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Stroke in Women: Risk and Prevention Throughout the Lifespan

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About 780,000 people in the United States suffer a stroke each year, and about 15% of these strokes are fatal. Of those who die from stroke, about 60% are women [1]. Women also tend to have worse outcomes (quality of life, depression, disability) than men [2–4]. Although the incidence of stroke is lower in women than men for most of their lifespan, a 65-year-old woman's lifetime risk of stroke is 1 in 5, whereas a 65-year-old man's risk is one in six [5]. There has been an increasing emphasis on gender differences and gender-specific issues in cardiovascular diseases. Therefore, randomized controlled trials and cohort studies limited to women have increased our understanding of the health-related issues that are specific to women. Although the majority of strokes occur in women who are older, it is important to consider the woman's lifespan to best appreciate the impact of stroke in women.

Stroke in girls

Stroke is rare in young children, occurring at a rate of 2.3 to 2.7 per 100,000 children in the United States [6–8]. There have been relatively few studies with adequate numbers of childhood stroke cases to determine differences by gender. However, a large epidemiology study of all children in California found that boys were at higher risk for all stroke types than girls (boys: 2.57/100,000; girls: 2.02/100,000; RR 1.28, 95% CI 1.17–1.39) [8].

Stroke during child-bearing years

Pregnancy

For women of child-bearing age, the incidence of stroke is low, about 11 per 100,000. During pregnancy, the rate of stroke appears to increase. Reported incidence has ranged from 4 to 34 per 100,000 (Table 1) [9–17]. Three population-based studies have used the Nationwide Inpatient Sample (NIS) to investigate stroke in pregnancy [13,14,18]. The NIS is a 20% stratified sample of all discharges in the United States available for assessments of hospitalization rates using specific ICD-9 codes. This is especially useful for conditions such as pregnancy, because the ICD-9 codes can designate antepartum, delivery, or postpartum hospitalizations. During 1979–1991, the rate of stroke (including intracranial venous thrombosis) was 29.1 per 100,000 deliveries [13], and from 1993 to 1994 the rate was 24.7 per 100,000 [14]. The analysis from 2000 to 2001 [16] reported a slightly higher rate (34.2 per 100,000) than the previous two analyses. This may be related to the use of specific ICD-9 codes for stroke (325, 430, 431, 434, and 436) in addition to the codes for cerebrovascular disorders

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in the puerperium (674.0) [16]. In addition, it is possible that the incidence of pregnancy-related stroke may be increasing.

The majority of pregnancy-related strokes occur postpartum. For example, of the stroke cases identified by James and colleagues [16], 48% occurred in the postpartum period, versus 41% at delivery, and 11% antepartum. In addition, the Baltimore Washington Cooperative Young Stroke Study found that stroke rate was not increased in pregnant compared with nonpregnant women, but during the postpartum period, there was a fivefold increased risk of ischemic stroke (RR 5.4; 95% CI 2.9–10.0), and an 18-fold increased risk of intracerebral hemorrhage (RR 18.2; 95% CI 8.7–38.1) [11]. In a case series of 20 women with postpartum stroke, eight (40%) occurred within the first 7 days of delivery, seven (35%) between 7 and 14 days, three (15%) between 14 and 21 days, and two (10%) between 28 and 36 days [19]. Although the underlying reason for the increased risk of stroke at delivery and postpartum is not certain, increased risk may be associated with a relative hypercoagulability and the natural selection to protect against fatal hemorrhage at delivery. Others have speculated that the large decrease in blood volume, the rapid fluctuations in hormone levels, or vessel wall changes could profoundly influence cerebral hemodynamics [11].

