Stroke During Pregnancy and Puerperium: Clinical Perspectives

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SUMMARY

Stroke is a rare but potentially devastating disease during pregnancy and puerperium. Pregnancy is well recognized as a risk factor for stroke. Accurate and timely identification of stroke is crucial for clinical practice. However, the optimal management of pregnant women with stroke remains a clinical challenge. Thus, identification of risk factors and modification of underlying pathophysiological mechanisms would be of great value for stroke prevention and management. In terms of pharmacological intervention, it is important to determine the safety of a drug for mothers, their fetuses, and nursing infants. Neurologists treat non-pregnant patients without those considerations. Based on the above issues, we have reviewed the current literature and summarized clinically relevant issues for obstetricians and neurologists in treating stroke during pregnancy and puerperium. [*Taiwan J Obstet Gynecol* 2010;49(4):395–400]

Key Words: cerebrovascular disease, pregnancy, puerperium, stroke

Introduction

Stroke or cerebrovascular disease (CVD), also known as cerebrovascular accident or apoplexy, ranks as the third leading cause of death in men and women in Taiwan. It is also the leading cause of major adult disability. Stroke is an uncommon event in young women of childbearing age. However, it has serious consequences, including long-term disability and death, in young women with newborns or unborn babies. Since stroke risk factors and pathophysiology are unique to women, especially during pregnancy and postpartum, we have reviewed the literature on pregnancy-related stroke including epidemiology, underlying pathophysiological mechanisms, diagnostic investigation, classification, and current management principles.

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Epidemiology

The estimated rate of all strokes in pregnant women varies from 4 to 26 per 100,000 compared with 3 to 10 per 100,000 in non-pregnant women [1]. The incidence of stroke during pregnancy and puerperium in Taiwanese women is reported to be 46.2 and 21.47 cases per 100,000 [2,3], respectively. There is a variable incidence among different stroke subtypes. Per 100,000 population, arterial ischemic stroke, venous ischemic stroke, and intracranial hemorrhage number 4, 10, and 4, respectively [1]. The relative risk of hemorrhagic and ischemic strokes persists for 12 months postpartum [3]. These important findings suggest that pre-eclampsia and eclampsia patients should be followed up for at least the first year postpartum to reduce stroke occurrence.

Risk Factors and Pathophysiology

Illnesses associated with stroke during pregnancy include hypertension, diabetes, heart disease, smoking, and thrombophilia. Multiparity, increased gestational age,

increased maternal age, strenuous labor, and cesarean delivery all appear to be risk factors of stroke. There are specific complications of pregnancy that may cause stroke. One of these complications, amniotic fluid embolism, is a catastrophic syndrome that can affect the brain and lead to profound neurological dysfunction (Figure 1).

The precise pathophysiology connecting CVD to pregnancy remains unclear. If the pathophysiology is known, it is possible to identify women at stroke risk prior to pregnancy and further develop rational preventative intervention. Research has focused on endothelial dysfunction for pregnancy-related stroke. Cerebral endothelial dysfunction has been demonstrated in a transcranial ultrasound study [4]. An increased propensity for thrombosis is another factor in the setting of peripartum stroke. In a study of 12 women with transient neurologic deficits during pregnancy, an inherited thrombophilia was identified in 10 women (83%) [5]. Oxidative stress and maternal systemic inflammatory response may be involved in pregnancy-related stroke [6]. In a nationwide US case-control study, data indicated a strong correlation between active peripartum migraines and vascular events including stroke [7].

