Strokes Associated With Pregnancy and Puerperium
A Nationwide Study by the Japan Stroke Society

Kazumichi Yoshida, MD, PhD; Jun C. Takahashi, MD, PhD; Yohei Takenobu, MD, PhD; Norihiro Suzuki, MD, PhD; Akira Ogawa, MD, PhD; Susumu Miyamoto, MD, PhD

Background and Purpose—The incidence and cause of strokes associated with pregnancy and the puerperium are still not fully understood. The aim of this study was to characterize pregnancy-related strokes in Japan using a large-scale survey with current imaging techniques.

Methods—A retrospective analysis was conducted based on clinical chart reviews in 736 stroke teaching hospitals certified by the Japan Stroke Society between 2012 and 2013, using a web-based questionnaire requesting the detailed clinical course without any personally identifying information. The collection rate of this questionnaire was 70.5%, with 151 pregnancy-associated strokes extracted.

Results—Hemorrhagic strokes were observed in 111 cases (73.5%), ischemic strokes in 37 (24.5%), and mixed type in 3 cases (2.0%). The estimated incidence of pregnancy-associated stroke was 10.2 per 100,000 deliveries. Major causes of hemorrhage were aneurysm (19.8%), arteriovenous malformation (17.1%), pregnancy-induced hypertension (11.7%), and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count) (8.1%). Preexisting cerebrovascular diseases responsible for hemorrhage were detected in 59 cases (53.1%). Among the ischemic strokes, 28 (75.7%) were arterial and 9 (24.3%) were venous infarctions. The most frequent cause of arterial infarctions was reversible cerebral vasoconstriction syndrome. Hemorrhagic stroke showed much poorer prognosis than ischemic stroke.

Conclusions—The incidence of pregnancy-associated stroke in Japan did not seem higher than that in other Asian and Western countries. The proportion of hemorrhagic stroke among Japanese women was much higher than that in white women. Preexisting cerebrovascular diseases and reversible cerebral vasoconstriction syndrome play a key role in hemorrhagic and ischemic stroke, respectively. (Stroke. 2017;48:276-282. DOI: 10.1161/STROKEAHA.116.014406.)

Key Words: cerebrovascular diseases ■ gestational age ■ morbidity ■ pregnancy ■ prognosis

Pregnancy-associated stroke is rare but is considered an important cause of morbidity and mortality in women of childbearing age.1 Previous studies dealing with the incidence of pregnancy-associated stroke have been performed using hospital-based, population-based, and nationwide methods, and most have been conducted in Western countries and Taiwan.2–10 The reported studies vary a great deal with respect to the reported causes and incidences of stroke, which could be partly attributed to selection biases because of population size or diagnostic imaging modality. In addition, racial and ethnic differences in stroke subtypes have been well recognized between Western and Asian populations.1,6,9,11–13 The aim of the present study was to elucidate the incidence and causes of pregnancy-associated strokes in Japanese women on a large scale in the era of magnetic resonance imaging (MRI).

Methods
This study was a retrospective analysis based on clinical chart review in 736 stroke teaching hospitals certified by the Japan Stroke Society. A nationwide survey was conducted in 2014 as an official project of the society. The target of the primary survey was all strokes occurring during pregnancy, delivery, and puerperium (within 6 weeks after delivery) that were treated in these hospitals within the 2-year period between January 2012 and December 2013. In the primary survey, all 736 training institutes were assigned to compile the number of patients with pregnancy-associated strokes treated in their own hospitals during this period. The results were emailed to the survey office without any clinical information. In the secondary survey, a web-based survey requesting detailed clinical information on each case without any personally identifying information was conducted. The clinical information included stroke type and time of stroke onset (gestational age or time after delivery), causes of hemorrhage, types of underlying cerebrovascular diseases (CVDs), types of obstetric systemic complications, time between symptom onset and initial computed tomography and MRI, and maternal prognoses. The
residual functional disability of patients was assessed using the modified Rankin scale on the day of discharge.

Feedback on the primary survey was obtained from 606 training hospitals (82.3%). The secondary web-based survey was conducted in those 126 hospitals that had experience with medical care for pregnancy-associated stroke; feedback was received from 108 of these hospitals (85.7%), involving 178 patients. After determining the eligibility of each case and eliminating duplications resulting from patient transfer between institutes, 151 pregnancy-associated strokes were finally extracted.

