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Pregnancy and stroke risk in women

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Abstract

Stroke, the sudden onset of brain dysfunction from a vascular cause, is one of the most common causes of long-term disability. Although rare during childbearing years, stroke is even more devastating when it occurs in a young woman trying to start a family. Pregnancy and the postpartum period are associated with an increased risk of ischemic stroke and intracerebral hemorrhage, although the incidence estimates have varied. There are several causes of stroke that are in fact unique to pregnancy and the postpartum period, such as preeclampsia and eclampsia, amniotic fluid embolus, postpartum angiopathy and postpartum cardiomyopathy. Data regarding these individual entities are scant. Most concerning is the lack of data regarding both prevention and acute management of pregnancy-related stroke. The purpose of this article is to summarize existing data regarding incidence, risk factors and potential etiologies, as well as treatment strategies for stroke in pregnancy.

Keywords

hemorrhage; pregnancy; stroke; women

Epidemiology of stroke in pregnancy

Pregnancy and the postpartum period are associated with an increased risk of stroke and cerebral hemorrhage. However, among the small number of investigations on this topic, estimates of both incidence and risk of stroke in pregnancy have varied greatly. The data from these studies are summarized in Table 1. There have been several population-based studies that have used variable inclusion criteria. One study using data from 46 hospitals in the Baltimore–Washington DC (USA) area concluded that the risk of ischemic stroke and intracerebral hemorrhage (ICH) were increased in the postpartum period, but not during pregnancy, with a relative risk of ischemic stroke of 8.7 and 28.3 for ICH [1]. They also found an attributable or excess risk of 8.1 strokes per 100,000 pregnancies. Two subsequent studies utilized data from the National Hospital Discharge Survey, with the first limiting cerebrovascular events to the hospitalization of delivery [2], and the second inclusive of antepartum and postpartum events [3]. The study focused on hospitalization found an

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incidence of 10.3 strokes (including ICH) and 8.9 cerebral venous thromboses (CVT) per 100,000 deliveries [2]. However, when antepartum and postpartum data were included, the incidence was 17.7 per 100,000 for strokes and 11.4 per 100,000 for CVT [3]. A third study by the same authors utilized the Nationwide Inpatient Sample from the years 1993 to 1994 and again restricted events to the hospitalization of delivery, with an incidence of 13.1 strokes and 11.6 CVT per 100,000 deliveries [4]. All three of these studies were somewhat limited by the use of the nonspecific ninth edition of the International Classification of Diseases (ICD-9) code 674.0 for 'cerebrovascular disorders in the puerperium', which includes subarachnoid hemorrhage, ICH and acute but ill-defined cerebrovascular diseases, as well as occlusions of the cerebral arteries that may or may not be associated with stroke. Another study using more recent data from the Nationwide Inpatient Sample from 2000 to 2001 found an overall incidence of 34.2 strokes per 100,000 deliveries, which included both ischemic and hemorrhagic events [5]. Compared with an incidence of 10.7 strokes per 100,000 woman-years among nonpregnant women of comparable age, this showed a threefold increase in pregnancy [6]. Finally, a third US study analyzed data from the Nationwide Inpatient Sample focused specifically on ICH, and found an incidence of 6.1 per 100,000 deliveries or 7.1 per 100,000 at-risk person-years [7]. For all age groups of pregnant women, the rate of hemorrhage was higher in the postpartum period than antepartum period or the control group. This corroborated findings from other studies that found the risk of ICH to be highest in the postpartum period [1,8]. However, it is important to highlight that different etiologies of hemorrhagic stroke vary in terms of onset. For example, in one study, 92% of hemorrhages due to rupture of a cerebrovascular malformation occurred antepartum [9].

Several studies from outside the USA have also utilized population-based or hospital-based samples to investigate the incidence of pregnancy-related stroke. In the Ile de France region, the incidence was 4.3 ischemic strokes and 4.6 ICHs (excluding subarachnoid hemorrhage) per 100,000 deliveries [8]. This study was somewhat limited by the definition of stroke as 'rapidly developing clinical symptoms and/or signs of focal, and at times global, loss of cerebral function with symptoms lasting more than 24 h', which included stroke-like deficits from eclampsia. Some of these events may have been related to a reversible cerebral vasoconstriction syndrome and not necessarily an ischemic infarct, leading to an overestimate of stroke incidence [10]. A single-center Canadian study found an incidence of 18 strokes and eight cerebral hemorrhages per 100,000 deliveries, with most ischemic strokes occurring in the postpartum period [11]. Studies in Asian populations suggest that ICH may be more common compared with Western populations. Liang *et al.* found an incidence of 13.5 strokes and 25.4 hemorrhages per 100,000 deliveries in a Taiwanese hospital, and also summarized data from a total of nine recent studies, which yielded an average incidence of 21.3 strokes per 100,000 deliveries [12].

Cerebral venous thrombosis represents approximately only 2% of all pregnancy-related strokes. The incidence is similar to ischemic stroke, at approximately 12 per 100,000 deliveries [13]. The highest risk period for CVT is third trimester and postpartum, similar to the time frame for risk of venous thromboembolic events [13].

