

Maternal Death Due to Stroke Associated With Pregnancy-Induced Hypertension

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Pregnancy and the postpartum period are associated with an increased risk of ischemic and hemorrhagic stroke and stroke is the leading cause of pregnancy-related disability. There are few long-term prospective studies of the incidence of stroke in pregnancy. The data from multiple retrospective studies about the incidence and mortality of stroke in pregnancy are summarized in **Table 1**. Various studies estimate the incidence of all types of stroke in pregnancy and puerperium between 25 and 34 per 100,000 deliveries.^{1–8} By comparison, the incidence of stroke in non-pregnant women in the 15–45 years age group is 11 per 100,000 women.⁵ A population-based retrospective study conducted from 1988 to 1991 found no increase during pregnancy but a relative risk of 8.7 during the first 6 weeks postpartum.³ Kuklina et al reported their recent analysis of hospital discharge data from the Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project, which is the largest nationwide all-payer inpatient care database in the United States.⁴ That report demonstrated that between 1994–1995 and 2006–2007, the rates of antenatal and postpartum hospitalizations for all types of stroke increased by 47% and 83%, respectively.

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Risk factors associated with pregnancy-related stroke include

hypertension, diabetes, valvular heart disease, hypercoagulable disorders, sickle cell disease, lupus, abuse of tobacco and other substances, and migraines.^{1,6} Several studies have demonstrated that hypertensive disorders are the leading cause of both hemorrhagic and ischemic strokes in pregnant and postpartum women.^{1–3,6,7} Preeclampsia/eclampsia and pregnancy-induced hypertension (PIH) are the 2 most important hypertensive disorders of pregnancy. Preeclampsia is defined as progressively worsening high blood pressure (BP) in pregnancy, occurring in the setting of proteinuria (≥ 300 mg of protein in a 24-h urine specimen).⁹ Eclampsia is preeclampsia that progresses to seizures. PIH is described as high BP (systolic BP ≥ 140 mmHg or diastolic BP ≤ 90 mmHg) after 20 weeks' gestation that occurs without the other signs and symptoms of preeclampsia.

Compared with women without hypertension, women with hypertension complicating pregnancy are 6–9-fold more likely to have a stroke.⁵ Therefore, control of PIH is considered to reduce the risk of maternal death from stroke (especially hemorrhagic stroke) during pregnancy. There are few reports about the relationship of maternal death due to stroke and PIH.

In this issue of the Journal, Hasagawa et al review case reports from medical institutions in Japan, and describe the clinical features of maternal death associated with PIH.¹⁰ In this review of maternal deaths in Japan between 2010 and

Table 1. Summary of Studies on the Incidence, Mortality and Morbidity of Pregnancy-Associated Stroke

Study date and first author	Subjects	Incidence (per 100,000 deliveries)	Mortality (%)
Sharshar (1995) ⁷	Pregnancy and 2 weeks PP 63 public maternities of the region of Ile de France (1989–1992)	Nonhemorrhagic stroke: 4.3 Hemorrhagic stroke: 4.6	0 (25)
Kittner (1996) ³	Women aged 15–44 years, pregnancy and 6 weeks PP 46 hospitals in central Maryland and Washington DC (1998–1991)	Ischemic stroke: 11 ICH: 9	
Lanska (1998) ⁵	Women aged 15–44 years National Hospital Discharge Survey in the USA (1979–1991)	All strokes: 17.7 CVT: 11.4	3.3 (0)
Lanska (2000) ⁶	Women aged 15–44 years National Hospital Discharge Survey in the USA (1993–1994)	All strokes: 13.1 CVT: 11.6	14.7 (0)
Jaigobin (2000) ⁸	Pregnancy and 6 weeks PP Toronto Hospital, Canada (1980–1997)	Ischemic stroke: 18 ICH: 8	0 (23)
James (2005) ¹	Pregnancy related discharges Nationwide Inpatient Sample in the USA (2000–2001)	All strokes: 34.2	4.1
Bateman (2006) ²	Women aged 15–44 years Nationwide Inpatient Sample in the USA (1993–2002)	ICH: 6.1	20.3

CVT, cerebral venous thrombosis; ICH, intracerebral hemorrhage; PP, postpartum.

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Table 2. AHA/ASA Recommendations for Treatment of Hypertension in Pregnancy and PP**Class I recommendation**

Severe hypertension in pregnancy should be treated with safe and effective antihypertensive medications, such as methyldopa, labetalol, and nifedipine, with consideration of maternal and fetal side effects (Level of Evidence A).

Class IIa recommendation

Consideration may be given to treatment of moderate hypertension in pregnancy with safe and effective antihypertensive medications, given the evidence for possibly increased stroke risk at currently defined systolic and diastolic BP cutoffs, as well as evidence for decreased risk for the development of severe hypertension with treatment (although maternal-fetal risk-benefit ratios have not been established) (Level of Evidence B).

After giving birth, women with chronic hypertension should be continued on their antihypertensive regimen, with dosage adjustments to reflect the decrease in volume of distribution and glomerular filtration rate that occurs after delivery. They should also be monitored carefully for the development of PP preeclampsia (Level of Evidence C).

Class III recommendation

Atenolol, angiotensin-receptor blockers, and direct renin inhibitors are contraindicated in pregnancy and should not be used (Level of Evidence C).

BP, blood pressure; PP, postpartum.