Pregnancy-related intracerebral hemorrhage (ICH) carries the highest morbidity and mortality of all stroke types [16]. The incidence of pregnancy-related ICH was also studied using the NIS database, and an analysis from 1993 to 2002 showed that the risk of ICH is higher in pregnant (7.1 per 100,000 at-risk person-years) than in nonpregnant women (5.0 per 100,000 person years) [17]. Similar to other stroke types, ICH predominantly occurred postpartum compared with antepartum. In addition, 20% of these women died in the hospital; 18% were discharged to a skilled nursing or other type of facility; and only 44% had routine discharges to home. Factors associated with maternal mortality included advanced maternal age, Hispanic race-ethnicity, and coagulopathy [17].

There are multiple risk factors that have been recognized as risk factors for stroke in pregnancy. One of the most important risks is advanced maternal age. For example, in the NIS analysis from 2000 to 2001, the incidence increased from 35.3 per 100,000 in those aged 30 to 34, to 58.1 per 100,000 in those aged 35 to 39 [16]. In addition, African American women have about a 50% higher risk of stroke than white women (odds ratio [OR] 1.5; 95% CI 1.2–1.9). Novel risk factors that were explored and found to be associated with pregnancy-related stroke in the most recent analysis of the NIS included migraine (OR 16.9; 95% CI 9.7–29.5), thrombophilia (OR 16.0; 95% CI 9.4–27.2), sickle cell disease (OR 9.1; 95% CI 3.7–22.2), and lupus (OR 15.2; 95% CI 7.4–31.2) [16]. Other expected pregnancy-related complications were also identified, such as postpartum infection, postpartum hemorrhage, transfusion, fluid/electrolyte imbalance, and preeclampsia/gestational hypertension [16].

Preeclampsia

One of the hypertensive disorders of pregnancy, preeclampsia occurs in about 5% of pregnancies in the United States; it is an important cause of maternal and infant morbidity and mortality [20,21]. Preeclampsia and gestational hypertension increase the risk of stroke during pregnancy as a result of severe hypertension and disturbed cerebral autoregulation. For example, preeclampsia has been associated with vasculopathies that overlap with hypertensive encephalopathy and lead to cerebral endothelial leakage. This causes an appearance of vasogenic edema on brain imaging, is typically reversible, and rarely associated with ischemic stroke. The other severe consequence of hypertension is the risk of pregnancy-related ICH. As shown in the NIS analysis from 1993 to 2002, preeclampsia/gestational hypertension was associated with a 10-fold risk of pregnancy-related ICH [22]. Preeclampsia can also occur postpartum, and under-recognition of the diagnosis could lead to substantial delays in treatment.

The pathophysiology of preeclampsia is believed to be related to endothelial dysfunction that occurs early during pregnancy [23]. The endothelial dysfunction may also persist following delivery. For example, Chambers and colleagues [24] showed that women with preeclamptic deliveries had poorer endothelial function than women with normal pregnancies, even after adjusting for cardiovascular risk factors. Another case–control study showed that women with a history of preeclampsia evaluated about 15 years after pregnancy had higher glycosylated hemoglobin levels and insulin levels, which were suggestive of metabolic syndrome, as well as an increase in circulating cellular adhesion molecules (intercellular adhesion molecule [ICAM] and vascular cell adhesion molecule [VCAM]) compared with controls [25]. A separate study demonstrated that women with preeclampsia onset before 34 weeks gestation had elevated carotid intimal medial thickness (ie, a measure of subclinical atherosclerosis), compared with women with normal pregnancies and nulliparous women [26]. These measurements were performed beyond the puerperium, but before lactation had ceased. Although this study was small (only 22 women in each group), it suggests that preeclampsia, in particular the early-onset type, may be associated with accelerated atherosclerosis [26].

The vascular and inflammatory changes in women with a history of preeclampsia may in part explain the observed increased risk of stroke later in life. In a study from Scotland, women with preeclampsia/eclampsia were four times more likely to have hypertension (OR 3.98; 95% CI 2.8–5.6) and three times more likely to have had a self-reported stroke (OR 3.4; 95% CI 0.95–12.2) [27]. The Stroke Prevention in Young Women Study, a case–control study of women with ischemic stroke between ages 15 and 44, showed a 50% higher prevalence of self-reported preeclampsia versus controls, although the association was diminished when adjusted for hypertension [28]. In addition, women with maternal placental syndrome, which includes gestational hypertension, preeclampsia/eclampsia, placental abruption, and placental infarction, have an increased risk of heart disease later in life [29].

