Maternal Death Due to Stroke Associated With Pregnancy-Induced Hypertension

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Background: The aim of this study was to clarify the clinical features of maternal death due to stroke associated with pregnancy-induced hypertension (PIH) in Japan.

Methods and Results: Reported maternal deaths occurring between 2010 and 2012 throughout Japan were analyzed by the Maternal Death Exploratory Committee. Among a total of 154 reports of maternal death, those due to stroke with (n=12) or without (n=13) PIH were compared. Cerebral stroke occurred more frequently in the third trimester and during the second stage of labor in deaths with PIH, whereas it occurred at any time point in deaths not involving PIH. Although 83% of patients with PIH who died had experienced initial symptoms in a hospital, more than half of them required maternal transport due to lack of medical resources. Among the patients without PIH, some vascular abnormalities were identified, but no evidence was found among the patients with PIH. In addition, 58% of PIH cases resulting in stroke were complicated by hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome.

Conclusions: Appropriate management of PIH during pregnancy and labor, including anti-hypertensive therapy and early maternal transport to tertiary hospital, may reduce the maternal death rate.

Key Words: Hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome; Intracerebral hemorrhage; Maternal death; Pregnancy-induced hypertension; Stroke

The pathophysiology of pregnancy-induced hypertension (PIH) is complex and involves multiple systems. In this disorder, increasing resistance of maternal systemic blood vessels adversely affects the blood flow in many organ systems, including the liver, kidneys, brain and placenta in pregnant women. Women with pre-eclampsia and eclampsia have a 3–25-fold increased risk of serious complications such as pulmonary edema, abruption, aspiration pneumonia, renal failure, hepatic failure, disseminated intravascular coagulation (DIC) and stroke. Without appropriate management, PIH progresses to severe maternal and fetal pathologies resulting in stillbirth as well as maternal death. Especially, pre-eclampsia is a known risk factor in 25–45% of stroke cases during pregnancy.

Conclusions: Appropriate management of PIH during pregnancy and labor, including anti-hypertensive therapy and early maternal transport to tertiary hospital, may reduce the maternal death rate. The purpose of the present study was to clarify the clinical features of maternal death associated with PIH in Japan.

Methods

Maternal deaths associated with PIH in Japan between 2010 and 2012 were reviewed to clarify patient clinical features. Then, the clinical characteristics in maternal death due to stroke...
associated with PIH were compared with that without PIH collected by the JAOG and analyzed by the Maternal Death Exploratory Committee.

When maternal death occurs in Japan, a detailed report is submitted to JAOG and the individual data are analyzed by the Maternal Death Exploratory Committee (Chairman: T. Ikeda). This committee consists of 15 obstetricians, 4 anesthesiologists, 2 pathologists, an emergency physician and various specialists who attend review sessions each month to make annual recommendations to reduce the maternal mortality rate. The present study was performed as part of a series analyzing maternal deaths in Japan by this committee.9

In cases of maternal death in which the mother died during pregnancy or within 1 year after delivery, report forms are submitted to the registration system. The report form contains 22 pages of approximately 100 questions to elicit detailed information regarding the clinical history of each death and the characteristics of the facility and personnel that participated in the patient’s care (Supplementary File 1). All anonymized reports are analyzed for factors associated with maternal mortality and the circumstances of death.

The definition and classification of PIH followed the guidelines published by the Japan Society for the Study of Hypertension in Pregnancy for Japanese obstetric care providers.10 PIH was defined as hypertension (blood pressure ≥140/90 mmHg) with or without proteinuria (≥300 mg/24 h) emerging after 20 weeks of gestation and resolving up to 12 weeks after delivery. Furthermore, it is recommended in the guidelines proposed by the Japan Society of Obstetrics and Gynecology that hypotensive drugs, including α-methyldopa (250–2,000 mg/day), hydralazine (30–200 mg/day), nifedipine (20–40 mg/day) or labetalol (150–450 mg/day), should be administered, if systolic blood pressure is ≥160 mmHg or if the diastolic blood pressure is ≥110 mmHg. When a sudden elevation of blood pressure occurs during labor (≥160/110 mmHg), the use of hydralazine or nicardipine should also be considered.11

