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# Preeclampsia-Eclampsia and the Risk of Stroke Among Peripartum in Taiwan

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***Background and Purpose***—The occurrence of preeclampsia-eclampsia during pregnancy has been reported to increase the risk of stroke in mainly Western populations. However, few studies have evaluated stroke risk in Asian populations and followed women beyond the early postpartum period. Thus, the present study determined the risk of stroke in women in Taiwan during pregnancy and the first postpartum year.

***Methods***—A population-based cohort study was performed on 1 132 019 parturients during 1999 to 2003 using a dataset linking birth certificates and National Health Insurance hospital discharge data. Stroke-free survival rates were estimated using the Kaplan–Meier method, and the log-rank test was used to examine the effect of preelampsia-eclampsia on the prevalence of stroke. Sociodemographic factors and obstetric complications were used in multivariate logistic regression models to determine the adjusted odds ratios of preeclampsia-eclampsia on the risk of hemorrhagic and ischemic stroke during pregnancy and within the first postpartum year.

***Results***—The incidence of stroke was 21.47 cases per 100 000 deliveries. There were 139 cases of hemorrhagic stroke and 107 cases of ischemic stroke. The respective adjusted relative risk of preeclampsia-eclampsia for hemorrhagic and ischemic stroke were 10.68 (95% CI, 3.40 to 33.59) and 40.86 (95% CI, 12.14 to 137.47) within 3 months antepartum; 6.45 (95% CI, 1.42 to 29.29) and 34.71 (95% CI, 11.08 to 108.68) in the first 3 days postpartum; 5.61 (95% CI, 0.71 to 44.10) and 11.23 (95% CI, 2.45 to 51.59) from 3 days to 6 weeks postpartum; 11.76 (95% CI, 4.05 to 34.11) and 11.60 (95% CI, 3.30 to 40.82) from 6 weeks to 6 months pospartum; and 19.90 (95% CI, 7.75 to 51.11) and 4.35 (95% CI, 0.58 to 32.92) from 6 months to 12 months postpartum.

***Conclusions***—Women with preeclampsia-eclampsia have a significantly higher risk of stroke during pregnancy and in the first postpartum year. These results suggest that women with preeclampsia-eclampsia should be closely monitored even after pregnancy. (***Stroke***. 2009;40:00-00.)

**Key Words:** stroke in young adults ■ preeclampsia-eclampsia ■ Taiwan

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Stroke is a leading cause of mortality and morbidity in women, accounting for about 50% of total cardiovascular deaths in the United States.[1] Furthermore, about two thirds of survivors suffer some residual disability.[2] Although women younger than 50 years-of-age have a stroke incidence <5%,[3] the effect of stroke on long-term disability is even greater in this age group. Stroke is a recognized complication of pregnancy, contributing to more than 12% of all maternal deaths. Estimated incidence rates vary considerably from 4.3 to 210 strokes per 100 000 deliveries.[4–10]

The underlying disease mechanism in this age group is different from other age groups because of pregnancy-related or unrelated risk factors. Pregnancy-related risk factors include hypertension,[4–8] multiple pregnancies,[9] and preeclampsia-eclampsia.[10–14] Studies have shown that up to 5% of pregnancies are affected by preeclampsia, and 1 in 200 of these women develops eclampsia.[15] The pregnancy-unrelated risk factors include the known medical conditions strongly linked to stroke in pregnancy, such as hypertension, diabetes, sickle cell disease, thrombophilia, smoking and cardiovascular
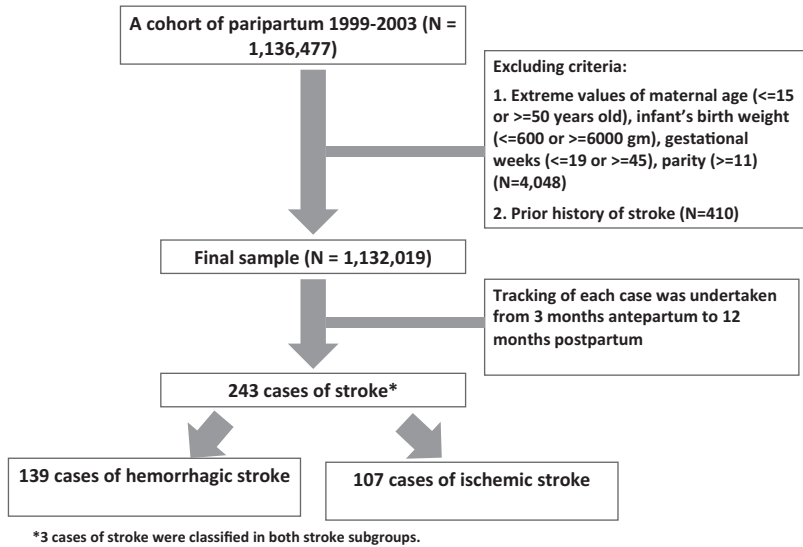
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**Figure 1.** Selection of study subjects and identification of stroke cases among parturients in Taiwan from 1999 to 2003.