Another important consequence of preeclampsia is the risk of infant morbidity and mortality. Preeclampsia was shown to be an independent risk factor for perinatal arterial stroke, increasing the odds by fivefold (OR 5.3: 1.3–22.0) [30]. Therefore, it is important to recognize that preeclampsia is a risk for vasculopathy or stroke during delivery and postpartum (especially ICH), and it poses a risk for stroke later in life as a result of endothelial dysfunction, hypertension, and an increase in cardiovascular risk factors.

Oral contraceptives

The risk of stroke with oral contraceptive pill (OCP) use has been extensively evaluated. The results of three separate meta-analyses summarizing over 30 years of studies have shown that oral contraceptive users have about a twofold increased risk of stroke over non-users [31–33]. Because the incidence of stroke is low in this age group, the absolute risk with oral contraceptive use is also low, at about 8 per 100,000 women [31]. Although most women who use these drugs are healthy, there are some medical conditions that are clearly associated with an accelerated risk. These conditions include hypertension, smoking, migraine headache with aura, thrombophilia, and obesity.

Hypertension is a major risk factor for stroke in women using OCPs [34–37]. When blood pressure is screened before prescribing OCPs—and appropriately managed—the risk of ischemic stroke is reduced [38,39]. It is therefore recommended that blood pressure be screened before prescribing OCPs. The American College of Obstetricians and Gynecologists recommends that if women are under age 35 with well-controlled and monitored hypertension who do not smoke or have evidence of end-organ vascular disease, a trial of low-dose OCPs is acceptable [40].

Like hypertension, cigarette smoking is a well-known risk factor for stroke in women using OCPs. This risk ranges from about twofold to eightfold in OCP users versus nonusers [32,

34–36,41,42]. It is recommended that women who plan to use OCPs avoid smoking while on these medications, particularly if the women are over the age of 35.

OCP users who also have migraine headaches have an increased risk of stroke versus women without migraine headaches. The World Health Organization (WHO) Collaborative Study showed that women with migraine headache who used OCPs were roughly eight times more likely to have ischemic stroke than those with either risk factor alone and more than 16 times as likely as those with neither risk factor [43]. When women with both risk factors also smoked, a greater than multiplicative effect was seen on stroke risk, with an OR of 34.4 compared with those with none of the risk factors. Another study found a nearly 14-fold increase in migraineurs who used OCPs compared with those with neither risk factor [44]. A pooled analysis of two studies from the United States found a lower, but still statistically significant, risk of ischemic stroke in migraineurs who used OCPs [45].

Women who have migraines without auras and no other stroke risk factors can safely take OCPs, whereas women with frequent, prolonged, complicated auras should avoid OCPs [46]. The International Headache Society Task Force on Combined Oral Contraceptives and Hormone Replacement Therapy recommends consideration of progestin-only pills in those with stroke risk factors [47]. They also suggest that further evaluation, and possibly cessation of OCPs, may be needed in users who develop new persisting headaches, new-onset migraine with aura, increased headache frequency or intensity, or unusual aura symptoms including prolonged aura [47].

OCP use alters a variety of coagulation factors that may play an important role in the increased risk of stroke in users. There is evidence that women who have underlying thrombophilic disorders are at increased stroke risk when using OCPs. Slooter and colleagues [48] found that OCP users with Factor V Leiden mutation were at a greater than 11-fold increased risk of stroke than nonusers without the mutation. OCP users with the MTHFR 677TT mutation were at a roughly fivefold increased risk compared with those with neither risk factor. The risk of stroke with OCP use and MTHFR mutation is more than double that of either risk factor alone [49].