Diagnostic Investigation

Neuroimaging approaches are important for probing the underlying vascular etiology in stroke patients. For urgent evaluation, cranial computed tomography (CT) may be performed with proper abdominal/pelvic shielding if the benefit outweighs the risk. CT is useful in separating ischemic from hemorrhagic stroke. However, the use of radiation during pregnancy should be kept to a minimum. Brain magnetic resonance imaging (MRI) is a preferred tool used during pregnancy, although teratogenic effects have been observed in pregnant mice exposed to a strong static magnetic field for short periods of time [8]. Gadolinium is a paramagnetic contrast agent used to enhance MRI images. The Food and Drug Administration (FDA) labeled it as a pregnancy category C because of a lack of epidemiological studies. In a prospective cohort study, 26 pregnant women exposed to gadolinium derivatives in the preconception and first trimester period did not appear to have any adverse effects during pregnancy or in the neonatal outcome [9].

One of the most common concerns about cerebral angiography during pregnancy is the potential risk of fetal malformation attributed to radiation exposure. Nevertheless, the benefits of angiography outweigh the risks. MRI arteriography and venography are non-invasive and radiation-free examinations that disclose intracranial aneurysm and cerebral venous thrombosis (CVT), respectively. If intracranial aneurysm needs to be treated, endovascular angiographic intervention has been reported to exhibit a low relative risk of radiation exposure to the fetus [10].

Extracranial and intracranial Doppler scans can serve as non-invasive studies to assess the status of cerebrovascular circulation. Sequential follow-up is easily performed to monitor disease progression and further measures hemodynamic conversion after intervention.

Evaluation for a patent foramen ovale is an important part of the cardiac assessment for a pregnant woman with an ischemic stroke, especially if hypercoagulopathy is identified. However, many cardiologists feel uncomfortable with administering microbubbles because of the theoretical potential for an air embolus

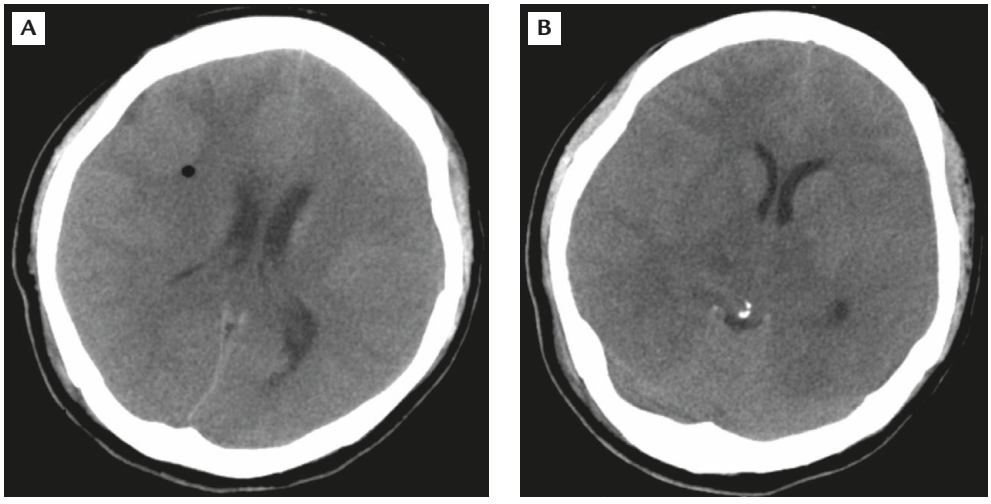

Figure 1. Fatal amniotic fluid embolism in a 26-year-old pregnant woman. (A) Air embolism and (B) bilateral thalamic low attenuation density are consistent with the postmortem diagnosis.

reaching the fetal circulation. In the setting of suspected hypercoagulopathy, investigations should be carried out for anticardiolipin, lupus anticoagulant, protein C, protein S, antithrombin III, d-dimer, and factor V Leiden.

Classification of CVD

In addition to arterial and venous occlusive strokes, intracranial hemorrhagic events including intracranial hemorrhage (Figure 2) and subarachnoid hemorrhage can develop during pregnancy. There are many causes of intracranial hemorrhage and subarachnoid hemorrhage during pregnancy. In one study, eclampsia accounted for 44% of the cases [11].