diseases. Other risk factors are ethnic background, age, alcohol, recreational drug abuse (particularly cocaine), the presence of a lupus anticoagulant or anticardiolipin antibody, multiple gestation and greater parity, and possible migraine headaches.[15]

Recent studies have shown that preeclampsia-eclampsia increases the risk of stroke during pregnancy mainly in Western populations.[10–14] However, few studies have evaluated stroke risk during pregnancy in Asian populations.[12,16] Hemorrhagic stroke is more common in Asians than in whites; thus, genetic factors may play a role in stroke risk during pregnancy in addition to alterations in hemodynamic and coagulation factors.[12,16] Moreover, few studies have looked at the period beyond postpartum.[4,9] This study is the first population-based study in an Asian population with an observation period that included pregnancy and the first postpartum year. The present report provides the incidence of stroke in Taiwanese women for the period of 1999 to 2003 based on birth certificate data linked with National Health Insurance (NHI) claims data.

## Methods

### Data Sources
The data for this study were obtained from 2 main sources. The first source was birth registries from 1999 to 2003 provided by the Ministry of the Interior. This dataset contains comprehensive information about birth and parents' data, including age, education, marital status, infant birth weight, gestational weeks, gender, and multiple births. The second source was the NHI hospital discharge data covering the years 1996 to 2004, a nationwide population-based data including more than 21 million enrollees, representing about 97% of the Taiwan population. It provided inpatient registries from all medical facilities contracted with the NHI and contained information on all admissions, including both inpatient stroke cases and all delivery cases with 1 principle and 4 secondary ICD-9-CM diagnosis codes. Multivariate analyses were used to determine the risk of stroke in women during pregnancy and within the first postpartum year.

The mother's date of birth and her unique personal identification number were used to link the birth certificate data and the NHI claims dataset. All personal identifiers were encrypted by the Bureau of NHI before release to the researchers. The confidentiality assurances were addressed by following the data regulations of the Bureau of NHI, and Institutional Review Board (IRB) approval was waived.

### The Study Cohort
The study cohort consisted of 1 136 477 birth records for the years 1999 to 2003, in which the birth certificate dataset and delivery entries in the NHI hospital discharge data were successfully linked. A total of 4048 data entries, representing 0.36% of the total sample, had extreme values of maternal age ($\leq$15 or $\geq$50 years old), infant's birth weight ($\leq$600 or $\geq$6000 gm), gestational weeks ($\leq$19 or $\geq$45), and parity ($\geq$11) were therefore excluded. In order to examine the
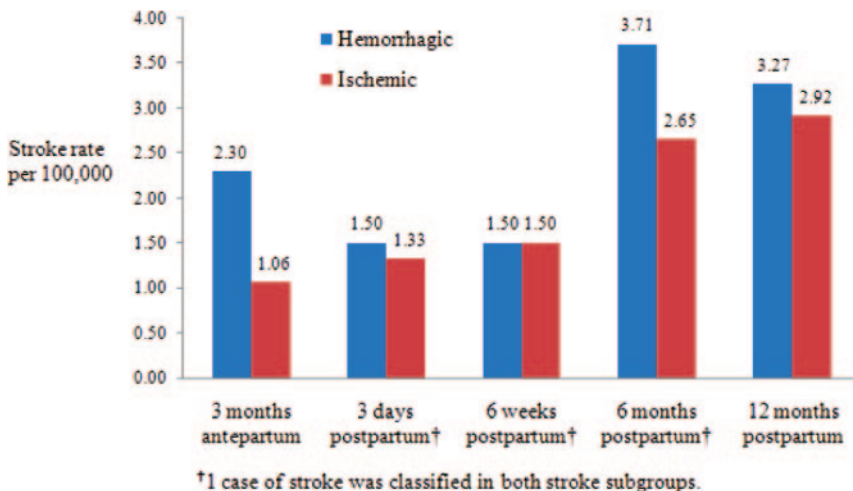


**Figure 2.** Event rate of stroke among parturients during 1999 to 2003 in Taiwan was shown by timing and types of stroke.