In Japan, pregnant women usually undergo regular prenatal checkups, which include blood pressure measurement and a urine test every 2 weeks after 26 weeks’ gestation and every week after 36 weeks. Thus, patients are evaluated for PIH at least every 2 weeks. Therefore, in the present study, “patients without PIH” were defined as those in whom PIH had not appeared by the final examination in a hospital or in the recent prenatal checkups. The diagnosis and location in the brain of intracerebral hemorrhage (ICH), subarachnoid hemorrhage and ischemic stroke

### Table 1. Characteristics of Maternal Death Associated With PIH

| ID no. | Age (years) | G | P | Height (cm) | Weight (kg) | At delivery | Before pregnancy | BMI at delivery | BP (mmHg)/medication | Direct cause of death | Onset GA (weeks) | BP (mmHg) |
|-------|-------------|---|---|-------------|-------------|-------------|------------------|------------------|---------------------|---------------------|-----------------|-----------|
| 1     | 40          | 0 | 0 | 162         | 67          | 25.5        | 150/90 (No)     | ICH (R nucleus caudatus) | 34                  | 190/115             |
| 2     | 23          | 1 | 0 | 62          | 49          | 141/94 (No) | ICH (bl. basal ganglia) | 37                  | 201/126             |
| 3     | 32          | 1 | 1 | 165         | 53          | 19.5        | 150/90 (No)     | ICH (L frontal lobe) | 39                  | 170/100            |
| 4     | 30          | 1 | 1 | 147         | 55          | 25.2        | 150/100 (No)    | ICH (L thalamus)    | 38                  | 179/116            |
| 5     | 36          | 1 | 1 | 158         | 60          | 24          | 164/100 (AMD)   | ICH (R lateral ventricle) | 36                  | 158/108            |
| 6     | 35          | 2 | 2 | 153         | 79          | 33.7        | 181/102 (No)    | ICH               | 41                  | 181/131            |
| 7     | 27          | 0 | 0 | 62          | 49          | 173/114 (hydralazine) | ICH (bl. cerebrum) | 38                  | 184/130             |
| 8     | 45          | 9 | 2 | 155         | 57          | 23.6        | 155/98 (No)     | ICH (L frontal, occipital) | 39                  | 192/100            |
| 9     | 33          | 0 | 0 | 152         | 62          | 26.8        | 194/134 (No)    | ICH (bl. temporal lobe) | 38                  | 222/123            |
| 10    | 38          | 1 | 0 | 164         | 66          | 24.5        | 141/81 (No)     | ICH (brainstem)     | 40                  | 166/95             |
| 11    | 28          | 0 | 0 | 155         | 63          | 166/108 (No) | ICH (L lateral ventricle) | 36                  | 180/110            |
| 12    | 34          | 1 | 1 | 158         | 64          | 25.6        | 170/98 (No)     | ICH (diffuse cerebrum) | 33                  | 170/107            |
| 13    | 36          | 2 | 2 | 155         | 57          | 23.7        | 164/86 (No)     | Pulmonary edema     | 38                  | 219/110            |
| 14    | 34          | 2 | 2 | 158         | 70          | 28.1        | 154/95 (No)     | Cardiomyopathy      | 38                  | 160/110            |
| 15    | 29          | 3 | 3 | 156         | 56          | 23          | 140/90 (No)     | Amniotic fluid embolism | 35                  | 80/22              |
| 16    | 34          | 0 | 0 | 156         | 67          | 27.7        | 141/81 (No)     | Unexplained         | 40                  | NR                 |
| 17    | 33          | 1 | 1 | 161         | 102         | 104         | 200/140 (hydralazine) | Unexplained         | 36                  | 90/40              |
Maternal Death Due to Stroke