The data from the Baltimore–Washington DC population-based study [1] and the Canadian study [11] both suggested that the highest risk period for stroke is postpartum. However, a detailed study of the timing of several different circulatory diseases (including ischemic stroke, hemorrhagic stroke and subarachnoid hemorrhage) associated with pregnancy showed that the majority of events occur at the delivery period, and the frequency of events decrease in the postpartum period [14]. This was also shown in a smaller case series, where the frequency of stroke decreased substantially 7 days or more after delivery [15]. These differences may be based on the cutoff at delivery (Ros *et al.* included the 2 days after

delivery in the delivery category [14]). Based on the available evidence, the highest risk periods appear to be the delivery period and up to 2 weeks postpartum.

Only a few of the studies previously cited reported mortality associated with pregnancy-related strokes. The three investigations by Lanska and Kryscio found no fatalities attributed to CVT, but stroke fatality rates of 2.2, 2, 3.3, 3 and 14.7 per 100,000 deliveries [4] in chronological order of analysis in the Nationwide Inpatient Sample database. The death rate from CVT is thought to be lower in pregnant than in nonpregnant women of comparable age [16]. The most recent Nationwide Inpatient Sample analysis reported a 4.1% case fatality rate associated with pregnancy-related stroke, and a mortality rate of 1.4 per 100,000 deliveries [5]. This was low compared with the average case fatality rate for stroke at any age (24%), and even compared with the range of case fatality rates for stroke in young adults (4.5–24%) [5]. The authors speculated that this could be due to missed deaths occurring weeks or months after discharge from the hospital, or better access to treatment if the patient is already hospitalized around the time of delivery. Liang *et al.* summarized mortality data from nine recent studies and found an average mortality rate of 13.8% for ICH and 3.9% for ischemic stroke [12].

Of all stroke types, pregnancy-related ICH leads to the highest risk of mortality. In the Nationwide Inpatient Sample, the in-hospital mortality rate for pregnancy-related ICH was 20.3%, although this was lower than previously reported mortality rates ranging from 25 to 40% [7]. However, ICH accounted for 7.1% of all pregnancy-related mortality in the Nationwide Inpatient Sample database [7]. This is comparable to previous studies suggesting that ICH is r esponsible for 5–12% of all maternal deaths [9].

Even fewer studies have examined poststroke morbidity in young women with pregnancy-related stroke. In the Ile de France population, 33% of women with ischemic stroke had mild-to-moderate residual deficits based on a modified Rankin score of 1–2 (minimal residual stroke disability for both scores), while one woman developed epilepsy. Conversely, 50% of women with ICH had mild-to-moderate deficits with Rankin scores of 1–3 (moderate disability and mobility impairment) [8]. The percentage of women discharged to facilities other than home ranged from 9 to 22% [4,5]. Another French study followed young women after a first stroke to determine the impact on subsequent pregnancies [17]. In total, 34% of the women followed in this study stated that they would have desired more pregnancies, and the most popular reasons for avoiding pregnancy were fear of recurrent stroke, medical advice against pregnancy and residual handicap from their initial stroke [17]. However, of these 441 women, there were 13 recurrent strokes. Only two of these strokes occurred in pregnancy, both in the setting of known underlying causes (antiphospholipid syndrome and thrombocythemia) [17]. In addition, of the 37 women whose initial stroke occurred during pregnancy, there were no recurrent strokes in a total of 24 subsequent pregnancies [17]. This suggests that a history of stroke should not be an automatic contraindication for subsequent pregnancy, but instead women should receive counseling regarding their specific underlying risk factors. There is also a need for additional research focused on pregnancy-related stroke outcomes.

Risk factors for pregnancy-related stroke & CVT

Young pregnant women may have risk factors that are typically associated with stroke in the general population, especially with the increasing prevalence of obesity at younger ages. Some of these 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 [4,5]. Hypertension in pregnancy may be pre-existing, gestational, or associated with preeclampsia or eclampsia. Compared with

women without hypertension, women with hypertension complicating pregnancy are six- to nine-fold more likely to have stroke [3,5]. Complications of pregnancy, labor and delivery have also been associated with increased risk of stroke, including hyperemesis gravidarum, anemia, thrombocytopenia, postpartum hemorrhage, transfusion, fluid, electrolyte and acid-base disorders, and infection [4,5]. Cesarean delivery has been associated with peripartum stroke, although a causal relationship has not been well established [2,4]. The association may reflect a higher likelihood for physicians to recommend cesarean delivery in women who suffer strokes during pregnancy. Historically, cesarean delivery has been advocated for women with ICH, particularly recent subarachnoid hemorrhage, untreated ruptured arteriovenous malformation (AVM) or unclipped ruptured aneurysm, to avoid potential risks during labor and delivery [2]. However, studies suggest that outcomes of vaginal and cesarean delivery are probably equivalent after ICH [18,19]. On the other hand, cesarean delivery may actually be a risk factor for postpartum stroke due to CVT. Normal physiologic changes during pregnancy, including resistance to activated Protein C and a decrease in functional Protein S, compounded by the transient hypercoagulability associated with surgery, may lead to clot formation [4]. Finally, age greater than 35 years increased the odds of stroke twofold, and African–American race-ethnicity increased the odds of stroke by 1.5-fold [5]. Similar results were reported in an analysis of pregnancy-related ICH alone [7].