Most pregnancy-related strokes occur in the third trimester and puerperium, and this is especially true for CVT [11,12] (Figure 3). CVT remains the leading cause of direct maternal death in the UK, with a four-fold increased incidence compared with that of the non-pregnant population [13]. Most clinical manifestations of CVT are distinct from arterial occlusive stroke. The onset is not acute. Moreover, headaches may be the only symptoms in patients with CVT [14]. Therefore, CVT is sometimes under-recognized and is under-treated.

In many studies, pre-eclampsia/eclampsia and pregnancy-related hypertension have been associated with ischemic and hemorrhagic strokes during pregnancy [15,16]. Hypertension-related cerebral vasculopathy may represent several different entities, but might share the same pathophysiology. These include

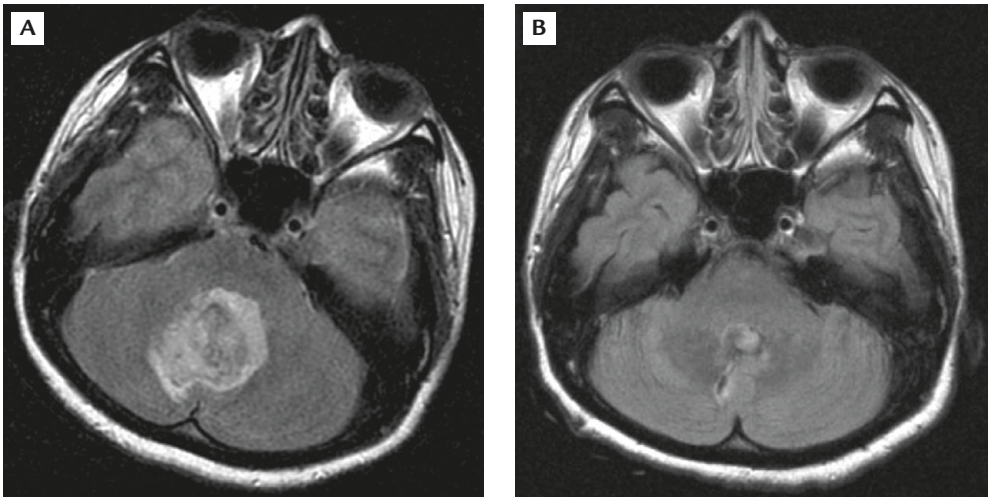

Figure 2. Cerebellar hemorrhage with brainstem compression in a 35-year-old pregnant woman. T2 fluid-attenuated inversion recovery magnetic resonance imaging (A) before removal of a hematoma and (B) after removal of hematoma show a substantial improvement of compression.