**Table 1.    Distribution of Cases of Stroke Among Groups Classified by Clinical and Sociodemographic Factors Among Parturients During 1999–2003 in Taiwan, by Timing and Type of Stroke**

| | Nonstroke | 3 Months Antepartum | | 3 Days Postpartum | | 6 Weeks Postpartum | | 6 Months Postpartum | | 12 Months Postpartum | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Hemorrhagic | Ischemic | Hemorrhagic | Ischemic | Hemorrhagic | Ischemic | Hemorrhagic | Ischemic | Hemorrhagic | Ischemic |
| Total No. of cases | 1 131 344 | 26 | 12 | 17 | 15 | 17 | 17 | 42 | 30 | 37 | 33 |
| Age <25, % | 21 | 12 | 0 | 24 | 20 | 6 | 18 | 21 | 10 | 24 | 21 |
| Age 25–34, % | 68 | 69 | 67 | 59 | 67 | 76 | 53 | 74 | 80 | 46 | 70 |
| Years of education ≤9, % | 22 | 42 | 8 | 41 | 13 | 47 | 35 | 29 | 23 | 35 | 36 |
| Married, % | 97 | 88 | 100 | 100 | 93 | 94 | 100 | 100 | 100 | 100 | 97 |
| Multiple gestation, % | 3 | 8 | 0 | 18 | 7 | 0 | 0 | 0 | 0 | 5 | 9 |
| Male baby, % | 52 | 50 | 67 | 76 | 60 | 41 | 53 | 45 | 67 | 59 | 39 |
| Birthweight ≥4000, % | 3 | 4 | 0 | 0 | 0 | 6 | 0 | 2 | 3 | 5 | 0 |
| Nulliparous, % | 46 | 38 | 67 | 65 | 53 | 29 | 35 | 40 | 50 | 46 | 24 |
| Cesarean delivery, % | 34 | 77 | 83 | 82 | 80 | 59 | 65 | 55 | 43 | 46 | 39 |
| Chronic hypertension, % | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pregnancy-related hypertension, % | 0 | 4 | 0 | 0 | 7 | 0 | 0 | 0 | 3 | 0 | 0 |
| Anemia, % | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 8 | 0 |
| Diabetes, % | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 |
| Antepartum hemorrhage, % | 2 | 0 | 0 | 0 | 7 | 6 | 0 | 12 | 3 | 0 | 0 |
| Postpartum hemorrhage, % | 1 | 0 | 8 | 6 | 7 | 6 | 0 | 2 | 3 | 0 | 0 |
| Preeclampsia-eclampsia, % | 1 | 15 | 42 | 12 | 33 | 6 | 12 | 10 | 10 | 16 | 3 |

risk factor of stroke occurring during the prenatal period, an index date was created by subtracting 90 days from the date of delivery. Cases that had stroke before the index date were excluded from the analyses (n=410) to avoid the potential confounding factor of a history of stroke. The final sample available for the analyses was 1 132 019 (Figure 1).

To identify all stroke events, each case was tracked from the index date until the end of 2004 or the date of death, whichever came first. Women who were alive without stroke occurrence were censored on December 31, 2004. According to the time when the stroke occurred, the stroke cases were further defined as the period between the delivery date and the admission date for stroke and classified as follows: (1) in the third trimester of pregnancy (3 months antepartum); (2) within 3 days after delivery; (3) from the fourth day to 6 weeks postpartum; (4) from 6 weeks to 6 months postpartum; (5) from 6 months to 1 year postpartum; and (6) beyond 1-year postpartum. Cases of stroke were further classified as hemorrhagic stroke (ICD-9-CM code 430 to 432) or ischemic stroke (ICD-9-CM code 433 to 437). We excluded the ICD-9 codes of occlusion or stenosis of precerebral (extracranial) arteries without infarction (430.00, 431.00, 433.20, 433.30, 433.80, 43.390, 434.90, 434.00, 434.10, and 434.90). Basilar, vertebral and subclavian artery syndrome (435.0 to 435.3) and 437.2 (hypertensive encephalopathy), 437.3 (cerebral aneurysm, nonruptured), 437.4 (cerebral arteritis) and 437.5 (Moyamoya disease) were also excluded unless accompanied with a code mentioned of cerebral infarction or cerebral hemorrhage.