Ethics
This study was approved by the ethics board of Kyoto University Graduate School of Medicine and Kyoto University Hospital, Kyoto, Japan, and conducted according to the Declaration of Helsinki. On the basis of analysis of reported forms from institutions whose patients' information was anonymized and deidentified, the requirement to obtain informed consent was waived and therefore not obtained from patients and their families in this study.

Results
Patient Demographics
Patient demographics are summarized in Table 1. The cases were divided into 111 hemorrhagic (intracerebral or subarachnoid hemorrhage) strokes (73.5%), 37 ischemic (e.g., arterial infarction or venous infarction) strokes (24.5%), and 3 mixed type (2.0%). Mixed type was defined as cases for which computed tomography and MRI at onset showed both hemorrhage and infarction simultaneously. Hemorrhagic infarction such as massive hemorrhage secondary to embolic infarction was classified as ischemic stroke, whereas infarction because of delayed vasospasm after subarachnoid hemorrhage was classified as hemorrhagic stroke. Strokes were confirmed on computed tomography or magnetic resonance angiography, digital-subtraction angiography, or computed tomography angiography, except for a few cases of early death in which further examinations were not possible. All patients who experienced ischemic and mixed-type stroke underwent MRI unless magnetic resonance evaluations were contraindicated. Mean age at the onset of each subtype was 32.7±5.2 years for hemorrhagic stroke, 30.2±6.2 years for ischemic stroke, and 37.0±1.7 years for mixed-type stroke. In hemorrhagic stroke, 55 events occurred during pregnancy, with a mean gestational age at onset of 25.3±10.3 weeks, 16 events occurred at delivery with a mean gestational age at delivery of 38.9±1.3 weeks, and 40 events occurred during puerperium. In ischemic stroke, 22 events occurred during pregnancy, with a mean gestational age at onset of 21.0±12.7 weeks, 4 events at delivery with a mean gestational age at delivery of 31.5±14.4 weeks, and 11 during puerperium. All mixed-type stroke events occurred during puerperium.

Frequency of Stroke Associated With Pregnancy and Puerperium
Recovery rates of the primary survey and secondary web-based survey were 82.3% and 85.7%, respectively, so, the final collection rate of this questionnaire reached 70.5%. The number of pregnancy-associated strokes finally extracted in this survey was 151, and the total number of pregnancy-associated strokes in Japan between 2012 and 2013 was estimated to be 215. According to the annual population survey report published online by the Japanese Ministry of Health, Labour and Welfare (http://www.mhlw.go.jp), the numbers of live births and fetal deaths during this survey period were 2,067,047 and 48,902, respectively; the estimated number of pregnant women was, therefore, 2,115,949. It follows that the estimated incidence of pregnancy-associated stroke in Japan was 10.2 per 100,000 deliveries.

Hemorrhagic Stroke
The causes and frequencies of the 111 hemorrhagic strokes were as follows: aneurysm, 22 (19.8%); arteriovenous malformation (AVM), 19 (17.1%); pregnancy-induced hypertension (PIH), 13 (11.7%); HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), 9 (8.1%), cavernous angioma, 8 (7.2%); reversible cerebral vasospasm syndrome (RCVS), 5 (4.5%); moyamoya disease, 2 (1.8%), other CVDs, 8 (7.2%); other obstetric complications, 7 (6.3%); and undetermined, 18 (16.2%; Table 2). Preexisting CVDs responsible for hemorrhage were detected in 59 cases (53.1%) and obstetric complications responsible for hemorrhage were discovered in 34 cases (30.6%) respectively. Patients with aneurysm, AVM, PIH, and HELLP syndrome comprised ≈60% of pregnancy-associated hemorrhagic stroke cases.

With respect to possible risk factors for pregnancy-associated stroke, 21 cases of obstetric complications such as PIH and preeclampsia and 2 cases of multiple pregnancy were found in 111 hemorrhagic strokes.