Obesity, as measured by body mass index and abdominal girth, has also been associated with a small but significant increased risk of stroke [50]. Obesity in combination with OCP use has been demonstrated to further increase the risk of stroke in young women. A large case-control study from the Netherlands noted a fourfold increase in stroke risk in obese OCP users compared with non-obese women who do not use OCPs and a twofold increased risk compared with nonobese women who use OCPs [36]. The best explanation for this synergistic risk is that obese women are at risk for hypercoagulability, insulin-resistance and diabetes, hypertension, and hyperlipidemia, which are all factors that increase the risk of stroke and which are perhaps synergistically increasing the risk in women using OCPs.

Stroke during mid-life

Women under age 50 are generally considered to have a lower incidence and prevalence of stroke than men [1]. However, data from the National Health and Nutrition Examination Survey (NHANES) has shown that women appear to be having a more substantial increase in the prevalence of stroke in midlife versus men. In this analysis, women age 45 to 54 had a significantly higher odds of stroke compared with men the same age (OR 2.39; 95% CI 1.32–4.32) [51]. Consistent with the surge in stroke events, there was a surge in cardiovascular risk in women greater than men, as well. For instance, systolic blood pressure (SBP) increased at a steeper rate in women with each decade from 35 to 44 years (average SBP 113.9 mm Hg), 45 to 54 years (average SBP 123.5 mm Hg), and 55 to 64 years (average SBP 132.0 mm Hg) [51]. Men, however, initially had a higher SBP between ages 35 and 44 (average SBP 120.0 mm Hg) than women, but men showed a more gradual increase to the ages of 55 to 64 (average

SBP 128.6 mm Hg). In addition, women had a substantial increase in total cholesterol, triglycerides, waist circumference, homocysteine, glycosylated hemoglobin, and a lowering of the ankle brachial pulsatility index between the ages of 45 to 54 and 55 to 64 [51]. These data suggest that there is an acceleration of multiple risk parameters in women a decade or more before cardiovascular and stroke events traditionally occur in women. Assuming these data are valid, there is a significant opportunity to increase efforts to recognize risk factors in women during midlife and improve prevention strategies.

Menopause

The midlife prevalence of stroke in women has been shown to occur as women would traditionally be experiencing the menopausal transition. Menopause occurs naturally in women with at least one intact and functioning ovary. During perimenopause, estradiol levels decline by about 60% [52]. After menopause, estradiol levels continue to decline but then plateau after one to three years. Overall, there is a sevenfold to 10-fold decrease in estradiol levels from the beginning to the end of the menopausal transition [53]. In contrast to the rapid decline in estradiol, circulating testosterone levels are decreasing more gradually during this period, [54] leading to a relative androgen excess [54].

The menopausal shifts in hormonal levels and ratios of estrogens to androgens are important because these sex steroids appear to have opposite effects on vascular risk. Estrogens have multiple beneficial effects on the cardiovascular system, including vasodilation and increased cerebral blood flow [55] by decreasing cerebral vascular tone and increasing arterial compliance [56].

In addition to the benefits on vessel function, estrogen may also reduce atherosclerotic risk through its impact on lipids. Exogenous estrogen replacement improves lipid profiles by lowering total and low-density lipoprotein (LDL) cholesterol, lipoprotein (a), and raising high-density lipoprotein (HDL) cholesterol [57,58].

Conversely, androgens have a detrimental effect on cerebral blood vessels by increasing arterial tone. They also lead to a pro-atherogenic profile by decreasing HDL, and by increasing triglycerides, LDL, and total cholesterol [54].

Concurrent with the decline in sex steroids, women develop changes in cardiovascular risk factors during menopause. Lipid measurements in women across the menopausal transition in the Healthy Women Study showed that LDL cholesterol and triglycerides increased and HDL cholesterol decreased during perimenopause, whereas fasting glucose and blood pressure levels increased during postmenopause [59]. Along with a change in body fat distribution leading to abdominal obesity, the lipid, blood pressure, and glucose changes are consistent with metabolic syndrome. In addition to the metabolic changes, estrogen deficiency during menopause also leads to a shift from anti-inflammatory to proinflammatory cytokines such as IL-1 β , IL-6, and TNF- α [60]. These cytokines are important because they have been associated with an increased risk of heart disease and stroke [61].