Potential causes of stroke identified in the literature include those that can occur in the young nonpregnant population, and those that are exclusive to pregnancy. Diagnoses that are not specific to pregnancy include venous sinus thrombosis, cardioembolism, CNS or systemic vasculitis. Those that are more specific complications of pregnancy include preeclampsia/eclampsia, amniotic fluid embolism and postpartum angiopathy [1,8,11,12,20]. Postpartum cardiomyopathy can result in cardioembolism, or less commonly, watershed infarction from hypotension.

Although CVT occurs due to thrombosis of the sinuses, cerebral veins or jugular veins, and ischemic stroke occurs as a result of an arterial thrombosis or hemodynamic cause, there is quite a bit of overlap in the risk factors for both types of strokes during pregnancy. The primary causes for both types of strokes are thought to be influenced by the prothrombotic state of pregnancy itself, often in the setting of dehydration or an underlying predisposition for thrombophilia [13]. The causes and risk factors for CVT and thrombophilias have been extensively reviewed and published recently [13]. The physiologic changes during pregnancy that may lead to arterial or venous thrombo embolism include decreases in circulating antithrombotic factors, venous stasis or sudden reduction in blood volume after delivery [18]. Identifiable etiologies of stroke in the population-based studies previously cited are summarized in Table 2.

Several studies have found that preeclampsia/eclampsia and underlying cerebrovascular malformations were the most common identifiable causes of pregnancy-related ICH (Table 3) [1,7,8,11,12,20]. Preeclampsia/eclampsia is a cause of reversible posterior leukoencephalopathy syndrome, which can be associated with reversible vasogenic edema, typically in the posterior portion of the brain, as well as ICH, presumably due to the abnormalities in autoregulation [21]. In addition, preeclampsia/eclampsia has been associated with the spectrum of reversible cerebral vasoconstriction syndromes, which is a clinical syndrome consisting of thunderclap headache with or without focal neurologic deficits, and reversible arterial segmental vasoconstriction [10]. These two reversible syndromes are most likely under-recognized and under-diagnosed because the primary manifestation may be headache plus visual scotomata, representing severe preeclampsia, and the most important priority is delivery of the infant, rather than diagnostic imaging [22].

There are several factors that may increase the risk of AVM or aneurysmal rupture during pregnancy, such as increased blood volume and cardiac output, and structural changes in the vascular wall [18]. However, whether pregnancy truly increases risk of rupture is a topic of ongoing debate. Bateman *et al.* found that the rate of hemorrhage attributable to cerebrovascular malformations was similar in pregnant and nonpregnant women, at 0.50 and 0.33 per 100,00 person-years, respectively [7]. Additional etiologies in pregnancy include metastatic choriocarcinoma, and abuse of other substances, including alcohol and methamphetamines [19,23].

Diagnosis of pregnancy-related stroke & CVT

Diagnosis of stroke in pregnancy may be hindered by fear of adverse fetal outcomes from specific diagnostic tests. For example, physicians may be hesitant to obtain an MRI because of the effects of the magnetic field on the fetus, especially in the first trimester. However, the American College of Radiology guidelines state that pregnant patients can undergo MRI if warranted by the risk–benefit ratio, although administration of gadolinium contrast should probably be avoided in most cases because it does cross the placenta and its effects on the fetus have not been studied [24]. In most cases, a complete stroke work-up, including brain CT scan and/or MRI, transthoracic echocardiogram and vascular ultrasound, should be completed in pregnant women. Echocardiography is a standard test in stroke patients to evaluate for sources of cardiac emboli, but this may be especially important in Asian populations. Two studies in Taiwan identified cardioembolism as the most common etiology of pregnancy-related stroke, possibly due to the persistent presence of rheumatic heart disease in some Asian countries [12,20].

In the past, prior to the advent of modern imaging techniques such as magnetic resonance venogram, the majority of pregnancy-related strokes were attributed to ‘cerebral thrombophlebitis’ [25]. Cross *et al.* challenged this idea in 1968 by demonstrating with carotid angiography that 70% of women with strokes (n = 31) were due to arterial occlusion [25]. Today, it is well documented that the majority of cerebral infarcts in pregnancy are related to arterial causes. However, CVT is an important diagnosis because it can lead to infarction or hemorrhage or both. The diagnosis of CVT can still be challenging, despite modern imaging capabilities, since it may present primarily as a severe headache with other signs of increased intracranial pressure, such as vomiting or papilledema, with or without subtle focal neurologic deficits due to venous infarction [26]. The best imaging modality for diagnosis is most likely MRI, with magnetic resonance venogram if possible, to evaluate for both thrombosis and acute stroke. The risk factors for CVT are classically related to dehydration, postpartum infection and thrombophilia, but also include those that overlap those for arterial stroke, including hypertension, older age and excessive vomiting [4,5]. One review of 67 cases of CVT suggested that morbidity and mortality is reduced in pregnancy-related CVT compared with those that occur outside pregnancy [16].