| ID no. | Onset | Maternal transfer (duration from onset to admission) | Hospital characteristics (JNS category) | HELLP syndrome | Complication |
|-------|-------|------------------------------------------------------|----------------------------------------|----------------|--------------|
| 1     | During pregnancy | 17:30 | Hypertension | Outside | Yes (5h) | Medical center (branch) | Yes |
| 2     | During pregnancy | 2:30  | Headache     | Outside | Yes (3h) | Medical center (branch) | Yes |
| 3     | During pregnancy | 4:55  | Chest pain   | General hospital | Yes (1h) | City hospital (branch) | Yes |
| 4     | During pregnancy | 13:20 | Consciousness disorder | General hospital | Yes (18h) | University hospital (core) | Yes |
| 5     | During pregnancy | 23:50 | Headache     | General hospital | Yes (4.5h) | City hospital (branch) | No |
| 6     | During labor (1st stage) | 17:50 | Consciousness disorder | Private clinic | Yes (4h) | City hospital (branch) | No |
| 7     | During labor (2nd stage) | 18:15 | Consciousness disorder | Private clinic | Yes (2h) | University hospital (core) | No |
| 8     | During labor (2nd stage) | 3:00  | Consciousness disorder | General hospital | No | University hospital (core) | No |
| 9     | During labor (2nd stage) | 14:25 | Consciousness disorder | General hospital | No | City hospital (branch) | Yes |
| 10    | During labor (2nd stage) | 23:35 | Headache     | General hospital | No | Medical center (branch) | No |
| 11    | Puerperium (4h) | 18:30 | Consciousness disorder | General hospital | No | General hospital (branch) | Yes |
| 12    | Puerperium (9h) | 17:00 | Consciousness disorder | General hospital | No | Medical center (core) | Yes |
| 13    | During pregnancy | 11:00 | Cough        | Private clinic | Yes (33h) | Medical center | No |
| 14    | Puerperium (day 10) | 9:00  | Edema        | General hospital | No | University hospital | No |
| 15    | During CS | 10:00 | Consciousness disorder | General hospital | No | City hospital | No |
| 16    | During labor (2nd stage) | 21:30 | Consciousness disorder | Private clinic | Yes (3h) | University hospital | No |
| 17    | Puerperium (9h) | 1:15  | Dyspnea      | General hospital | No | Medical center | No |

were based on the interpretation of imaging by a radiologist and/or neurosurgeon using computed tomography (CT) and/or magnetic resonance imaging (MRI), and/or based on the findings during surgery or autopsy.

Statistical significance was defined as P<0.05. The data were entered into SPSS (Windows version 20.0 J; SPSS, Chicago, IL, USA). Continuous variables are reported as the median and range according to Mann-Whitney U-test. Categorical variables are reported as frequencies and were compared using Fisher’s exact test.

Ethics

This study was approved by the ethics board of National Cerebral and Cardiovascular Center, Osaka, Japan and the JAOG. This investigation was conducted according to the principles expressed in the Declaration of Helsinki. Informed consent was not obtained from patients and their family, because this study was based on analysis of reported forms from institution, and patient records/information was anonymized and de-identified prior to analysis.

Results

A total of 154 reports of maternal death (reports sent from 151 institutions in a total of 2,683 institutions that provide maternity services across Japan identified from a hospital list of the JAOG) were analyzed by the Maternal Death Exploratory Committee between 2010 and 2012. The maternal death rate (per 100,000 births) was 4.8 in 3,236,452 births after 12 weeks of pregnancy in Japan between 2010 and 2012. Of these, 17 met the criteria for PIH at the onset of initial symptoms (11% of all maternal deaths). The characteristics of the patients with maternal death associated with PIH are given in Table 1. The final diagnosis of the direct cause of maternal death was cerebral stroke in 12 cases (71%) of maternal death associated with PIH. Of the remaining 5 maternal deaths associated with PIH, direct cause of death was pulmonary edema in 1 case, cardiac myopathy in 1 case, amniotic fluid embolism in 1 case, and not clearly explained due to the presence of multifactorial factors in 2 cases.

The clinical characteristics of the maternal deaths due to stroke associated with PIH were compared with those of the 13 cases without PIH collected by the JAOG and analyzed by the Maternal Death Exploratory Committee. The characteristics of the maternal deaths due to stroke without PIH are listed in Table 1.