The timing of presentation of hemorrhagic stroke as a whole was 36 cases (50.5%) in pregnancy, 16 cases (14.4%) at delivery, and 39 cases (35.1%) during puerperium. On closer examination of the timing of onset for the 4 major causes of hemorrhagic stroke (aneurysm, AVM, PIH, and HELLP syndrome), the number of aneurysm ruptures increased with
pregnancy course and had a greater tendency to occur during the third trimester and postpartum period (≥24 h) whereas the number of AVM ruptures peaked in the second trimester and decreased after delivery (Figure 1). Among the 8 patients with cavernous angioma, 3 presented during the first trimester, 4 during the third trimester, and 1 during the postpartum period (≥24 hours), making characteristic temporal patterns difficult to derive because of the lack of sufficient numbers of patients. In contrast to the high incidence of hemorrhage because of preexisting CVDs during pregnancy and the later postpartum period without a characteristic tendency, whereas venous infarction predominated during the postpartum period (Figure 3).

### Types of Stroke and Patient Outcome

Patient outcome according to each stroke type was determined. Thirteen of the 111 patients with hemorrhagic stroke

| Table 2. Causes and Frequency of Pregnancy-Associated Stroke in Study Patients |
|-------------------------------|-------------------|
| **Hemorrhagic stroke (n=111)** | **Number (%)** |
| Aneurysm | 22 (19.8) |
| AVM | 19 (17.1) |
| PIH | 13 (11.7) |
| HELLP syndrome | 9 (8.1) |
| Cavernous angioma | 8 (7.2) |
| RCVS | 5 (4.5) |
| Moyamoya diseases | 2 (1.8) |
| Other CVDs | 8 (7.2) |
| Other obstetric complication | 7 (6.3) |
| Undetermined | 18 (16.2) |
| **Ischemic stroke (n=37)** | **Arterial infarction** |
| RCVS | 9 (24.3) |
| Coagulopathy | 6 (16.2) |
| Cardiogenic embolism | 2 (5.4) |
| ATBI | 2 (5.4) |
| Small vessel | 2 (5.4) |
| Paradoxical embolism | 1 (2.7) |
| Dissection | 1 (2.7) |
| Moyamoya disease | 1 (2.7) |
| Undetermined | 4 (10.8) |
| Venous infarction | 9 (24.3) |

ATBI indicates atherothrombotic brain infarction; AVM, arteriovenous malformation; CVD, cerebrovascular disease; HELLP, hemolysis, elevated liver enzymes, and low platelet count; PIH, pregnancy-induced hypertension; and RCVS, reversible cerebral vasoconstriction syndrome.

embolism, 2 (5.4%); atherothrombotic brain infarction, 2 (5.4%); small vessel disease, 2 (5.4%), paradoxical embolism, 1 (2.7%); dissection, 1 (2.7%); moyamoya disease, 1 (2.7%); and undetermined, 4 (10.8%; Table 2).

In terms of possible risk factors, 8 cases of obstetric complications were confirmed in 37 hemorrhagic strokes, with no cases of multiple pregnancy.

About the timing of onset in ischemic strokes, arterial infarction occurred during pregnancy and the postpartum period without a characteristic tendency, whereas venous infarction predominated during the postpartum period (Figure 3).

### Mixed Type

The radiological findings of all mixed-type strokes were arterial infarction with cortical subarachnoid hemorrhage; causes were RCVS in 2 cases and HELLP syndrome in 1 patient. All patients manifested strokes during the postpartum period; 2 of the strokes occurred within 24 hours after delivery, and 1 stroke occurred >8 days after delivery.

**Ischemic Stroke**

Among the 37 patients with ischemic stroke, 28 (75.7%) experienced arterial infarction and 9 (24.3%) experienced venous infarction. Causes of arterial infarction were as follows: RCVS, 9 (24.3%); coagulopathy, 6 (16.2%); cardiogenic
(11.7%) and 1 of the 37 patients with ischemic stroke (2.7%) died during the hospital stay, whereas all patients with mixed-type stroke survived. Poor outcome (modified Rankin scale score at discharge ≥3) was confirmed in 44 patients (39.6%) with hemorrhagic stroke, 6 patients (16.2%) with ischemic stroke, and none with mixed-type stroke, respectively. Hemorrhagic stroke showed a significantly higher rate of poor outcome than ischemic and mixed-type stroke. About outcomes for the 4 leading causes of hemorrhagic stroke, poor outcome was observed in 7 of the 22 patients (31.8%) with aneurysm, 6 of the 19 patients (31.6%) with AVM, 6 of the 13 patients (46.2%) with PIH, and 6 of the 9 patients (66.7%) with HELLP syndrome. The prognosis of hemorrhagic stroke because of obstetric complications (PIH and HELLP) was observed to be extremely poor.