Postpartum angiopathy is a unique condition associated with pregnancy, and it falls within the spectrum of disorders known as reversible cerebral vasoconstriction syndromes [10]. Although the pathophysiology may be similar, postpartum angiopathy is not confined to patients with history of preeclampsia or eclampsia and frequently occurs in patients who had uncomplicated pregnancies and deliveries. Patients classically present within days of delivery with thunderclap headache, vomiting, altered mental status and/or focal neurologic deficits. Such deficits may be transient or may be a result of ischemic stroke or cerebral hemorrhage [10]. Diagnosis is made with angiography, which demonstrates multifocal segmental narrowing in the large and medium-sized cerebral arteries, with a similar appearance to vasculitis. The cerebrospinal fluid is typically normal. By definition, the process is generally self-limited, with resolution of angiographic abnormalities within 4–6

weeks and typically complete resolution of symptoms [10]. However, owing to its association with both infarction and hemorrhage, postpartum angiopathy does carry a risk of morbidity and mortality. Some studies have also suggested an association between postpartum angiopathy and cervical arterial dissection [27,28].

Subarachnoid hemorrhage should be considered in pregnant patients with sudden onset of severe headache, particularly in the setting of neck stiffness, altered mental status, nausea and vomiting, seizure, focal neurologic signs and/or hypertension. It is important to note that these symptoms may be mistaken for preeclampsia/eclampsia, especially when protein-uria is present [19]. If subarachnoid hemorrhage is suspected, emergent uninfused CT scan should be performed. If this test is carried out within 24 h, it will detect subarachnoid blood in approximately 90–95% of cases, although the sensitivity decreases with time [29]. If angiography is indicated, special modifications, such as shielding of the fetus, fetal monitoring, and maternal hydration to avoid fetal dehydration due to contrast, should be made [30].

Stroke prevention during pregnancy

Very minimal data exists on preventative treatment of stroke in pregnancy, and there are no randomized controlled trials. Use of aspirin, in particular, has been a source of debate because animal studies have suggested an increased risk of congenital anomalies. In addition, several human studies reported increased risks of specific malformations including heart defects, neural tube defects, hypospadias, cleft palate, gastroschisis and pyloric stenosis [31]. Other potential risks include maternal or fetal bleeding and premature closure of the patent ductus arteriosus. A meta-analysis in 2002 showed no overall increase in risk of congenital malformations associated with aspirin, but determined that there may be an association between aspirin use in the first trimester and gastroschisis [31]. However, a subsequent meta-analysis study in 2003 failed to find any increased risk associated with aspirin, including placental abruption, fetal intraventricular hemorrhage or congenital malformations [32]. Notably, a recent meta-analysis suggests that aspirin is beneficial in preventing preeclampsia when started earlier than 16 weeks' gestation, but not when initiated after 16 weeks [33]. In that study, early treatment with aspirin also resulted in a decrease in gestational hypertension and preterm birth.

Owing to the limited data and lack of randomized controlled studies, current guidelines regarding the recommendations for aspirin in pregnant women vary. According to the American Heart Association/American Stroke Association guidelines, women at increased risk of stroke in whom antiplatelet therapy would likely be considered outside of pregnancy, may be considered for unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) during the first trimester, followed by low-dose aspirin [34]. The American College of Chest Physicians (ACCP) has published guidelines for the management of thromboembolism and thrombophilia in pregnancy, and although they do not specifically address stroke, they recommend low-dose aspirin throughout pregnancy for women at high risk of preeclampsia [35]. This may include women with preexisting hypertension, diabetes, renal disease, obesity, of age greater than 35 years and prior preeclampsia. According to the document [35]:

> "If the indication for aspirin is clear and there is no satisfactory alternative agent, clinicians should offer first-trimester patients aspirin."

There are virtually no data available regarding use of other antiplatelet agents, such as clopidogrel or aspirin-dipyridamole, in pregnancy. A 2008 survey polled US neurologists regarding which antithrombotic they would choose for stroke prophylaxis during the first trimester in pregnant women with and without history of previous stroke [36]. A total of

75% responded that they would use prophylaxis, most commonly aspirin 81 mg, for women without a history of stroke. In total, 88% chose prophylactic therapy, most commonly aspirin 81 mg followed by LMWH, for women with previous stroke. However, this study was significantly limited in that treatment choice is typically dependent on the mechanism of stroke, and the physicians surveyed were not provided with any background information on these hypothetical patients [36].