Hormone therapy (including selective estrogen receptor modulators)

Replacing the depletion of endogenous estradiol with replacement hormone therapy was widely believed to be an effective method to reduce cardiovascular disease in women. However, randomized trials of hormone therapy with conjugated equine estrogens (CEE), CEE with medroxyprogesterone acetate (MPA), and 17-beta estradiol showed no benefit for secondary prevention of heart disease [62] and stroke, [63] as well as an increased risk of both types of events in healthy women (ie, the Women's Health Initiative [WHI]) [64]. Multiple analyses of the WHI results have not revealed any particular subgroup of women who are at higher or

lower risk of cardiovascular events with hormone therapy (HT). However, a post hoc analysis of events based on the time of initiation following menopause showed that there was a trend for a reduced risk for heart disease for women who initiated HT within 5 years of menopause, but the risk of stroke with HT was elevated regardless of the timing of initiation [65].

Selective estrogen receptor modulators (SERMs) have anti-estrogenic effects in mammary tissues and estrogenic effects on bone and cholesterol levels, making these drugs useful for prevention of breast cancer and osteoporosis. Tamoxifen has been used as adjuvant therapy for surgical resection, radiation and chemotherapy in breast cancer, as well as prevention for high-risk women. Tamoxifen increases the risk of venous thrombosis by twofold to fourfold in users, and it may also be associated with an increased risk of ischemic stroke. A meta-analysis of prevention and adjuvant therapy trials found an 80% increased risk of ischemic stroke (OR 1.82; 95% CI 1.41–2.36), whereas there was a nonsignificant increase in all strokes combined (OR 1.29; 95% CI 0.92–1.81) [66]. A large case-control study, however, found that there was no association between stroke and tamoxifen use in women following breast cancer diagnosis, but that the use of any chemotherapy, regardless of regimen or whether it was combined with tamoxifen, was associated with stroke (OR 2.3; 95% CI 1.4–3.8). Raloxifene, a separate SERM, has been studied in a similar fashion as tamoxifen, but primarily for breast cancer prevention and for osteoporosis. Although an early analysis of cardiovascular events in the Multiple Outcomes of Raloxifene Evaluation suggested protection against cardiovascular events in women at high risk for cardiovascular disease, [67] the Raloxifene Use for the Heart trial showed no protection against heart disease and total strokes, but an increased risk for fatal stroke (OR 1.49; 95% CI 1.00–2.24) [68]. Raloxifene also significantly reduced the risk of invasive breast cancer [68]. Another trial compared the effects of tamoxifen and raloxifene on these same risks in the Study of Tamoxifen and Raloxifene trial [69]. This trial showed no difference in the rates of heart disease or stroke in the two treatment groups, although the risk of venous thromboembolism was lower with raloxifene.

Based on the strong evidence from these trials, the only recommended use for hormone therapy is for treatment of vasomotor symptoms (ie, hot flashes) and osteoporosis [70]. The cardiovascular disease prevention guidelines for women state that neither hormone therapy nor SERMs should be used for primary or secondary prevention (class III, level A) [71].

Stroke in older women

The impending epidemic

The prevalence of stroke is lower in women than men until the ages of 75 [72] to 85 [73]. With the exception of the NHANES analysis suggesting a midlife surge, women appear to be protected from stroke until the oldest age groups. From a population-based perspective, women make up about half of the population at age 50, but the ratio of women to men increases with each decade to a ratio of 2.70 at age 90 [74]. As a result of the larger number of women in older age groups, women comprise an excess of stroke deaths, which will increase as the population ages. Weighing all these factors together, there may be an impending epidemic of women dying from stroke. Health care providers need to be prepared for this by recognizing the risk factors and optimizing prevention in older women. The risk factors for stroke include hypertension, smoking, hyperlipidemia, atrial fibrillation, diabetes mellitus, carotid stenosis, prior stroke or transient ischemic attack, and coronary artery disease.