2012, 11% of all maternal deaths were associated with PIH. More than 70% of the causes of maternal death associated with PIH were due to stroke, and 12 of 25 deaths (48%) due to stroke were associated with PIH. In this series, the most frequent type of stroke was intracerebral hemorrhage (ICH). Of all stroke types, ICH during pregnancy and the puerperium leads to the highest risk of morbidity and mortality. Pregnancy increases the risk of hemorrhagic more than ischemic stroke (relative risk of 2.5 and 28.5 during pregnancy and the postpartum period).³ The underlying mechanism of pregnancy-related hemorrhage is likely to be the consequences of physiologic changes, such as blood volume expansion and vascular tissue remodeling in pregnancy, plus the risk from the strain and trauma of labor and delivery. Major causes of pregnancy-related hemorrhage are preeclampsia and eclampsia, which contribute to a large proportion of cases, followed by intracerebral aneurysm, arteriovenous malformation and moyamoya disease.^{11,12} The present study revealed that PIH is strongly related with poor outcomes of stroke, especially ICH, associated with pregnancy in Japan.

In February 2014, the American Heart Association and the American Stroke Association released their first guideline focused on stroke prevention in women.¹³ Their recommendations are shown in Table 2. Regarding control of hypertension during pregnancy, they recommend that severe hypertension should be treated with safe and effective antihypertensive medications, such as methyldopa, labetalol, and nifedipine, with consideration of maternal and fetal side effects (Class I, Level of Evidence A). For moderate hypertension, consideration may be given with safe and effective antihypertensive medications, given the evidence for possibly increased stroke risk at currently defined systolic and diastolic BP cutoffs, as well as evidence for decreased risk for the development of severe hypertension with treatment (although maternal-fetal risk-benefit ratios have not been established) (Class IIa, Level of Evidence B). In this guideline, high BP during pregnancy is defined as mild (diastolic BP 90–99 mmHg or systolic BP 140–149 mmHg), moderate (diastolic BP 100–109 mmHg or

systolic BP 150–159 mmHg), or severe (diastolic BP ≥ 110 mmHg or systolic BP ≥ 160 mmHg). They mention that the goal of BP management in pregnancy is to maintain systolic BP between 130 and 155 mmHg and diastolic BP between 80 and 105 mmHg. These recommendations are based on studies of European and American populations. Because there are differences among the races for stroke risk in pregnancy, prospective randomized controlled trials assessing antihypertensive interventions to reduce stroke risk are needed.

An important point in the present study is that although 83% of patients with PIH who died had experienced initial symptoms in a hospital, more than half required medical transport due to lack of local medical resources. They point out that such delays in receiving proper treatment sometimes resulted in maternal death. Although the mortality rate associated with cardiovascular disease such as stroke or acute myocardial infarction is not high in Japan,^{10,14} timely transport and treatment of patients who have risk factors in pregnancy, especially PIH, is important for improving the outcome of pregnancy in Japan.

Disclosures

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References

- James AH, Bushnell CD, Jamison MG, Myers ER. Incidence and risk factors for stroke in pregnancy and the puerperium. *Obstet Gynecol* 2005; **106**: 509–516.
- Bateman BT, Schumacher HC, Bushnell CD, Pile-Spellman J, Simpson LL, Sacco RL, et al. Intracerebral hemorrhage in pregnancy: Frequency, risk factors, and outcome. *Neurology* 2006; **67**: 424–429.
- Kittner SJ, Stern BJ, Feaser BR, Hebel R, Nagey DA, Buchholz DW, et al. Pregnancy and the risk of stroke. *N Engl J Med* 1996; **335**: 768–774.
- Kuklina EV, Tong X, Bansil P, George MG, Callaghan WM. Trends in pregnancy hospitalizations that included a stroke in the United States from 1994 to 2007. *Stroke* 2011; **42**: 2564–2570.
- Lanska DJ, Kryscio RJ. Stroke and intracranial venous thrombosis during pregnancy and puerperium. *Neurology* 1998; **51**: 1622–1628.
- Lanska DJ, Kryscio RJ. Risk factors for peripartum and postpartum stroke and intracranial venous thrombosis. *Stroke* 2000; **31**: 1274–1282.
- Sharshar T, Lamy C, Mas JL. Incidence and causes of strokes associated with pregnancy and puerperium: A study in public hospitals of Ile de France: Stroke in Pregnancy Study Group. *Stroke* 1995; **26**: 930–936.
- Jaigobin C, Silver FL. Stroke and pregnancy. *Stroke* 2000; **31**: 2948–2951.
- American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy: Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol* 2013; **122**: 1122–1131.
- Hasegawa J, Ikeda T, Sekizawa A, Tanaka H, Nakata M, Murakoshi T, et al. Maternal death due to stroke associated with pregnancy-induced hypertension. *Circ J* 2015; **79**: 1835–1840.
- Takahashi JC, Iihara K, Ishii A, Watanabe E, Ikeda T, Miyamoto S. Pregnancy-associated intracranial hemorrhage: Results of a survey of neurosurgical institutes across Japan. *J Stroke Cerebrovasc Dis* 2014; **23**: e65–e71, doi:10.1016/j.jstrokecerebrovasdis.2013.08.017.
- Takahashi JC, Ikeda T, Iihara K, Miyamoto S. Pregnancy and delivery in moyamoya disease: Results of a nationwide survey in Japan. *Neurol Med Chir (Tokyo)* 2012; **52**: 304–310.
- Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, et al. Guidelines for the prevention of stroke in women: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014; **45**: 1545–1588.
- Satoh H, Sano M, Suwa K, Saotome M, Urushida T, Katoh H, et al. Pregnancy-related acute myocardial infarction in Japan: A review of epidemiology, etiology and treatment from case reports. *Circ J* 2013; **77**: 725–733.