According to American Heart Association/American Stroke Association stroke secondary prevention guidelines, three options may be considered for pregnant women with ischemic stroke and 'high-risk thromboembolic conditions such as hypercoagulable state or mechanical heart valves': UFH throughout pregnancy, LMWH throughout pregnancy or UFH/LMWH until week 13, followed by warfarin until the middle of the third trimester, then UFH/LMWH up to the time of delivery [34]. The ACCP has identical recommendations for high-risk women with mechanical valves [34,35]. Women with a history of venous thromboembolism plus a known thrombophilia, particularly antithrombin-III deficiency, antiphospholipid antibody syndrome, prothrombin gene mutation or Factor V Leiden, may be treated with prophylactic-dose LMWH or UFH during pregnancy followed by postpartum anticoagulation with warfarin [34,35]. For women with antiphospholipid antibody syndrome and no history of venous thromboembolism, but recurrent pregnancy loss, prophylactic UFH or LMWH plus aspirin throughout pregnancy is recommended [34,35]. Standard management of CVT and arterial dissection during pregnancy also includes anticoagulation [35]. LMWH is the most attractive option owing to more predictable dose response and ease of use compared with UFH, as well as decreased risk of osteoporosis and thrombocytopenia. Some authors have suggested a transition to UFH just prior to delivery to decrease the risk of epidural hematoma associated with regional anesthesia [37]. AHA/ASA stroke secondary prevention guidelines recommend anticoagulation for at least 3 months in the setting of CVT, followed by antiplatelet therapy [34].

Treatment of acute pregnancy-related stroke

Treatment of acute arterial stroke in pregnancy is also controversial. Recombinant tissue plasminogen activator (rtPA) is a drug that lyses clot when given intravenously or inta-arterially to patients with acute ischemic stroke. Randomized clinical trial evidence demonstrated that if rtPA is administered within 3 h of ischemic stroke onset in nonpregnant patients, this drug decreases the risk of mortality and improves outcome at 90 days poststroke compared with placebo [38]. However, there is an approximate 6% risk of hemorrhage, and this risk increases with administration greater than 3 h after onset of the stroke symptoms [38]. Thrombolytic drugs can be administered intra-arterially for proximal middle cerebral artery occlusions effectively and relatively safely [39]. In addition, there are devices that have been approved for mechanical thrombectomy, such as the Merci device [40]. or the Penumbra device [41]. In some cases, intra-arterial rtPA can be combined with mechanical thrombectomy. Patients tend to have optimal outcomes if whatever method is used leads to partial or complete recanalization of the occluded artery.

Recombinant tissue plasminogen activator does not cross the placenta and there has been no evidence of teratogenicity in animal studies [42]. It is listed as a category C drug and pregnancy is considered a relative contraindication for administration, but there are multiple case reports of successful use in pregnant women. In one instance, rtPA was given intra-arterially in the third trimester, 5 h after onset of left hemiplegia, with catheter angiogram demonstrating a right middle cerebral artery trunk occlusion [43]. The infant was delivered without complication 3 days later, and at 2-month follow-up the mother had no residual neurologic deficits. Several other case reports and case series have reported successful

outcomes after use of thrombolytics for mothers, and in most cases for infants when mothers did not choose elective termination (Table 4) [44-47]. Risks and benefits should be carefully weighed, but it appears that thrombolytics can be used both intravenously and intra-arterially in pregnancy with positive outcomes.

There are no clear guidelines for medical management of subarachnoid or ICH in pregnancy. Drugs used on a routine basis in nonpregnant patients, such as mannitol for elevated intracranial pressure, antiepileptics for prevention or management of seizures, and nimodipine for vasospasm, must be utilized with caution in pregnant women. Mannitol may result in fetal hypoxia and acid-base shifts, antiepileptic drugs are associated with varying degrees of teratogenic risk, and nimodipine has been linked with teratogenicity in some animal experiments, but there is minimal data in humans [19,29]. However, ultimately, the use of these agents in critically ill pregnant patients may outweigh the potential risks. Obviously, careful monitoring of hemodynamic parameters in both the mother and fetus are a priority. Some authors advocate emergent cesarean delivery, if near term, prior to attempting surgical management of vascular malformations [29]. However, studies have suggested that surgical management of ruptured aneurysms during pregnancy is associated with significantly lower maternal and fetal mortality [9]. This did not hold true for surgical excision of arteriovenous malformations, despite a high risk of rebleeding (up to 30%) within the same pregnancy [9,19]. Since AVMs are now frequently repaired endovascularly, benefits may still outweigh the risks. Studies have suggested that route of delivery, cesarean versus vaginal, does not affect outcome in patients with a v ascular anomaly [18].

Conclusion

Although the reported incidence is variable, stroke is a significant cause of morbidity and mortality in pregnancy and the postpartum period, and presents special challenges in diagnosis and management. Future studies are required to develop guidelines for appropriate preventative and acute treatment of ischemic stroke in pregnancy, since there is little data available regarding the safety and efficacy of commonly used drugs, such as aspirin, aspirin/extended-release dipyridamole, clopidogrel and rtPA. Management of ischemic stroke or hemorrhage during pregnancy may require interdisciplinary care from neurosurgery, neurocritical care and obstetrics.