## Definition of Independent Variables and Confounding Variables

The exposure of interest is preeclampsia-eclampsia, which was defined by ICD-9-CM codes 642.4 to 642.7 as the secondary diagnosis in the index discharge of delivery. The regression models also adjusted for maternal characteristics that increase stroke risk, such as age, education, marital status, and parity. In addition, the models adjusted for infant's characteristics, such as gender, birth weight and gestational week. Details on selected pregnancy and obstetric complications (ICD-9-CM diagnosis codes in parentheses), including multiple gestation (651), diabetes mellitus (648.0/250), chronic hypertension(401-405), pregnancy-related hypertension

(642.0-642.3/642.9/760.0), anemia (648.2/285.0), antepartum hemorrhage (641/640.9), postpartum hemorrhage (666/667/669.1), and cesarean delivery (procedure code: 74.0-74.4) were also extracted from the claims data at the time of the discharge for delivery. Multiple pregnancy, diabetes, chronic hypertension, pregnancy-related hypertension, cesarean delivery, and preeclampsia-eclampsia were entered because they were risk factors of stroke reported by previous studies.[4–15] Other factors, such as age, education level, marital status, gender of baby, parity, gestational weeks, birthweight, postpartum hemorrhage and antepartum hemorrhage were entered to examine their possible association with the risk of stroke.

## Statistical Analyses

The distribution of stroke cases was determined among groups classified by clinical and sociodemographic factors. A univariate logistic regression model was performed first to calculate the crude odds ratios and 95% CIs for the associations between the incidence of stroke and each of the potential clinical and sociodemographic risk factors. Because stroke was an uncommon outcome, the odds ratios derived from the logistic regression approximate the relative risks (RRs). Risk factors with $P<0.05$ in the univariate model were then entered into an adjusted multivariate regression model. Multivariate logistic regression models were used to examine the independent effect of preeclampsia-eclampsia on the risk of stroke during 3 months antepartum, within 3 days after delivery, postpartum after 3 days up to 6 weeks, postpartum after 6 weeks up to 6 months, and postpartum after 6 months up to 12 months postpartum. RR along with the 95% CIs were determined and $P<0.05$ was considered statistically significant. The stroke-free survival rates were estimated using the Kaplan–Meier method, and the log-rank test was used to examine the effect of preeclampsia-eclampsia on the stroke-free survival rate. All analyses were stratified by stroke types and were performed using the SAS/Stat system for Windows, version 9.01 (SAS Institute, Cary, NC).

## Results

Among the 1 132 019 pregnancies, there were a total of 243 cases of stroke that occurred during 3 months antepartum and within 1-year postpartum. The number of cases of stroke by
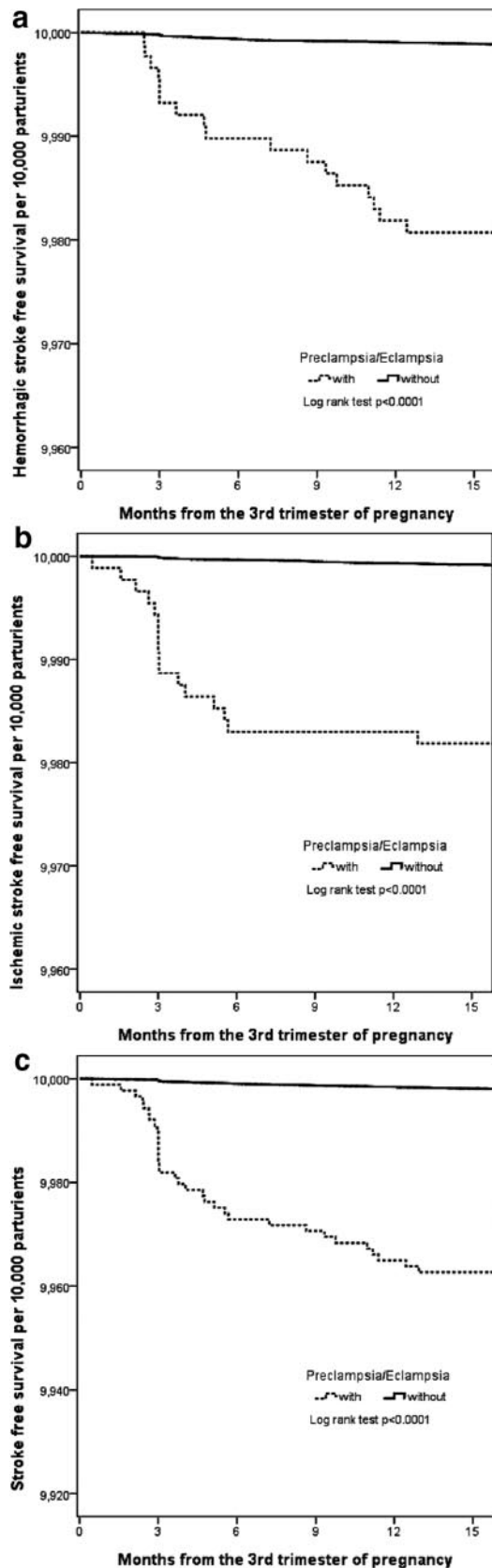
**Figure 3.** a, Hemorrhagic stroke-free survival rate per 10 000 parturients with and without preeclampsia-eclampsia. b, Ischemic stroke-free survival rate per 10 000 parturients with and without preeclampsia-eclampsia. c, Stroke-free survival rate per 10 000 parturients with and without preeclampsia-eclampsia.

