causal relationship with the disease. Some of the classic risk factors that previously have been identified for stroke are hyperlipidemia, hyperhomocysteinemia, hypertension, diabetes mellitus, smoking, and obesity[1]; there are various other elements that are beginning to emerge within the general profile of stroke risk, including certain genetic polymorphisms.[2]

An association has been reported in a number of studies between pregnancy and delivery and an increased risk of stroke; however, much more detailed analysis would seem to be warranted. The World Health Organization has warned that, as a direct result of cesarean section (CS) deliveries, the risk of postpartum death can be up to 3.6 times higher than that for conventional vaginal deliveries.[3,4] Although the limit recommended by the World Health Organization for the proportion of CS deliveries relative to all deliveries is just 15%, the CS rates in many regions remain at very high levels, which is particularly the case in Asian countries.[5,6]

It has been suggested that, as compared with vaginal deliveries, CS deliveries raise not only the overall healthcare costs but also the risk of morbidity and death among mothers and babies.[7] CS delivery has been associated with a significant increase in maternal death from cardiac arrest, complications from anesthesia, puerperal infection, and venous thromboembolism[8]; indeed, stroke has been singled out as a crucial cause of maternal morbidity and death during pregnancy and puerperium.[9] Nevertheless, to the best of our knowledge, very few studies have used large-scale (nationwide population) datasets to explore the risks of postpartum stroke between the 2 different delivery modes (CS delivery vs vaginal delivery).

There was 1 particular study, undertaken by Lanska and Kryscio, [10] in which the estimation of the risk of peripartum and postpartum stroke was undertaken through the examination of a total of 1,408,015 deliveries in community hospitals in 17 states in the United States. They observed 183 cases of peripartum stroke and 170 cases of peripartum intracranial venous thrombosis among these

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TABLE 1
Distribution of sample patient characteristics by mode of delivery, 1998-2002

	CS delivery[a]		Vaginal delivery[a]		
Variable	**N**	**%**	**N**	**%**	***P* value**
Demographic factor					
Patient age at delivery (y)					<.001
<30	167,462	51.2	433,224	65.6	
30-34	108,961	33.3	173,664	26.1	
>34	50,575	15.5	53,124	8.1	
Geographic location					<.001
Northern	152,057	46.5	293,717	44.5	
Central	72,490	22.2	176,613	26.8	
Southern	96,152	29.4	172,658	26.2	
Eastern	6,299	1.9	17,024	2.6	
Pregnancy factor					
Premature labor					<.001
Yes	13,016	4.0	19,168	2.9	
No	313,982	96.0	640,844	97.1	
Preeclampsia/eclampsia					<.001
Yes	7,875	2.4	1,788	0.3	
No	319,123	97.6	658,224	99.7	
Dystocia					<.001
Yes	87,776	26.8	6,137	0.9	
No	239,222	73.2	653,875	99.1	
Breech presentation					<.001
Yes	63,809	19.5	776	0.1	
No	263,189	80.5	659,236	99.9	
CS delivery history					<.001
Yes	117,486	35.9	2,228	0.3	
No	209,512	64.1	657,784	99.7	
Fetal distress					<.001
Yes	25,999	8.0	2,673	0.4	
No	300,999	92.0	657,339	99.6	
Maternally requested					
Yes	16,241	5.0	—	—	
No	310,757	95.0	—	—	

[a] Total sample number was 987,010 (CS deliveries, 326,998; vaginal deliveries, 660,012).

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sampled deliveries. However, their examination involved only the early postpartum period, from the time of the delivery until the time of discharge from hospital. Furthermore, their study was reliant heavily on data from only subgroups of populations, such that their findings could not be generalized to the population as a whole.

This study used a nationwide population-based dataset to explore any association between CS delivery and increased risk of postpartum stroke during the 3-, 6-, and 12-month periods after the index delivery, as compared with vaginal deliveries.

METHODS

Dataset

This study used 1998-2003 data from the National Health Insurance Research Database (NHIRD) that was published by the Taiwan National Health Research Institute. The National Health Insurance (NHI) program was initiated in Taiwan in March 1995 as a means of financing healthcare for all citizens of Taiwan. The NHI system has a unique combination of characteristics that include universal coverage, a single-payer payment system with the government as the sole insurer, comprehensive benefits, and access to any medical institution of the patient's choice.