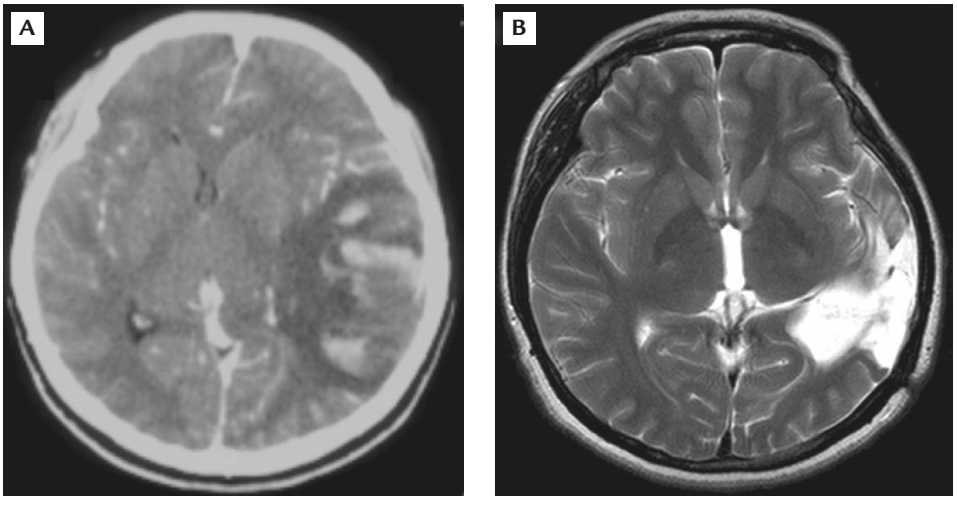

Figure 3. Cerebral venous thrombosis complicated with hemorrhagic transformation in a 29-year-old pregnant woman. (A) Computed tomography before craniotomy and (B) T2 weighted imaging after decompressive surgery show a significant reduction of compressive effect.

posterior reversible encephalopathy syndrome, reversible cerebral vasoconstriction, and postpartum angiopathy. Posterior reversible encephalopathy syndrome may result from endothelial dysfunction and failure of cerebral autoregulation with subsequent of vasogenic edema. Postpartum angiopathy, a subtype of reversible cerebral vasoconstriction, also involves reversible vasoconstriction, and may be more commonly associated with ischemic stroke than with cerebral edema. Diffusion-weighted imaging can differentiate between vasogenic edema and cytotoxic edema. Cytotoxic edema indicates the propensity to ischemic infarction [17].

Acute Treatment of Stroke During Pregnancy

Tissue plasminogen activator (tPA) has been approved for the treatment of acute ischemic stroke with symptoms confirmed to be less than 3 hours. Fundamental harmful considerations of tPA in pregnancy include potential teratogenicity, placental bleeding/abruption, premature labor, peripartum uterine bleeding, and postpartum hemorrhage. Discrepant results from case reports on tPA treatment during pregnancy [18,19] clearly indicate further investigation. The decision to treat with tPA in pregnant women is still debatable because of limited information.

Both low-molecular-weight heparin (LMWH) and unfractionated heparin do not cross the placenta, and several reports have indicated a lack of adverse fetal effects. LMWH has an advantage over unfractionated heparin because it has a longer half-life, greater bioavailability, and decreased affinity for heparin-binding proteins [20]. Currently, it is unclear if it is safe to use LMWH with acute arterial stroke. However, LMWH is generally accepted for patients with CVT because it does not increase the likelihood of cerebral hemorrhagic complications. LMWH is safe for the fetus because it does not cross the placenta. Although no randomized controlled trials have been conducted for pregnant women with CVT to guide decision making, benefits should be obtainable by reducing thrombotic progression and balancing the small risk of bleeding.

To improve neurological outcome, an unstable pregnant stroke patient may require transfer to a neurologic intensive care unit. The use of comprehensive monitoring can provide extensive care for the most complicated cases. Urgent evaluation and intervention is of paramount importance to prevent the human brain from being rapidly and permanently injured. When cardiopulmonary arrest occurs, perimortem cesarean delivery must proceed to increase the chances of maternal and fetal survival.

In patients with massive cerebral infarction and impending herniation, early decompressive craniotomy can reduce mortality and increase the likelihood of favorable outcome [21]. Decompressive surgery is a challenging task in dealing with pregnant women with stroke. A previous study found that in a patient with intracerebral hemorrhage secondary to cerebral sinus thrombosis who was pregnant for 12 weeks, neurologic outcome was considerably improved after decompressive craniotomy was carried out [22].

Preventive Treatment of Stroke During Pregnancy and Lactation

Because pregnancy is a period of increased risk of intracranial thrombotic and hemorrhagic events, prophylaxis should be used for subsequent pregnancies following a stroke event. Although the risk of recurrent CVT seems to be low, this should not have a negative impact on stroke prevention [23]. Benefits from stroke prevention will counterbalance the risk from pharmacological therapy. Caution should be exhibited during the prescription of drugs, particularly concerning teratogenicity, tocolytic actions to prolong labor, and postpartum women attempting to breast feed.