timing and type of stroke is shown in Figure 2. Accordingly, the incidence of stroke was 21.47 cases per 100 000 deliveries, and age-adjusted incidence of stroke was 11.53 per 100 000 populations based on the age-structure of a world standard population.[17] In terms of the stroke types, there were 139 cases of hemorrhagic stroke and 107 cases of ischemic stroke. Three cases of stroke were classified in both stroke types as the principal/secondary diagnoses at the time of hospitalization for stroke. In terms of stroke timing, 38 cases (15.6%) occurred in the third trimester of the pregnancy, 31 cases (12.8%) occurred within the first 3 days postpartum, 33 cases (13.6%) occurred from the fourth day to 6 weeks postpartum, 71 cases (29.2%) occurred from 6 weeks to 6 months postpartum, and 70 cases (28.8%) occurred from 6 months to 1 year postpartum.

The distribution of stroke cases among sociodemographic and clinical groups by timing and stroke type is shown in Table 1. The incidences of hemorrhagic stroke among women with and without preeclampsia-eclampsia were 1.09 (122/1 122 668) and 19.29 (17/8815) per 100 000 deliveries, respectively. The attributable risk (excess risk) of preeclampsia-eclampsia for hemorrhagic stroke was 18.20 per 100 000 deliveries. The incidences of ischemic stroke among women with and without preeclampsia-eclampsia were 0.81 (91/1 122 637) and 18.15 (16/8814), respectively. The attributable risk of preeclampsia-eclampsia for ischemic stroke was 17.34 per 100 000 deliveries.

Figure 3 shows the stroke-free survival rates per 10 000 parturients associated with preeclampsia-eclampsia for hemorrhagic, ischemic and all strokes, respectively. For hemorrhagic, ischemic and all strokes, the survival rates for women with preeclampsia-eclampsia were higher than the rates of women without preeclampsia-eclampsia, which indicates women with preeclampsia-eclampsia are more likely to develop stroke. The log-rank tests indicated that the probability values were significant ($P < 0.0001$) for the effect of preeclampsia-eclampsia on the risk of hemorrhagic, ischemic and all strokes.

The results of univariate logistic regression by stroke type are summarized in Table 2. Univariate analyses were not performed on variables with zero sample size among sociodemographic and clinical groups. Women with preeclampsia-eclampsia showed a significantly increased risk of hemorrhagic stroke with up to 24.70-fold elevated stroke risk during pregnancy and the first year postpartum than women without it. In addition, the RRs of women with preeclampsia-eclampsia indicate a U-shape trend of stroke risk from antepartum to 1-year postpartum (RR: 23.20, to 17.01, to 7.98, to 13.43, to 24.70). In comparison with the risk of hemorrhagic stroke, women with preeclampsia-eclampsia showed an even higher risk of ischemic stroke with up to 91.14-fold elevated stroke risk than women without it. Contrary to the U-shape trend of hemorrhagic stroke risk, the RRs of preeclampsia-eclampsia showed a decreased trend of ischemic stroke risk from antepartum to 1-year postpartum (RR: 91.14, to 63.80, to 17.01, to 14.18, to 3.99). A significantly increased risk of both stroke types was also observed in women with cesarean delivery during pregnancy and up to 6 months postpartum. Women with ≤9 years of