Types of Stroke and Manner of Delivery
To elucidate the influence of the manner of delivery on the type of stroke, especially for hemorrhagic stroke, the number of patients presenting during or within 24 hours of delivery was examined based on the delivery method. The numbers of patients with hemorrhagic and ischemic strokes who gave birth by vaginal delivery were 24 and 5 compared with 7 and 1 who gave birth by cesarean section, respectively. The proportion of hemorrhagic stroke to ischemic stroke did not differ significantly between vaginal delivery and cesarean section.

Discussion
Frequency of Stroke Associated With Pregnancy and Puerperium
With respect to the incidence of pregnancy-associated stroke, no long-term prospective study has been published to date. Various population-based, single hospital-based, and nationwide retrospective studies have reported the risk of any stroke in pregnancy and puerperium to be between 8.9 and 67.1 per 100000 deliveries (Table 3). The wide range in stroke incidence can be attributed to several factors including study design, population size, times of study implementation, and regional differences. The estimated incidence of pregnancy-associated stroke in the present study was 10.2 per 100000 deliveries, relatively lower than results from the previous studies. For a long time, pregnancy and delivery have been widely believed to increase the risk of stroke. However, recent evidence has suggested that pregnancy itself is associated with a relatively low risk of stroke, whereas the risks become higher during the postpartum period. Kittner et al reported that the relative risks of ischemic stroke during pregnancy and the postpartum period were 0.7 and 8.7, respectively, whereas the relative risks of hemorrhagic stroke during pregnancy and the postpartum period were 2.5 and 28.3, respectively. More recently, Scott et al conducted a nationwide survey in the United Kingdom and estimated the incidence of pregnancy-associated stroke to be only 1.5 per 100000 women delivering, although stroke during the postpartum period was not included. The low incidence of the present study seems to be a reasonable finding given the results of current large-scale surveys, although the approach of our survey could potentially have led to an underestimation of pregnancy-associated stroke in Japan.

The substantial proportion of hemorrhagic stroke (73.5%) was a prominent feature of the present study (Table 3). Previous investigations conducted in Western countries have found that ischemic stroke is more frequent than hemorrhagic stroke in the pregnant population. The proportion of hemorrhagic stroke in 4 studies conducted in the United States ranged from 29% to 45%.11,12,13,19 and is reported to be 38% in Canada11 and 52% in France.5 On the contrary, surveys conducted in Taiwan have reported hemorrhagic stroke as slightly more common than ischemic stroke, ranging from 43% to 69%.5,8 Although previous studies and the present survey did not investigate the details of racial differences in the study population, >98% of the population in the present study seemed to be Japanese, and the surveyed women were almost entirely Asian (Japanese, Korean, and Chinese), according to the population survey report in 2013 published online by the Japanese Ministry of Health, Labour and Welfare. In light of studies demonstrating that hemorrhagic stroke is twice as common in Japanese and Chinese than in white people,3,6,7 it seems reasonable to consider that the high incidence of hemorrhagic stroke has much to do with racial differences.

Hemorrhagic Stroke
A wide variety of causes for pregnancy-associated hemorrhagic stroke has been reported in previous studies, many of which have not closely investigated preexisting CVDs. In the present study, the most common causes of hemorrhagic stroke were aneurysm (19.8%) and AVM (17.1%). The diagnostic rate of preexisting CVDs was as high as 53.1%, whereas the rate in Western countries is generally low, ranging from 21.4% to 37.5%. The previous Japanese nationwide survey for pregnancy-associated intracranial hemorrhage demonstrated preexisting CVDs in 55.7% of patients.6 The high rate of CVDs could be caused in part by racial differences. Concerning the natural history of unruptured aneurysms, a recent systematic review and pooled analysis of individual patient data from 8382 participants in 6 prospective cohort studies with subarachnoid hemorrhage demonstrated that Japanese people had a 2.8-fold increased risk of aneurysm rupture.18 For AVM, the rupture risk of nonwhite races, including Asian, is reported to be 3.09-fold higher than that in white
preexisting CVDs in this study had remained undiagnosed

Although most patients with hemorrhagic stroke because of

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controversial. These pregnancy-related hypertensive disorders

a severe form of preeclampsia, but the relationship remains

seizures. HELLP syndrome has been speculated to represent

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tonic–clonic seizures in a woman with preeclampsia with-

organ dysfunction. Eclampsia refers to the development of

Preeclampsia comprises PIH plus either proteinuria or end-

ence of protein in the urine or other signs of preeclampsia.