Women with a history of cardiac valve replacement or atrial fibrillation often receive long-term anticoagulant therapy for stroke prevention. Ideally, prescribing anticoagulants to pregnant women should be redundant for the majority of clinicians who concern about bleeding event during peripartum. Risk and benefit should be balanced for maternal and fetal concerns. Unlike LMWH, warfarin can cross the placenta and thereby pose the risk of teratogenicity. Thus, warfarin is the mainstay of anticoagulants only for postpartum stroke prevention. Furthermore, warfarin does not provoke anticoagulant effects in the breast-fed infant. Therefore, warfarin can be given to a nursing mother. An international normalized ratio of 2.0–3.0 is the optimal goal for patients taking warfarin.

Substituting warfarin with LMWH between 6 and 12 gestational weeks reduces the risk of teratogenicity [24]. Because patients with mechanical heart valves are at increased risk for thrombotic and hemorrhagic transformation following a stroke event, aggressive monitoring of clinical features instead of the international normalized ratio is warranted in pregnant women undergoing therapy with LMWH [25]. Vaginal delivery without the Valsalva maneuver is favored to avoid bleeding complications in pregnant women with anticoagulant therapy.

Aspirin is widely used in stroke prevention in non-pregnant women. Aspirin is likely to be safe at a dose less than 150 mg during the second and third trimesters, based on current evidence. However, the safety of higher doses of aspirin during the first trimester remains unclear [26]. Low doses of aspirin have also been assessed for use in prevention of pre-eclampsia and its consequences [27]. According to a survey of 230 clinicians, most of them agreed that women with a stroke history received stroke prevention during the first trimester. However, there is great disagreement among clinicians with regard to the candidate drug [28]. Although aspirin is secreted in breast milk in low concentrations, no adverse effects have been reported. The American Academy of Pediatrics has suggested cautious use of aspirin during lactation [29].

Aspirin increases the likelihood of peptic ulcer disease. Clopidogrel or ticlopidine can be an alternative anti-platelet during pregnancy. Because of very limited information on the use of those two drugs in pregnancy, no conclusion has been reached regarding the effects on the fetus. One case report has described a patient with a past history of myocardial infarction treated with clopidogrel through pregnancy without any complications [30].

Hypertension is one of the most common risk factors for atherosclerosis. In general, maternal adverse effects from all drugs for treating hypertension are not different from those in non-pregnant women. Antihypertensive drugs may cross the placenta and are categorized according to the level of risk to the fetus. Only limited controlled trials have been conducted, and most of them are classified as FDA category C, which suggests that drugs should be given only if the potential benefit justifies the potential risk to the fetus [31]. According to a study of 139,681 postmenopausal women, women who breastfed their babies for more than 1 year were 10% less likely to have a heart attack or stroke than women who never breastfed. This study encourages women to breastfeed their infants to reduce the risk of stroke [32]. The Table shows the FDA categories and lactation safety for antihypertensive drugs during pregnancy.

Table. Safety of antihypertension medication for pregnant women and their lactation

	FDA category	Safety in lactation
ACEI and ARB	C	ACEI (O) ARB (?)
β-Blocker	Metoprolol (B) Atenolol (C)	All β-blockers (X)*
(CCB)	C	All CCB (X)†
Diuretics	C	No human data

**Nursing infants should be checked for adverse effects because all beta-blockers are excreted in greater concentrations in breast milk than in plasma; †diltiazem, nifedipine, and verapamil accumulate in human milk; therefore, breastfeeding is not recommended for women taking these drugs. FDA = Food and Drug Administration; ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin-receptor blocker; CCB = calcium channel blocker.*

Conclusion

It is crucial to identify, at an early stage, pregnant women suffering from stroke or CVD. Accordingly, prompt intervention may diminish morbidity/mortality and promote functional outcomes. For pregnant women with stroke events, an obstetrician will be the first physician that they encounter. It is important to have an awareness of stroke for every obstetrician.

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