**Table 2.    Crude Relative Risks for Hemorrhagic and Ischemic Stroke for the Risk Factors Among Parturients During 1999–2003 in Taiwan, by Timing and Type of Stroke**

| | 3 Months Antepartum | | 3 Days Postpartum | | 6 Weeks Postpartum | | 6 Months Postpartum | | 12 Months Postpartum | |
|---|---|---|---|---|---|---|---|---|---|---|
| | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI |
| **Hemorrhagic stroke** | | | | | | | | | | |
| Age <25 | 0.30 | (0.07–1.27) | 0.67 | (0.15–3.01) | 0.17 | (0.02–1.62) | 2.27 | (0.49–10.51) | 0.41 | (0.17–1.00)* |
| Age 25–34 | 0.57 | (0.21–1.53) | 0.53 | (0.15–1.91) | 0.68 | (0.20–2.40) | 2.44 | (0.59–10.20) | 0.24 | (0.11–0.52)‡ |
| Years of education ≤9 | 2.59 | (1.19–5.64)* | 2.47 | (0.94–6.50) | 3.14 | (1.21–8.14)* | 1.41 | (0.72–2.76) | 1.91 | (0.97–3.76) |
| Married | 0.22 | (0.07–0.75)* | | | 0.47 | (0.06–3.51) | | | | |
| Multiple gestation | 2.68 | (0.63–11.34) | 6.89 | (1.98–23.99)† | | | | | 1.84 | (0.44–7.64) |
| Male baby | 0.91 | (0.42–1.97) | 2.96 | (0.97–9.08) | 0.64 | (0.24–1.68) | 0.75 | (0.41–1.38) | 1.34 | (0.69–2.58) |
| Birthweight ≥4000 | 1.38 | (0.19–10.20) | | | 2.16 | (0.29–16.28) | 0.84 | (0.12–6.13) | 1.98 | (0.48–8.21) |
| Nulliparous | 0.73 | (0.33–1.60) | 2.13 | (0.79–5.75) | 0.48 | (0.17–1.37) | 0.79 | (0.43–1.46) | 0.99 | (0.52–1.88) |
| Cesarean delivery | 6.36 | (2.56–15.84)‡ | 8.91 | (2.56–30.99)‡ | 2.73 | (1.04–7.16)* | 2.31 | (1.26–4.24)† | 1.62 | (0.85–3.10) |
| Chronic hypertension | 185.43 | (25.03–>999)‡ | | | | | | | | |
| Pregnancy-related hypertension | 11.21 | (1.52–82.76)* | | | | | | | | |
| Anemia | | | | | | | 1.57 | (0.22–11.39) | 5.67 | (1.74–18.45)† |
| Diabetes | | | | | | | | | | |
| Antepartum hemorrhage | | | | | 2.98 | (0.40–22.47) | 6.44 | (2.53–16.40)‡ | | |
| Postpartum hemorrhage | | | 10.34 | (1.37–77.95)* | 10.34 | (1.37–77.95)* | 4.03 | (0.56–29.33) | | |
| Preeclampsia-eclampsia | 23.20 | (7.99–67.33)‡ | 17.01 | (3.89–74.40)‡ | 7.98 | (1.06–60.14)* | 13.43 | (4.79–37.64)‡ | 24.70 | (10.30–59.21)‡ |
| **Ischemic stroke** | | | | | | | | | | |
| Age <25 | | | 0.76 | (0.13–4.53) | 0.30 | (0.07–1.27) | 0.51 | (0.10–2.50) | 1.18 | (0.31–4.56) |
| Age 25–34 | 0.32 | (0.10–1.05) | 0.79 | (0.17–3.60) | 0.28 | (0.10–0.85)* | 1.26 | (0.38–4.19) | 1.21 | (0.36–4.03) |
| Years of education ≤9 | 0.32 | (0.04–2.49) | 0.54 | (0.12–2.41) | 1.93 | (0.71–5.21) | 1.08 | (0.46–2.51) | 2.02 | (0.99–4.10) |
| Married | | | 0.41 | (0.05–3.11) | | | | | 0.93 | (0.13–6.84) |
| Multiple gestation | | | 2.30 | (0.30–17.47) | | | | | 3.22 | (0.98–10.54) |
| Male baby | 1.82 | (0.55–6.05) | 1.37 | (0.49–3.84) | 1.03 | (0.40–2.66) | 1.82 | (0.85–3.89) | 0.59 | (0.30–1.19) |
| Birthweight ≥4000 | | | | | | | 1.19 | (0.16–8.75) | | |
| Nulliparous | 2.32 | (0.70–7.70) | 1.33 | (0.48–3.65) | 0.63 | (0.23–1.71) | 1.16 | (0.57–2.37) | 0.37 | (0.17–0.82)* |
| Cesarean delivery | 9.54 | (2.09–43.55)† | 7.64 | (2.15–27.06)† | 3.50 | (1.30–9.46)* | 1.46 | (0.71–3.01) | 1.24 | (0.62–2.49) |
| Chronic hypertension | | | | | | | | | | |
| Pregnancy-related hypertension | | | 20.03 | (2.63–152.29)† | | | 9.68 | (1.32–70.97)* | | |
| Anemia | | | | | | | | | | |
| Diabetes | | | | | | | 26.04 | (3.55–191.30)† | | |
| Antepartum hemorrhage | | | 3.41 | (0.45–25.90) | | | 1.64 | (0.22–12.07) | | |
| Postpartum hemorrhage | 15.04 | (1.94–116.46)† | 11.81 | (1.55–89.84)* | | | 5.70 | (0.78–41.86) | | |
| Preeclampsia-eclampsia | 91.14 | (28.92–287.20)‡ | 63.80 | (21.80–186.68)‡ | 17.01 | (3.89–74.40)‡ | 14.18 | (4.30–46.74)‡ | 3.99 | (0.55–29.18) |