Guidelines for cardiovascular disease prevention in women

The most recent American Heart Association evidence-based guidelines for Cardiovascular Disease Prevention in Women contains updated clinical information relevant to the care of women at risk of stroke. Although these guidelines are not specific for stroke alone, the majority

of the risk factors for stroke and heart disease overlap, and the prevention strategies are relevant for both conditions.

In this update, classification of risk was modified to include high risk, at risk, and optimal risk (Box 1). The rationale for reclassifying women is related to the very high lifetime risk of cardiovascular disease. In fact, the lifetime risk of stroke in women is about 20%, [5] and for all cardiovascular disease, this approaches 40% [75]. The traditional Framingham risk score limits the prediction to 10 years or less, but it may underestimate the future risk of CVD in women who are found to have subclinical disease, measured with coronary artery calcium or carotid intimal-medial thickness [71]. In addition, because women are frequently misclassified as having lower than actual risk by physicians, [76] this redefinition was intended to increase recognition of risk and guide appropriate prevention strategies for women based on a simpler risk classification [71].

The guidelines for women who are not actively being treated for an acute cardiovascular event can be summarized as follows: (1) all women, regardless of risk, should be counseled on class I, level B lifestyle recommendations (smoking cessation, heart-healthy eating patterns, regular physical activity, and weight management); (2) blood pressure control (class I, level A for pharmacotherapy and level B for lifestyle changes), LDL goal < 100 mg/dL (class I, level B), aspirin (class I, level A) or other antiplatelet agents (class I, level B), glycemic control in diabetic women (class I, level B), and aldosterone blocker (class I, level B) in selected women are recommended for high risk women who have not had a recent cardiovascular event and do not meet requirements for acute cardiac or stroke rehabilitation [71]; (3) weight maintenance/reduction be pursued in all women, regardless of risk, to a goal BMI of 18.5 to 24.9 kg/m² and a waist circumference of ≤ 35 in through a balance of physical activity, caloric intake, and formal behavioral programs when indicated (class I, level B) [71]. Recommended diets are those rich in fruits and vegetables, whole-grain, high-fiber foods, fish (especially oily fish) at least twice a week, as well as very limited proportions of saturated fats and trans fatty acids (class I, level B); (4) physical activity recommendations for women include an accumulated total of at least 30 minutes of moderate-intensity physical exercise (eg, brisk walking) on most days of the week (class I, level B). Women who are working to lose weight or sustain weight should increase to 60 to 90 minutes of moderate-intensity activity on most, if not all, days of the week (class I, level C) [71].

Box 1

Risk classification for cardiovascular disease

High risk

- Established coronary heart disease
- Cerebrovascular disease
- Peripheral arterial disease
- Abdominal aortic aneurysm
- End-stage or chronic renal disease
- Diabetes mellitus
- 10-year Framingham global risk > 20%

At risk

- >1 major risk factor for CVD, including:
- Cigarette smoking

Poor diet

Physical inactivity

Obesity, especially central adiposity

Family history of premature CVD (CVD at <55 years of age in male relative and <65 years of age in female relative)

Hypertension

Dyslipidemia

Evidence of subclinical vascular disease (eg, coronary calcification or carotid intimal-medial thickness)

Metabolic syndrome

Poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise

Optimal risk

Framingham global risk <10% and a healthy lifestyle with no risk factors

Adapted from Mosca L, Banka C, Benjamin E, et al. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *Circulation* 2007;115:1481–501; with permission.