Future perspective

There are many gaps in our knowledge about pregnancy-related stroke, including detailed knowledge about mechanisms and outcomes post-hospital discharge. Although administrative databases allow estimation of incidence and prevalence, the patient-level detail is lacking. Therefore, in order to better understand pregnancy-related stroke causes and outcomes, the development of multisite, multidisciplinary registries are needed. In addition, it seems likely that in the next 5–10 years, more pregnant women with acute stroke will be treated with rtPA as neurologists and interventional radiologists develop new or improved imaging strategies (e.g., MRI perfusion) to identify women who would clearly benefit from reperfusion while minimizing risk to the fetus. In the next couple of years, new anticoagulants, such as direct thrombin inhibitors (dabigatran) [48], may be used in pregnancy, especially for women who cannot receive heparin or warfarin. Dabigatran is currently US FDA category C for pregnant women, but more testing in humans will be required in order to determine the number of adverse pregnancy outcomes and the risk–benefit ratio for preventing stroke and CVT during pregnancy.

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Executive summary

Epidemiology of stroke in pregnancy

- The incidence of stroke during pregnancy ranges from approximately 9 to 34 per 100,000 deliveries worldwide.
- Of all stroke types, intracerebral hemorrhage during pregnancy and the puerperium carries the highest morbidity and mortality, with an in-hospital mortality of 20%.
- Although infrequently reported, the morbidity following pregnancy-related stroke is lower than for typical stroke patients, and the risk for recurrent stroke in subsequent pregnancies is very low.
- Causes of pregnancy-related stroke include those that are unique to pregnancy (preeclampsia/eclampsia, postpartum angiopathy, amniotic fluid embolism and postpartum cardiomyopathy) and causes seen in nonpregnant women, including hypertension, diabetes, vasculitis, arteriovenous malformations or aneurysms.

Risk factors for pregnancy-related stroke & cerebral venous thrombosis

- The women who are at the highest risk for pregnancy-related stroke are those who are over the age of 35 years; those who are of African–American race-ethnicity; and those with preeclampsia/eclampsia/gestational hypertension, thrombophilias, migraine headaches, diabetes, prepregnancy hypertension, hyperemesis gravidarum, anemia, thrombocytopenia, postpartum hemorrhage, transfusion, fluid, electrolyte and acid-base disorders and infection.

Diagnosis of pregnancy-related stroke & cerebral venous thrombosis

- Brain imaging is essential in order to determine whether a pregnant woman has suffered an intracerebral hemorrhage. Brain MRI and magnetic resonance venogram are generally considered the gold standard for the diagnosis of ischemic stroke and cerebral venous thrombosis, respectively.
- The timing of scans may depend on the stage of pregnancy and the risk–benefit ratio of performing these scans. The risk from MRI is generally considered lower after the first trimester, and the risks with administration of gadolinium is still under debate.

Stroke prevention during pregnancy

- Strategies to prevent stroke during pregnancy in high-risk women mimic those used for thromboprophylaxis, which include either unfractionated or low-molecular-weight heparin to 13 weeks' gestation, followed by warfarin until the middle of the third trimester, then heparin until delivery and warfarin for 6 weeks postpartum.
- There are no randomized controlled trials of acute stroke treatment with thrombolysis or mechanical thrombectomy to guide decision-making in the pregnant population.

Treatment of acute pregnancy-related stroke

- Treatment of acute stroke in pregnant women is still controversial, but not strictly contraindicated. Several case reports have documented successful reperfusion, in addition to satisfactory maternal and fetal outcomes.

- However, there are no trials of anticoagulation or antiplatelet therapies for stroke prevention in pregnancy.

Future perspective

- There are many gaps in our knowledge about pregnancy-related stroke, including detailed knowledge about mechanism outcomes posthospital discharge, due to the lack of patient-level detail.
- In order to better understand pregnancy-related stroke causes and outcomes, the development of multisite, multidisciplinary registries are needed.
- In the next 5–10 years, it is most likely that an increasing number of pregnant women with acute ischemic stroke will be treated with recombinant tissue plasminogen activator as neurologists and interventional radiologists develop new or improved imaging strategies (e.g., MRI perfusion) to identify women who would clearly benefit from reperfusion while minimizing the risk to the fetus.
- In the next couple of years, new anticoagulants, such as direct thrombin inhibitors (dabigatran), may be used in pregnancy, especially for women who cannot receive heparin or warfarin. Dabigatran is currently US FDA category C for pregnant women, but more testing in humans will be required in order to determine the number of adverse pregnancy outcomes and the risk–benefit ratio for preventing stroke and cerebral venous thrombosis during pregnancy.

Table 1

Summary of the published incidence, mortality and morbidity of pregnancy-related stroke.