*$P<0.05$; †$P<0.01$; ‡$P<0.001$.
Univariate analyses were not performed on variables with zero sample size among socio-demographic and clinical groups.

education showed a significantly higher risk of hemorrhagic stroke in only some of the follow-up periods. Women with multiple gestations were at a high risk for both types of stroke within the first 3 days postpartum. Chronic hypertension and pregnancy-related hypertension were also significant risk factors for the occurrence of both types of stroke in some of the follow-up periods. The distributions of stroke risks based on the other clinical factors were relatively unstable due to the small sample size.

Table 3 shows the adjusted RR for both hemorrhagic and ischemic stroke for preeclampsia-eclampsia. After adjusting for other clinical and sociodemographic factors, the adjusted RR for preeclampsia-eclampsia were of considerably smaller magnitude when compared to the unadjusted risks for both types of stroke in all follow-up periods. However, preeclampsia-eclampsia still exhibited a strong and consistent effect with up to a 19.90-fold and 40.86-fold elevated risk of hemorrhagic stroke and ischemic stroke, respectively. The

**Table 3.    The Adjusted Relative Risks for Hemorrhagic and Ischemic Stroke for Preeclampsia-Eclampsia Among Parturients During 1999–2003 in Taiwan, by Timing and Type of Stroke**

|  | 3 Months Antepartum | 3 Days Postpartum | 6 Weeks Postpartum | 6 Months Postpartum | 12 Months Postpartum |
|---|---|---|---|---|---|
| Hemorrhagic stroke |  |  |  |  |  |
| Adjusted RR | 10.68 | 6.45 | 5.61 | 11.76 | 19.90 |
| (95% CI) | (3.40–33.59)‡ | (1.42–29.29)* | (0.71–44.10) | (4.05–34.11)‡ | (7.75–51.11)‡ |
| Ischemic stroke |  |  |  |  |  |
| Adjusted RR | 40.86 | 34.71 | 11.23 | 11.60 | 4.35 |
| (95% CI) | (12.14–137.47)‡ | (11.08–108.68)‡ | (2.45–51.59)† | (3.30–40.82)‡ | (0.58–32.92) |

RR indicates relative risks.

*$P<0.05$; †$P<0.01$; ‡$P<0.001$.

Logistic regression analyses were adjusted for age, years of education, marital status, multiple gestation, birthweight, parity, anemia, diabetes, cesarean delivery, chronic hypertension, pregnancy-related hypertension, antepartum hemorrhage, and postpartum hemorrhage.

effect of preeclampsia-eclampsia on the risk of hemorrhagic stroke from the 4th day to 6 weeks postpartum, and on the risk of ischemic stroke during 6 to 12 months postpartum did not reach statistical significance. However, the RRs of preeclampsia-eclampsia were all with wide confidence intervals which were likely associated with the small sample sizes.