PIH is defined as the development of new hypertension in a

pregnant woman after 20 weeks' gestation without the pres-

sions such as PIH and HELLP syndrome carried a grave

hemorrhagic stroke, hemorrhage secondary to obstetric com-

prognosis in the present study, suggesting possible beneficial

early treatment for obstetric complications.

Hypertensive disorders of pregnancy have been classified

into types such as PIH and preeclampsia/eclampsia according-

to the severity of systemic and neurological symptoms. PIH is
defined as the development of new hypertension in a preg-
nant woman after 20 weeks' gestation without the presence

of protein in the urine or other signs of preeclampsia. Preeclampsia

comprises PIH plus either proteinuria or end-organ dysfunction. Eclampsia refers to the development of
tonic–clonic seizures in a woman with preeclampsia without

other neurological conditions that could account for the

seizures. HELLP syndrome has been speculated to represent

a severe form of preeclampsia, but the relationship remains

controversial. These pregnancy-related hypertensive disorders

were collectively considered obstetric complications in the

present study.

With regard to the timing of hemorrhagic stroke, a distinct-

ive and similar trend as in previous reports was confirmed

in the present study.2,18,19 Hemorrhage because of obstetric

complications was concentrated around the time of deliver-

y, whereas hemorrhage secondary to rupture of preexis-
ting CVDs was confirmed in each trimester (Figures 1 and

2). The number of patients with ruptured aneurysm tended
to increase from the third trimester to the late postpartum

period, whereas ruptured AVM was observed to frequently

occur in the second trimester. These findings strongly suggest

that multiple physiological changes such as cerebral blood

flow, blood pressure, and vascular endothelial cell function
during pregnancy have significant impacts on the vasculature

of AVM and aneurysms, and pregnancy itself could be a risk

factor for rupture.20,21 The exact reason why AVM and aneu-

rysm have such characteristic timing of rupture is unclear.

Although most patients with hemorrhagic stroke because of

preexisting CVDs in this study had remained undiagnosed

until the onset of bleeding, the characteristic temporal pat-

tern of rupture of aneurysms and AVM might suggest the

possible effectiveness of prophylactic surgery for such

CVDs at least before the second trimester in cases where

asymptomatic aneurysm or AVM is diagnosed before mid-to

late pregnancy.

The prognosis of pregnancy-associated hemorrhagic stroke

has previously been reported to be more severe than ischemic

stroke, which also held true in the present study.2,7,13 Although

no reports have described detailed prognoses for each cause of

hemorrhagic stroke, hemorrhage secondary to obstetric com-

plications such as PIH and HELLP syndrome carried a grave

prognosis in the present study, suggesting possible beneficial

effects of regular medical checkups for pregnant women and

early treatment for obstetric complications.

Ischemic Stroke

Few studies have clarified detailed causes in patients with

pregnancy-associated ischemic stroke. Sharshar et al7 dem-

onstrated in their French study that the most frequent cause was
eclampsia, accounting for 47% of nonhemorrhagic stroke,
followed by vertebral artery dissection, postpartum cerebral
angiopathy, protein S deficiency, and amniotic fluid embolism
at 6.7% each, with undetermined causes found in 26.7%. Most
cases of eclampsia were clinically diagnosed by the sudden
manifestation and focal neurological deficits and reportedly
resolved within a few days. However, in the present study,
eclampsia was considered not to be an etiologic factor but
rather a risk factor for ischemic stroke because the mechanism
by which eclampsia causes cerebral infarcts has not been fully
elucidated to date.