Study (year)	Population sampled (years)	Inclusion	Incidence (per 100,000 deliveries)	Mortality/morbidity (%)	Ref.
Cross *et al.* (1968)	Killearn Hospital, Glasgow, Scotland, UK (1956–1967)	Carotid artery distribution infarcts in pregnancy plus up to 16 days PP	5	Mortality 26	[25]
Wiebers *et al.* (1985)	Rochester, MN, USA (1955–1979)		3.8		[49]
Simolke *et al.* (1991)	Parkland Memorial Hospital, Dallas, TX, USA (1984–1990)	Stroke: included CVT ICH: included SAH	Stroke: 10 ICH: 6.7	Overall: morbidity 40, mortality 20	[50]
Sharshar *et al.* (1995)	Hospitals in region of ile de France (1989–1992)	Stroke: 'stroke-like deficits', excluded CVT ICH: excluded SAH Pregnancy plus 2 weeks PP	Stroke: 4.3 ICH: 4.6	Stroke: morbidity 33, mortality 0 ICH: morbidity 50, mortality 25	[8]
Kittner *et al.* (1996)	Hospitals in Baltimore–Washington DC, USA (1988–1991)	Stroke: included CVT ICH: excluded SAH Pregnancy plus 6 weeks PP Women aged 15–44 years	Stroke: 11 ICH: 9		[1]
Lanska and Kryscio(1997)	National Hospital Discharge Survey (1979–1991)	Diagnosis codes 674.0† or 671.5‡from hospitalization of delivery	Stroke: 10.3† CVT: 8.9	Stroke: mortality 2.2 CVT: mortality 0	[2]
Lanska and Kryscio(1998)	National Hospital Discharge Survey (1979–1991)	Diagnosis codes 674.0 or 671.5, not restricted to hospitalization of delivery Women aged 15–44 years	Stroke: 17.7† CVT: 11.4	Stroke: mortality 3.3 CVT: mortality 0	[3]
Lanska and Kryscio (2000)	Nationwide Inpatient Sample (1993-1994)	Diagnosis codes 674.0 or 671.5 from hospitalization of delivery Women aged 15-44 years	Stroke: 13.1† CVT: 11.6	Stroke: mortality† 14.7 CVT: mortality 0 9.3 of those discharged had postacute care needs	[4]
Jaigobin and Silver (2000)	Toronto Hospital, Canada (1980–1997)	Stroke: included CVT ICH: included SAH	Stroke: 18 ICH: 8	Stroke: mortality 0 ICH: mortality 23	[11]
James *et al.* (2005)	Nationwide Inpatient Sample (2000–2001)	Included hemorrhage, arterial stroke, CVT or diagnosis code 674.0	34.2	Mortality 4.1 22 discharged to facility other than home	[5]
Bateman *et al.* (2006)	Nationwide Inpatient Sample (1993–2002)	ICH: diagnosis code 431 Women aged 15–44 years	ICH: 6.1	Mortality 20.3	[7]
Liang *et al.* (2006)	Chang Gung Memorial Hospital, Taiwan (1992–2004)	Stroke: included CVT ICH: included SAH	Stroke: 13.5 ICH: 25.4		[12]

CVT: Cerebral venous thrombosis; ICH: Intracerebral hemorrhage; PP: Postpartum; SAH: Subarachnoid hemorrhage.

†The ninth edition of the International Classification of Diseases (ICD-9) 674.0 includes the following ICD-9 codes, occurring during pregnancy, childbirth or the puerperium: 430 SAH; 431 ICH; 432 other and unspecified intracranial hemorrhage; 433 occlusion and stenosis of precerebral arteries; 434 occlusion of cerebral arteries; 436 acute, but ill-defined cerebrovascular disease (which includes apoplectic

apoplexy and cerebral seizure); 437 other and ill-defined cerebrovascular disease (which includes cerebral atherosclerosis, hypertensive encephalopathy, cerebral aneurysm unruptured, cerebral arteritis, Moyamoya disease, nonpyogenic thrombosis of the intracranial venous sinus and transient global amnesia).

‡ICD-9 671.5: CVT.

Table 2

Published causes of ischemic stroke during pregnancy.

Etiologies of ischemic stroke	Preeclampsia/ eclampsia (%)	CNS vasculopathy (%)	Arterial dissection (%)	TTP/DIC (%)	Thrombophilia (%)	Amniotic fluid embolism (%)	Cardioembolic (%)	Atherosclerosis (lacune) (%)	Ref.
Kittner *et al.*, n (%) (total n = 17)	4 (24)	3 (18)	1 (6)	1 (6)	–	–	–	–	[1]
Sharshar *et al.*, n (%) (total n = 15)	7 (47)	1 (7)	1 (7)	–	1 (7)	1 (7)	–	–	[8]
Jaigobin *et al.*, n (%) (total n = 21)	6 (29)	–	1 (5)	–	5 (24)	–	4 (19)	–	[11]
Jeng *et al.*, n (%) (total = 27)	1 (4)	–	–	–	10 (37)	–	9 (33)	–	[20]
Liang *et al.*, n (%) (total n = 11)	2 (18)	–	–	–	–	1 (9)	4 (36)	1 (9)	[12]

DIC: Disseminated intravascular coagulation; TIP: Thrombotic thrombocytopenic purpura.

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Table 3

Published causes of pregnancy-related intracerebral hemorrhage.