The database provides registries of medical facilities that contract with the Bureau of the National Health Insurance and board-certified physicians and monthly claim summaries for all inpatient claims for a population in excess of 20 million people, with 1 principal ICD-9-CM diagnosis and up to 4 secondary diagnoses being listed for each patient. The NHIRD is possibly 1 of the largest and most comprehensive population-based data sources to be available currently anywhere.

Because these were deidentified secondary data that were released for public access for research purposes, the study was exempt from full review by the Internal Review Board of our university.

Study sample

Our study sample was based on the records of 987,010 singleton deliveries in hospitals or obstetric clinics between January 1998 and December 2002. The subjects were identified from the database by drug-related group (DRG) codes 0371A (CS delivery), 0373A (vaginal delivery), and 0373B (maternally requested CS delivery).

Statistical analysis

The SAS statistical package (SAS System for Windows, version 8.2; SAS Institute

TABLE 2
Crude and adjusted HRs of stroke among the sample patients during the 3-, 6-, and 12-month follow-up periods of discharge from the index delivery, 1998-2002[a]

Development of stroke	Total		Vaginal delivery		CS delivery					
					All cases		Limited to women with previous CS delivery		Excluding women with previous CS delivery	
	N	%	N	%	N	%	N	%	N	%
Panel A: 3-mo follow-up period										
Yes	236	0.02	123	0.02	113	0.03	27	0.02	86	0.04
No	986,774	99.98	659,889	99.98	326,885	99.97	117,459	99.98	209,426	99.96
Crude HR (95% CI)	—		1.00		1.86 (1.44-2.39)[b]		1.23 (0.81-1.87)		2.20 (1.67-2.90)[b]	
Adjusted HR (95% CI)[c]	—		1.00		1.67 (1.29-2.16)[b]		1.01 (0.66-1.54)		2.06 (1.560-2.72)[b]	
Panel B: 6-mo follow-up period										
Yes	370	0.04	197	0.03	173	0.05	48	0.04	125	0.06
No	986,640	99.96	659,815	99.97	326,825	99.95	117,438	99.96	209,387	99.94
Crude HR (95% CI)	—		1.00		1.77 (1.45-2.18)[b]		1.37 (0.99-1.88)		2.00 (1.60-2.50)[b]	
Adjusted HR (95% CI)[c]	—		1.00		1.61 (1.31-1.98)[b]		1.16 (0.84-1.60)		1.87 (1.50-2.35)[b]	
Panel C: 12-mo follow-up period										
Yes	595	0.06	329	0.05	266	0.08	88	0.07	178	0.08
No	986,415	99.94	659,683	99.95	326,732	99.92	117,398	99.93	209,334	99.92
Crude HR (95% CI)	—		1.00		1.63 (1.39-1.92)[b]		1.50 (1.19-1.90)[b]		1.71 (1.42-2.05)[b]	
Adjusted HR (95% CI)[c]	—		1.00		1.49 (1.27-1.76)[d]		1.27 (0.99-1.62)		1.62 (1.34-1.94)[b]	

[a] Total sample number, 987,010 patients.

[b] $P < .001$.

[c] Adjustments made for patient age and geographic region.

[d] $P < .01$.

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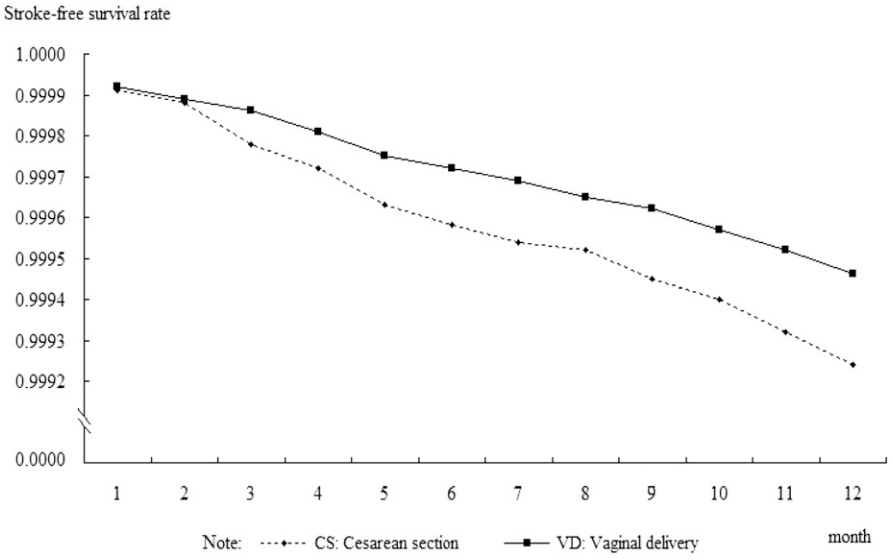
Inc, Cary, NC) was used to perform the statistical analyses on all of the data in this study. The primary endpoint of this study was whether a patient had used emergency medical services or undergone hospitalization for the management of any type of stroke (ICD-9-CM codes 430-438). The 3-, 6-, or 12-month stroke-free survival time was then defined as the period between the index delivery and admission for any type of stroke. The survival time was censored if the patient was stroke-free for the study period. All information on discharge dates and admission dates are recorded within the NHIRD.