The clinical features of the maternal deaths due to stroke vs. the presence of PIH are listed in Table 3. The maternal characteristics did not differ between the patients with and without PIH. The median gestational age at the onset of ICH was 38 weeks (range, 33–41 weeks) in the patients with PIH, whereas stroke occurred at any time point, ranging from 9 to 39 weeks’
## Table 2. Characteristics of Maternal Death Due to Stroke Without PIH

| ID no. | Age (years) | G | P | Height (cm) | Weight (kg) | BMI at delivery | Direct cause of death | GA (weeks) | BP (mmHg) | Timing |
|--------|-------------|---|---|-------------|-------------|-----------------|-----------------------|-------------|-----------|--------|
| 1      | 33          | 1 | 1 | 154         | 62          | 26.1            | ICH (brainstem)       | 9           | 140/90    | After artificial abortion |
| 2      | 22          | 0 | 0 | 162         | 100         | 97              | ICH (thalamus)        | 17          | Unknown   | During pregnancy          |
| 3      | 32          | 2 | 2 | 154         | 62          | 26.1            | Subarachnoid bleeding | 22          | Unknown   | During pregnancy          |
| 4      | 33          | 1 | 1 | 154         | 62          | 26.1            | Subarachnoid bleeding | 23          | Unknown   | During pregnancy          |
| 5      | 28          | 1 | 1 | 155         | 47          | 19.6            | ICH                  | 29          | Unknown   | During pregnancy          |
| 6      | 40          | 2 | 2 | 161         | 80          | 30.9            | ICH                  | 31          | Unknown   | During pregnancy          |
| 7      | 32          | 0 | 0 | 152         | 60          | 26              | ICH (bl. lateral ventricle) | 33          | 203/146   | During pregnancy          |
| 8      | 40          | 3 | 3 | 156         | 72          | 29.6            | ICH (bl. lateral ventricle) | 37          | NR        | During pregnancy          |
| 9      | 37          | 0 | 0 | 156         | 72          | 29.6            | ICH (R frontal lobe)   | 39          | 119/76    | During labor (1st stage)  |
| 10     | 35          | 1 | 1 | 155         | 53          | 22.1            | ICH (L frontal lobe)   | 38          | 146/70    | Puerperium (9h)           |
| 11     | 37          | 0 | 0 | 157         | 54          | 21.9            | Subarachnoid bleeding | 33          | 200/100   | Puerperium (1 day)        |
| 12     | 38          | 1 | 0 | 175         | 72          | 23.5            | Subarachnoid bleeding | 38          | 195/120   | Puerperium (1 day)        |
| 13     | 32          | 0 | 0 | 166         | 62          | 22.5            | Ischemic stroke       | 35          | NR        | Puerperium (9 days)       |

### Table 2. Characteristics of Maternal Death Due to Stroke Without PIH

| ID no. | Time (h) | Onset | Symptom | Location      | Maternal transfer (duration from onset to admission) | Hospital characteristics (JNS category) | HELLP syndrome | Complication |
|--------|----------|-------|---------|---------------|-----------------------------------------------------|----------------------------------------|----------------|--------------|
| 1      | 11:00    | NR    | Headache| Outside       | Yes (50min)                                         | University hospital (core)              | No             |              |
| 2      | NR       | NR    | Headache| Outside       | Yes (3h)                                            | City hospital (branch)                  | No             |              |
| 3      | 14:15    | NR    | Headache| Outside       | Yes                                                 | Medical center (branch)                 | No             |              |
| 4      | 14:00    | NR    | Headache| Outside       | Yes (50min)                                         | University hospital (core)              | No             |              |
| 5      | 20:30    | NR    | Headache| Outside       | Yes                                                 | City hospital (branch)                  | No             |              |
| 6      | 7:00     | NR    | Headache| Private clinic| No                                                  | Medical center (branch)                 | No             | ITP, moyamoya |
| 7      | 14:00    | NR    | Headache| General hospital| No                                                 | University hospital (core)              | No             | AVM          |
| 9      | 6:50     | NR    | Headache| Private clinic| Yes (2h)                                            | University hospital (core)              | No             | Suspected AVM |
| 10     | 22:00    | NR    | Headache| General hospital| Yes (3h)                                           | General hospital (branch)               | No             | Aneurysm, PA, DIC |
| 11     | 11:00    | NR    | Hypertension| General hospital| Yes (30min)                                         | City hospital (branch)                  | No             | Aneurysm, PA, DIC |
| 12     | 7:18     | NR    | Headache| General hospital| Yes (2h)                                            | City hospital (branch)                  | No             |              |
| 13     | 12:00    | NR    | Headache| General hospital| No                                                  | Medical center (branch)                 | No             | Massive bleeding, DIC    |

AVM, arteriovenous malformation; DIC, disseminated intravascular coagulation; ITP, idiopathic thrombocytopenic purpura; moyamoya, moyamoya disease; PA, placental abruption. Other abbreviations as in Table 1.
gestation, in the patients without PIH. Cerebral stroke occurred more frequently during the second stage of labor (33%) among the patients with PIH, whereas this symptom was more likely to occur after delivery (40%) among the patients without PIH.