Etiologies of ICH	Preeclampsia/eclampsia (%)	Vascular anomaly (%)	Cocaine (%)	CNS vasculopathy (%)	DIC/coagulopathy (%)	Ref.
Kittner *et al.*, n (%) (total n = 14)	2 (14)	3 (21)	2 (14)	2 (14)	–	[1]
Bateman *et al.*, n (%) (total n = 423)	129 (31)	30 (7)	–	–	36 (9)	[7]
Sharshar *et al.*, n (%) (total n = 16)	7 (44)	6 (38)	–	–	–	[8]
Jaigobin *et al.*, n (%) (total n = 13)	1 (8)	8 (62)	–	–	2 (15)	[11]
Jeng *et al.*, n (%) (total = 22)	7 (32)	8 (36)	–	–	1 (5)	[20]
Liang *et al.*, n (%) (total n = 21)	5 (24)	6 (29)	–	–	4 (19)	[12]

DIC: Disseminated intravascular coagulation; ICH: Intracerebral hemorrhage.

Table 4

Summary of cases of recombinant tissue plasminogen activator for pregnant women with acute ischemic stroke.

Study (year)	Patient age, gestation, risk factors and presenting symptoms	Thrombolytic	Maternal outcome	Fetal outcome	Ref.
Murugappan *et al.* (2006)	37 years of age AA, known pregnancy at 12 weeks Mechanical valve, off anticoagulation L hemiparesis, NIHSS 19	IV rtPA	NIHSS eventually improved to 4 Small intrauterine hematoma	Elective termination	[44]
Murugappan *et al.* (2006)	31 years of age, unknown pregnancy at approximately 4 weeks R hemiparesis, expressive aphasia	IV rtPA	NIHSS eventually improved to 4	Elective termination	[44]
Murugappan *et al.* (2006)	29 years of age, unknown pregnancy AVR, off anticoagulation L hemiplegia, NIHSS 13	IV rtPA	No improvement, died during subsequent angioplasty owing to arterial dissection	Maternal demise	[44]
Murugappan *et al.* (2006)	43 years of age, known pregnancy at 37 weeks AT-111 and functional protein C deficiency R hemiparesis, global aphasia, NIHSS 25	IV rtPA	Improved to NIHSS 11; 90 days after event had no residual deficits	Healthy infant delivered at term via spontaneous vaginal delivery	[44]
Murugappan *et al.* (2006)	28 years of age, known pregnancy in first trimester Protein C and S deficiencies, PFO, L iliac DVT Vertigo, nausea/vomiting and eventually coma due to basilar occlusion	IA UK	Improved Buttock hematoma	Healthy infant delivered at term	[44]
Murugappan *et al.* (2006)	25 years of age, known pregnancy in first trimester MVR with endocarditis R hemiparesis, expressive aphasia	IA UK	Improved; 4 months later no residual deficits Asymptomatic ICH	Spontaneous abortion	[44]
Murugappan *et al.* (2006)	40 years of age, known pregnancy at 6 weeks Polycythemia vera, essential thrombocytosis Nausea/vomiting, papilledema, CN VI palsy due to CVT	Local UK	Improved; residual visual field deficit	Spontaneous abortion (lethal chromosomal abnormalities)	[44]
Murugappan *et al.* (2006)	21 years of age, known pregnancy at 8 weeks Antiphospholipid antibody syndrome HA, nausea/vomiting, altered mental status, seizures, R hemiparesis due to CVT	Local UK	Improved; residual short-term memory deficit Asymptomatic ICH at ventriculostomy site	Elective termination	[44]
Wiese *et al.* (2006)	33 years of age, known pregnancy at 13 weeks Mechanical valve, transitioned from warfarin to subcutaneous heparin due to pregnancy R hemiparesis, expressive aphasia, NIHSS 13	IV rtPA	NIHSS eventually improved to 4	Healthy infant delivered at term via cesarean section	[46]
Dapprich (2002)	First trimester	IV rtPA	Improved	Healthy infant delivered at term	[47]
Elford *et al.* (2002)	28 years of age s/p *in vitro* fertilization, with ovarian hyperstimulation syndrome L hemiplegia, NIHSS 11 (angiogram showed R M1 occlusion)	IA rtPA	Improved to NIHSS 3, then worsened and found to have R basal ganglia hemorrhage, ultimately improved	Healthy infant delivered at term via SVD	[45]
Johnson *et al.* (2005)	39 years of age with known pregnancy at 37 weeks L hemiplegia, NIHSS 20 (angiogram showed R M1 occlusion)	IA rtPA	Improved to NIHSS 7; ultimately no residual deficits	Healthy infant delivered at term via SVD	[43]

AA: African–American; AT-III: Antithrombin III; AVR: Aortic valve replacement; CN: Cranial nerve; CVT: Cerebral venous thrombosis; DVT: Deep venous thrombosis; HA: Headache; IA: Intra-arterial; ICH: Intracerebral hemorrhage; IV: Intravenous; L: Left; MVR: Mitral-valve replacement; NIHSS: NIH Stroke Scale; PFO: Patent foramen ovale; R: Right; rtPA: Recombinant tissue plasminogen activator; sip: Status post; UK: Urokinase.