Aspirin for stroke prevention in women

Aspirin has long been the mainstay of secondary prevention of cardiovascular disease. An analysis from the Nurses' Health Study showed that women who used aspirin long-term had significantly lower mortality, especially cardiovascular mortality [77]. The Women's Health Study, a randomized controlled trial of 100 mg of aspirin every other day compared with placebo in healthy women over age 45, is the only study of aspirin for primary prevention in women [78]. The primary result of the trial showed no overall benefit in the composite outcome of first major cardiovascular event (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular disease) for the aspirin treated subjects [78]. However, there was a beneficial decrease in ischemic stroke events. The guidelines for cardiovascular prevention in women currently recommend aspirin therapy in doses of 75 to 325 mg per day for high-risk women unless contraindicated (class I, level A), and in women age 65 years or older, aspirin should be considered in doses of 81 mg daily or 100 mg every other day if blood pressure is controlled and the benefit for preventing ischemic stroke or myocardial infarction outweighs the risk of gastrointestinal bleeding and hemorrhagic stroke (class IIa, level B). In women younger than 65 years of age, aspirin should be considered when the benefit for preventing ischemic stroke is likely to outweigh the adverse effects of therapy (class IIb, level B) [71].

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Table 1

Incidence studies of pregnancy-related stroke

Author	Data source	Stroke cases/pregnant population	Incidence (per 100,000 deliveries)	Causes/risk factors
Sharshar et al [9]	Hospital records, France	31/348,295	Non-ICH: 4.3 ICH: 4.6	Eclampsia, AVM, cervical artery dissection, PPA, PS deficiency, DIC
Jaigobin and Silver [10]	Hospital records Toronto, Canada	34/50,711	All: 26 Infarction: 18 ICH: 8	Coagulopathy, preeclampsia, smoking, hypertension, AVM, DIC, aneurysm
Kittner et al [11]	Baltimore-Wash. Cooperative Young Stroke Study Hospital records	31/234,023	All: 8.1	Preeclampsia, CNS vasculopathy, dissection, TTP, cortical vein thrombosis, vasculitis, AVM, cocaine
Ros et al [12]	Inpatient register Sweden, 1987–1995	144/1,003,489 deliveries	Infarction: 4.0 ICH: 3.8 SAH: 2.4	Maternal age > 35, parity ≥ 4, 2 days before to 1 day after delivery
Lanska and Kryscio [13]	National Hospital Discharge Survey (1979–1991)	8,918/50,264,631 deliveries	Stroke: 17.7	Age 35–44, hypertension
Lanska and Kryscio [14]	Nationwide inpatient sample releases 2 and 3	183/1,408,015 deliveries	Stroke: 13	Age 35–44, hypertension, Cesarean delivery, fluid/electrolyte, acid-base disorder, rheumatic fever/valvular heart disease, pneumonia, vomiting
Jeng et al [15]	National Taiwan University Hospital young stroke registry medical records	49/49,796 deliveries	Infarction: 8 ICH: 9 SAH: 1	Hypertension, cardiac disease, hypercholesterolemia, preeclampsia, AVM, aneurysm, coagulopathy
James et al [16]	Nationwide inpatient sample 2000–2001	2,850/8,322,799 deliveries	Stroke: 34	Maternal age > 35, African American race, hypertension, heart disease, thrombophilia, sickle cell disease, anemia, thrombocytopenia, lupus, diabetes, migraine headaches, alcohol/substance abuse, smoking, preeclampsia, postpartum hemorrhage, transfusion, postpartum infection, fluid/electrolyte imbalance
Bateman et al [17]	Nationwide inpatient sample 1993–2002	423/6,969,553 deliveries	ICH: 6.1	Maternal age > 35, African American race, hypertension, preeclampsia/eclampsia, coagulopathy, tobacco abuse

Abbreviations: AVM, arteriovenous malformation; CNS, central nervous system; DIC, disseminated intravascular coagulation; ICH, intracerebral hemorrhage; PPA, post-partum angiopathy; SAH, subarachnoid hemorrhage; TTP thrombotic thrombocytopenic purpura.

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