Stroke occurred outside of the hospital in 38% of patients without PIH, and in 17% of those with PIH. Whereas 83% of patients with PIH who died had experienced initial symptoms in a general or private hospital, more than half of these patients required maternal transport due to a lack of medical resources, such as specialists (brain surgeons and/or emergency physicians), medical staff, stored blood, imaging modalities, such as CT and MRI, and/or intensive care units.

The cause of cerebral stroke was ICH in all patients with PIH, whereas, in the patients without PIH, ICH was noted in 8 (62%), with subarachnoid hemorrhage being diagnosed in 4 of the 13 patients (31%) and hemorrhagic infarction in 1. Among the patients without PIH, moyamoya disease, cerebral aneurysm, arteriovenous malformation, and protein S deficiency were considered to be causes of cerebral stroke and maternal death. Moreover, there were 2 cases of stroke possibly induced by massive bleeding complicated by DIC during delivery. Among patients with PIH, however, no evidence of vascular abnormalities was found except for PIH itself. In addition, 7 of the 12 PIH patients who had ICH (58%) also had hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome.

### Discussion

In this review of maternal deaths in Japan between 2010 and 2012, 11% of all maternal deaths were associated with PIH. More than 70% of the causes of maternal death associated with PIH was due to stroke (ICH), and 12 of 25 deaths (48%) due to stroke were associated with PIH, similar to the previous reported rate of eclampsia and pre-eclampsia in patients with ICH ranging from 14% to 50%.12-15

Stroke associated with PIH occurred more frequently in the third trimester, especially during the pushing stage of labor, and less frequently after delivery in the patients with PIH, in comparison with maternal deaths due to stroke without PIH.

It is thought that pre-existing cerebral vascular disease plays a significant role in the onset of pregnancy-associated hemorrhagic stroke.16 In the present case series, stroke occurred at any time period, ranging from 9 to 39 weeks’ gestation in the patients without PIH. It has also been reported that hemorrhagic stroke without pre-existing cerebral vascular disease occurred significantly later than that associated with such disorders (mean, 33.7±8.7 weeks vs. 25.3±9.6 weeks, respectively).16 In patients without PIH, pre-existing brain vascular abnormalities with possible associations with stroke, such as moyamoya disease, cerebral aneurysm and arteriovenous malformation, were reported at imaging facilities in the present study.

ICH is a subtype of stroke that occurs within the brain tissue itself and is a serious medical emergency, because it can increase intracranial pressure.17 Pregnancy-related ICH has an estimated mortality rate of 9–38%.13,14,17-19 Because PIH is a disease involving damaged endothelial cells, cerebral ischemia due to spasms and the leakage of cerebral blood vessels may cause cerebral edema and hemorrhage. The higher rate of ICH observed in patients with PIH may be explained by these changes induced by PIH.

More than half of all cases of PIH in our series involved ICH complicated by HELLP syndrome. A previous report showed that 45% of maternal deaths due to HELLP syndrome are associated with cerebral hemorrhage.20 In addition to hypertension and endothelial dysfunction of the cerebral vasculature, decreased platelet count and coagulation factors may contribute to the high mortality of ICH associated with HELLP syn-