Among the identifiable causes of ischemic stroke, RCVS
was the most common (24.3%) in the present study. The
patients with RCVS were diagnosed by infarcts proven with
diffusion-weighted imaging and temporary narrowing of
responsible arteries confirmed on serial magnetic resonance
angiograms. These patients generally experienced a favorable
clinical course, as did patients with postpartum vasculopa-
thy (now classified as RCVS) in the French study.7 In light
of the similar clinical courses, many of the cases diagnosed

<table>
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<th>First Author</th>
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<th>Country</th>
<th>Study Design</th>
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<th>Incidence per 100,000 Deliveries</th>
<th>Ischemic Stroke, %</th>
<th>Hemorrhagic Stroke, %</th>
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as eclampsia in previous studies could have included patients with RCVS. This needs to be clarified in future investigations.

Other causes of pregnancy-associated ischemic stroke are much rarer. Many of them are well-known causes seen outside of pregnancy, including cardiogenic embolism, atherothrombotic brain infarction, small vessel disease, paradoxical embolism, arterial dissection, and moyamoya disease (Table 2). Etiologic factors should, thus, be fully evaluated as in non-pregnant patients, and appropriate treatment for the prevention of recurrence should be initiated when needed.

Ischemic stroke can have both arterial and venous origins. Arterial occlusion, other than venous thrombosis, has generally been accepted as a predominant cause of pregnancy-associated ischemic stroke, constituting ≈60% to 80% of cases in Western countries. For example, Cross et al confirmed the incidence of ischemic stroke from venous origin to be 1 in 20,000 pregnancies in Scotland, and Wiebers et al. reported 1 patient in 26,000 deliveries at the Mayo Clinic. On the contrary, previous studies in Asian countries have demonstrated venous thrombosis as a more common cause of ischemic stroke than in Western countries. Khan et al. studied 110 pregnancy-related ischemic strokes in 5 Asian countries (80 patients from Pakistan, 26 from India, 2 from Syria, and 1 each from Thailand and Sri Lanka) and reported that almost half the strokes (49.1%) were secondary to venous thrombosis. Jeng et al. observed 11 cases of venous thrombosis among 27 nonhemorrhagic strokes in Taiwanese pregnant women. The proportion of venous thrombosis in ischemic stroke in the present study was only 24.3% (Table 2), which indicated a tendency similar to that of Western countries. The reason for such differences in the frequency of venous thrombosis is unclear, but racial differences might not be an essential factor in light of previous studies and our results. A recent study using a health insurance database also demonstrated a lower incidence of pregnancy-associated venous thrombosis in Korea. A country’s stage of development, in terms of both public health and availability of various diagnostic imaging modalities, could have a great influence on the frequency of venous thrombosis.

Limitations
The present study had several potential limitations. First, this retrospective study was performed via a questionnaire survey of institutes; the number of patients with pregnancy-associated stroke could, therefore, have been underestimated, although the survey was conducted through a web-based questionnaire and the final collection rate was as high as 70.5%. Second, although the surveyed institutes comprised 736 stroke teaching hospitals throughout Japan certified by the Japan Stroke Society and most patients with pregnancy-associated stroke seemed to present at such hospitals, patients with mild symptoms treated at small-scale hospitals would have been excluded from the present survey. Third, our findings could not exactly correspond to Japanese pregnant women, because this survey did not contain any questionnaire item on racial background. However, it is reasonable to consider that our results are substantially limited to Japanese women according to the data of domestic deliveries published by the Japanese Ministry of Health, Labour and Welfare. Fourth, the actual condition of prognosis after pregnancy-associated strokes could not be elucidated in this study, which was conducted through a questionnaire survey of hospitals where patients underwent acute-phase treatment. As is the often case with younger stroke patients, those with pregnancy-associated strokes could achieve significant recovery from symptoms over several months of rehabilitation, so a long-term follow-up study of patients should be undertaken in the future. Finally, this survey was performed on physicians engaged in stroke treatment, and sufficient investigation about possible risk factors for pregnancy-associated stroke such as obstetric/gynecological complications and number of pregnancies could not be performed.

Summary
This survey provided information on the cause and estimated incidence of both hemorrhagic and ischemic stroke in Japan based on a large number of pregnant women diagnosed using current imaging modalities. The study results suggest that the incidence of pregnancy-associated stroke among Japanese women may not be higher than in other Asian and Western countries. As in previous reports from Taiwan, hemorrhagic stroke was more common than in Western countries, suggesting that racial differences as a possible mechanism underlying the different distribution of stroke. Preexisting CVIs and RCVS play a key role in hemorrhagic and ischemic stroke, respectively.

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Disclosures
None.

References


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