The key independent variable of interest to this study was the mode of delivery (CS vs vaginal delivery). Descriptive statistical analyses, including frequency and percentage, were performed on all of the identified variables; chi-square tests were used to examine the potential correlation between stroke, the mode of delivery, the patient's age, and geographic location. The geographic location in which patients resided was taken into consideration in this study because geographic variations in the incidence of strokes have been demonstrated clearly in a previous study.[11]

The 3-, 6- and 12-month stroke-free survival rates subsequently were estimated by the Kaplan-Meier method; the log-rank test was used to examine the difference between the mode of delivery and stroke. Cox proportional hazard regressions were conducted to compute the 3-, 6-, and 12-month stroke-free survival rates after adjustment for the aforementioned variables. Hazard ratios (HR) are presented along with the 95% CIs. The Breslow approximation was used to adjust the tied data. Furthermore, the assumptions for the proportional hazard regression were examined with the residuals and estimated survival curves. In addition, because CS delivery was the main exposure of interest, women with multiple (previous) CS deliveries may be inherently different from those who have had only 1 CS delivery. We separated all patients who were delivered by CS into 2 groups (multiple CS deliveries vs single CS delivery) to examine the relationship between the mode of delivery and postpartum stroke.

We also examined the risk of stroke for patients with complications such as premature labor (ICD-9-CM code 644),

FIGURE
Stroke-free survival rates for singleton deliveries in Taiwan by delivery mode, 1998-2002



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preeclampsia or eclampsia (codes 642.4, 642.5, 642.6, or 642.7), multiple gestation (code 651), dystocia (codes 653 and 660-662, with the exception of 661.3), breech presentation (codes 652.2 and 669.6), history of CS delivery (code 654.2), fetal distress (code 656.3), and maternally requested CS delivery (DRG code 0373B).

As a result of the high degree of correlation with the mode of delivery, separate Cox regression analyses were performed on all patients who were delivered by CS to examine the relationships between these pregnancy factors and to determine whether a postpartum stroke had developed subsequently. A significance level of $<.05$ was adopted for this study.

RESULTS

CS deliveries accounted for 33.9% of all deliveries that took place in Taiwan between 1998 and 2002 among patients with a mean age of 28.2 years (SD, 5.1 years). Details on the distribution of the patients, in terms of pregnancy and demographic factors, are presented in Table 1 by delivery mode. The patients who had undergone CS deliveries were more likely to be older (mean age, 27.5 vs 29.1 years). As expected, patients who underwent CS deliveries had a greater propensity for pregnancy complications.

The crude and adjusted HRs of postpartum stroke within the 3-, 6-, and 12-month follow-up periods after discharge from the index delivery are presented in Table 2.

As compared with those patients who had delivered vaginally, those women whose deliveries were performed by CS had significantly higher postpartum stroke rates within the 3-month (0.03% vs 0.02%), 6-month (0.05% vs 0.03%), and 12-month (0.08% vs 0.05%) periods after the index delivery (all $P < .001$; Figure).

After adjustment for patient age and geographic location, the adjusted HRs indicated that, as compared with those patients who had delivered vaginally, the HR for postpartum stroke for those whose deliveries were performed by CS were 1.67 (95% CI, 1.29-2.16; $P < .001$) times as high within the 3-month postdelivery period, 1.61 (95% CI, 1.31-1.98; $P < .001$) times as high within the 6-month postdelivery period, and 1.49 (95% CI, 1.27-1.76; $P < .001$) times as high within the 12-month postdelivery period. Interestingly, the HR for postpartum stroke for those who had undergone multiple CS deliveries was not significantly increased relative to vaginal deliveries within the 3 postdelivery periods.