## Discussion

Although pregnancy-associated stroke is uncommon, the risk of stroke is greatly increased above the low baseline rate in young patients during late pregnancy and, even more so during puerperium. Stroke is a major contributor to the serious morbidity and mortality of pregnancy.[20] This population-based study showed that preeclampsia-eclampsia increases the risk of stroke during pregnancy and during the first postpartum year. The risk of stroke was significantly elevated even after adjustment for age, year of education, marital status, multiple gestation, birthweight, parity, anemia, diabetes, cesarean delivery, chronic hypertension, pregnancy-related hypertension, antepartum hemorrhage, and postpartum hemorrhage in multivariate analysis. Based on a cohort of parturients during 1999 and 2003 in Taiwan, the incidence rate of stroke was 21.47 cases per 100 000 deliveries, and the age-adjusted rate of stroke was 11.53 per 100 000 populations based on the age-structure of a world standard population,[17] which is compatible with those of previous studies lying between 11 and 26 deliveries per 100 000 parturients.[4–10,15]

Our study demonstrated the differences in the distribution and trend of developing the cases with hemorrhagic stroke and ischemic stroke (Figures 2 and 3), and that preeclampsia-eclampsia in Taiwanese women is associated with a high stroke risk in both hemorrhagic stroke (adjusted RR range from 5.61 to 19.90,) and ischemic stroke (adjusted RR range from 4.35 to 40.86; Table 3) from 3 months antepartum up to 12 months postpartum. These important findings imply that we should carefully follow the preeclampsia-eclampsia patients for at least the first year postpartum to try to reduce their risk.

Previous studies also reported an increased risk of stroke with preeclampsia-eclampsia. Wilson et al[14] reported a 3.59-fold elevation in the risk of stroke (95% CI: 1.04 to 12.4) in women with preeclampsia-eclampsia. The difference between Asian and Western countries may be due to the different patterns of stroke, because hemorrhagic stroke is more common in Asia and carries a higher mortality.[16,19] Brown et

al[10] found that women with preeclampsia were 60% more likely to have ischemic stroke (RR: 1.63; 95% CI: 1.02 to 2.62) than women without it. Liang et al[16] also showed that intracranial hemorrhage is slightly more common than cerebral infarction in Asian than in Western countries.

The physiological hormonally mediated changes in circulation, vascular tissue structure, and coagulation status, and the pathological state of preeclampsia-eclampsia, such as endothelial dysfunction, contribute to this increased risk of stroke.[15–23] Among pregnancy-associated strokes, hemorrhagic strokes are mainly due to rupture of aneurysms and arteriovenous malformations and ischemic strokes are mainly owing to late pregnancy and postpartum cerebral venous thrombosis, and strokes associated with preeclampsia-eclampsia may be contributed from cardioembolism, especially in populations at risk from a high rate of underlying rheumatic valvular heart disease.[15,18]

A strong association of cesarean delivery with stroke during pregnancy and postpartum was also observed in our study, which is similar to previous findings.[6,24] In previous studies, an association was observed between pregnancy-related hypertension and stroke.[6,15] Our study also supports such a finding; however, due to the small number of cases the correlation was not consistent. Diabetes mellitus was shown as a risk factor for stroke in a previous study.[25,26] Our study shows that diabetes does increase the risk of stroke during pregnancy and postpartum; however, the increase was not statistically significant across all periods of observation.

## Limitations

Several limitations in this study need to be emphasized. First, there were a limited number of stroke cases, despite the fact that this was a population-based study that covered a 5-year period. A larger number of strokes could increase the significance of the associations that were identified. Based on our national insurance system, almost all clinics are linked to NHI; but we still might miss some cases that died of stoke at home. Second, 3 important clinical parameters were not available in the NHI claims database including clinical/imaging information, the severity of stroke, and body mass index. This could alter the results of the study because body mass index correlates with stroke in young women.[10] Thirdly, the NHI claims data does not include a history of smoking.

Thus, we are unable to determine the effect of smoking on our data even though smoking has been identified as an important stroke risk factor.[10] Lastly, the stroke cases in our study were identified by ICD-9 codes 430 to 437, but these codes might not be all specific for stroke.[27]

Despite such limitations, the NHI claims database and birth certificate dataset provides valuable information for understanding the association between stroke and pregnancy. Young women suffering from stroke have received more attention lately not only because of a high death rate, but because stroke sequelae are greater in this age group. These strokes place a large burden on society and health-care system, and there should be increased effort to prevent them. In summary, women with preeclampsia-eclampsia have a significantly higher risk of stroke, both hemorrhagic and ischemic, during pregnancy, and their risk remains significant at least 12 months for hemorrhagic stroke and at least 6 months for ischemic stroke. Our results suggest that there should be close monitoring of women with preeclampsia-eclampsia during pregnancy and up to at least 1-year postpartum.

## Disclosures

None.

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