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### Table 3. Clinical Features of Maternal Death Due to Stroke vs. Presence of PIH

| Maternal characteristics | With PIH (n=12) | Without PIH (n=13) | P-value |
|--------------------------|----------------|--------------------|---------|
| Age (years)              | 34 (23–45)     | 33 (20–44)         | 0.810   |
| Gravidia                 | 1 (0–9)        | 1 (0–3)            | 1.000   |
| Parity                   | 1 (0–2)        | 1 (0–5)            | 0.799   |
| Height (cm)              | 157 (147–165)  | 157 (152–175)      | 0.631   |
| Weight before pregnancy (kg) | 49 (42–74)  | 51 (39–97)         | 1.000   |
| At delivery (kg)         | 62 (53–79)     | 65 (47–100)        | 0.863   |
| BMI at delivery          | 25.2 (19.5–33.7) | 24.7 (19.6–38.1) | 1.000   |
| Onset of cerebral stroke |                |                    |         |
| Gestational weeks at onset (delivery) | 38 (33–41) | 33 (9–39) | 0.009   |
| Blood pressure (mmHg) at initial symptom |              |                    |         |
| Systolic                 | 170 (112–192)  | 171 (119–203)      | 0.750   |
| Diastolic                | 100 (89–134)   | 95 (70–146)        | 0.616   |
| Timing of onset          |                |                    |         |
| Before onset of labor    | 42 (5)         | 54 (7)             | 0.695   |
| During first stage of labor | 8 (1)      | 8 (1)              | 1.000   |
| During second stage of labor | 33 (4)    | 0 (0)              | 0.039   |
| Puerperium               | 17 (2)         | 31 (4)             | 0.363   |
| Location at onset        |                |                    |         |
| Outside hospital         | 17 (2)         | 38 (5)             | 0.223   |
| Private clinic           | 17 (2)         | 23 (3)             | 1.000   |
| General Hospital         | 67 (8)         | 38 (5)             | 0.238   |
| Maternal transport       | 58 (7)         | 77 (10)            | 0.411   |

Data given as median (range) or % (n). Abbreviations as in Table 1.
The physiological changes that occur during pregnancy have a significant impact on the vasculature in cases of arteriovenous malformation, and rupture during pregnancy is by no means coincidental. The significance of pregnancy-associated ischemic and hemorrhagic stroke has been emphasized in patients with moyamoya disease. It should also be noted that not only hypertension during labor, but also pregnancy itself induced stroke in patients with pre-existing vascular abnormalities in the brain.

After a review of these case series, the Maternal Death Exploratory Committee considered most of the cases of stroke without PIH to be unpreventable as a result of sudden unforeseen onset without control outside of the hospital. In contrast, given that most of the cases of ICH occurred around delivery in women with PIH that was not treated using hypnotropic drugs before the onset of initial symptoms, such as headache and consciousness disorder, there may be a possibility to avoid maternal death by allowing for the appropriate control of hypertension, termination of the pregnancy or improvement of the medical resources (transfer to a different hospital). Clark et al reported the results of a retrospective evaluation of maternal deaths from 2007 to 2012 after the introduction of disease-specific protocols that included blood pressure management for severe intrapartum or postpartum hypertension based on 2000–2006 data, and noted that there was a significant decline in the rate of deaths from pre-eclampsia. We feel that better recommendations for blood pressure control during pregnancy are needed in Japan.

There are limitations, however, associated with the prevention of maternal death, because it remains unclear whether the ICH in women with PIH was associated with pre-existing brain vascular abnormalities. It was previously reported that the detection rate of hemorrhage in patients with cerebral vascular disease is 71.7% during pregnancy, 23.1% at delivery and 33.5% in the postnatal period. In addition, even if diagnostic imaging of women with pre-existing occult brain vascular diseases was performed during pregnancy, it is unclear whether these diseases can be detected. It also might be difficult to evaluate the details of the blood pressure control in the present case series, because this study was based on analyses of report forms sent from each institution.

Conclusions
ICH was the final causative disease in more than two-thirds of maternal deaths associated with PIH. Although many women were hospitalized due to delivery or the management of PIH, they could not be appropriately treated for PIH at their local hospital, and thus initially experienced serious symptoms. As a result, such women had to be transported to tertiary medical centers due to a lack of medical resources and such delays in receiving proper treatment sometimes resulted in maternal death. Although most maternal deaths are not preventable after the onset of ICH, an increased recognition of PIH, which is directly associated with maternal death, is needed.

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Supplementary Files
Supplementary File 1
Report form for submitting to the maternal death registration system (in Japanese)
Please find supplementary file(s):
http://dx.doi.org/10.1253/circj.CJ-15-0297