The adjusted HRs of postpartum stroke within the 3 follow-up periods from the index delivery for all patients who had delivered by CS are presented in Table 3. Rather interestingly, it is consistently shown throughout Table 3 that those patients whose condition was complicated by preeclampsia or eclampsia were 3.89-4.66 times more likely than their counterparts to experience a stroke within the follow-up periods from their index deliveries. Furthermore, the regression modeling also indicated that patients with a history of CS delivery were less likely to experience a stroke.

COMMENT

This nationwide population-based study is believed to be the first of its kind to carry out an investigation into the relationship between delivery modes and the risk of postpartum stroke. Our results are based on a population of 1,000,394 women who were admitted to hospitals or obstetric clinics for deliveries between January 1998 and December 2002.

After adjusting for potential stroke risk factors, we have found that, as compared with those patients who had delivered vaginally, the risk of postpartum stroke among women who had undergone CS deliveries during the period under examination were 44.7% higher during the 3-month postdelivery period ($P < .001$), 43.6% higher during the 6-month postdelivery period ($P < .001$), and 32.5% higher during the 12-month postdelivery period ($P < .01$).

Our findings demonstrate that CS delivery is itself an important factor for postpartum stroke, which is a finding that is consistent with the results of the studies that were undertaken by Witlin et al[9] and Lanska and Kryscio,[10] both of which reported that CS delivery had a significant correlation with postpartum stroke. Our study has also shown that the postpartum stroke rate within the 3-month postdelivery period was 0.0300%, which is a figure that is eminently comparable with the 0.0342% rate reported in the United States.[3,12] Although the risk of postpartum stroke in-

creased with cesarean delivery when compared with vaginal delivery, the absolute risk of postpartum stroke remains low.

There are 3 mechanisms that may have potential contributions to the increased risk of postpartum stroke for patients who have undergone CS deliveries. First, CS delivery itself influences hemodynamic changes, which will ultimately result in hypo- or hyperperfusion of the brain. Serial hemodynamic investigations have been undertaken previously on 15 women who delivered by elective CS under epidural anesthesia at 38-40 weeks of gestation. Although there were no changes in hemodynamic condition after anesthesia, there were significant increases in stroke volume and cardiac output after delivery of the placenta, which remained elevated until the end of the operation.

Maternal hemodynamics during CS delivery with spinal anesthesia, which was studied by the whole-body impedance cardiography, showed sudden and significant changes at the moment of delivery; these changes persisted for an average of 10 minutes. This reveals a 47% increase in the cardiac index and a 39% reduction in the systemic vascular resistance index, although mean arterial pressure remained stable.[13-15]

Second, surgery could induce stress responses, which would potentially alter many physiologic conditions; for example, surgery can reduce the concentration of protein C. Any operation will damage tissue and lead to the activation of the clotting system, followed by an increase the amount of thrombin, which then enhances the clearance of protein C. This cascade of interactions will accelerate the formation of blood clots naturally.[16,17] Third, anesthesia also influences the hemodynamic situation.

The study of thoracic electrical bioimpedance in CS delivery with spinal or epidural anesthesia has revealed an increase in maternal cardiac output and a reduction in the systemic vascular resistance index after induction.[18,19] Anesthetic procedures could change both the functions of blood vessels and cerebrospinal fluid circulation. The imaging features of cerebrospinal fluid leaks after postlumbar puncture have been recog-

TABLE 3
Adjusted HRs of stroke during the 3-, 6-, and 12-month follow-up periods from index delivery for patients who underwent CS delivery, 1998-2002[a]

	Follow-up period					
	3-mo		6-mo		12-mo	
Variable	HR	95% CI	HR	95% CI	HR	95% CI
Age (y)						
<30	1.00		1.00		1.00	
30-34	1.44	0.94-2.21	1.22	0.86-1.73	1.19	0.89-1.58
>34	2.38[b]	1.50-3.78	2.23[b]	1.54-3.23	1.99[b]	1.47-2.70
Geographic location						
Northern	1.00		1.00		1.00	
Central	1.38	0.86-2.23	1.17	0.79-1.72	1.13	0.83-1.53
Southern	1.62[c]	1.06-2.48	1.36	0.96-1.91	0.98	0.73-1.30
Eastern	1.08	0.26-4.47	0.64	0.16-2.61	0.75	0.28-2.03
Premature labor						
Yes	1.69	0.93-3.05	1.58	0.94-2.64	1.34	0.86-2.07
No	1.00		1.00		1.00	
Preeclampsia/eclampsia						
Yes	4.16[b]	2.37-7.29	3.89[b]	2.40-6.31	4.66[b]	3.17-6.86
No	1.00		1.00		1.00	
Dystocia						
Yes	0.62	0.37-1.03	0.75	0.50-1.11	0.66[c]	0.47-0.92
No	1.00		1.00		1.00	
Breech presentation						
Yes	0.70	0.41-1.21	0.62[c]	0.40-0.98	0.79	0.55-1.12
No	1.00		1.00		1.00	
CS delivery history						
Yes	0.50[d]	0.31-0.82	0.61[c]	0.42-0.90	0.77	0.57-1.05
No	1.00		1.00		1.00	
Fetal distress						
Yes	1.28	0.72-2.28	1.09	0.66-1.80	1.00	0.65-1.55
No	1.00		1.00		1.00	
Maternally requested						
Yes	1.12	0.50-2.52	1.24	0.66-2.33	0.81	0.44-1.49
No	1.00		1.00		1.00	

[a] Total sample number, 326,998 patients.

[b] $P < .001$.

[c] $P < .05$.

[d] $P < .01$.

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nized as resulting in intracranial hypotension.[20] Ergonovine use after CS delivery has also been linked to cerebral infarction.[21]

Interestingly, our study has also found that a history of CS delivery could be a protective factor against postpartum stroke within the 6-month postdelivery period. The real causes of this phenomenon are unclear, but preconditioning mechanisms might be involved. Preconditioning, which indicates a sublethal injury, is a well-known mechanism for reduction in brain damage after a stroke.[22,23] Preconditioning is also a potential tool for stroke prevention. Given that CS delivery may be involved in changes in hemodynamic and coagulation status, thereby initiating a prevention mechanism for stroke, the role of a history of CS delivery in stroke prevention would seem to warrant further investigation.

Preeclampsia/eclampsia (odds ratio, 3.89-4.66) among the CS delivery group was found to increase the risk of the occurrence of stroke. These findings indicate that both hemodynamic and coagulation status could be the most important factors in stroke after CS deliveries. It is also suggested that a strategy of prevention should be developed for those mothers in the CS delivery group who are at a higher risk of stroke.

There are 2 caveats to this study. First, the NHIRD is based on claims data and therefore lacks certain clinical details, such as the propensity for cigarette smoking, alcohol consumption, and body mass index values; failure to account for these risk factors in the regression model potentially may compromise our findings. Second, the stroke diagnoses, which are totally reliant on claims data that are reported by either physicians or hospitals, may be less accurate than those undertaken individually. However, virtually all hospitals that are capable of admitting stroke patients are also equipped with computed tomography or magnetic resonance imaging scanners, which can increase the overall validity of the stroke diagnoses.

Based on the results of this study, a reduction in the CS delivery rate should prove to be beneficial for stroke prevention, which suggests that, as far as possible, vaginal deliveries should be encouraged. Does that mean that we should refuse all maternally requested CS deliveries in the future? In a study that involved a questionnaire that was distributed among 1031 fellows at the American College of Obstetricians and Gynecologists, the results revealed that approximately one half of the respondents believed that a woman should have the right to undergo a CS delivery if she requested it.[24]

Nevertheless, the US National Institutes of Health concluded that there was only moderate support for a handful of the risks and benefits of maternally requested CS delivery, as compared with vaginal delivery. There is general consensus within the National Institutes of Health that a maternally requested CS delivery should not be recommended for women who were planning to have several children, because the risks of placenta previa and placenta accreta are increased greatly with each CS delivery.[25] Furthermore, although our results provide support for the argument that a history of CS delivery may reduce the risk of postpartum stroke after a subsequent CS delivery, insufficient evidence exists to undertake any comprehensive evaluation of the benefits and risks of maternally requested CS delivery, as compared with vaginal delivery.

Based on the findings of this large-scale nationwide study, we conclude that CS delivery is an independent risk factor for stroke, with the risk declining along certain time intervals during the 1-year period after the CS delivery. Preeclampsia/eclampsia play important roles in the occurrence of stroke among women with CS delivery; thus, a reduction in the CS delivery rate should prove to be beneficial to stroke prevention. Rather interestingly, a history of CS delivery is found to be a preventive factor against stroke in women who undergo subsequent CS deliveries. The mechanisms of precondition and the development of novel strategies for a reduction of CS deliveries among women who are at high risk clearly will require further studies. ■

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