Stroke in pregnancy

The incidence, causes and optimum management of stroke in pregnancy are poorly understood, which largely reflects the inconsistency and limitations of the published data available. Women who have had a stroke in pregnancy are anxious about subsequent pregnancies, particularly as there is a lack of definitive information and guidance that general physicians and obstetricians are able to provide.

The prevalence of stroke in women of childbearing age averages 10.7 per 100 000 (Sibai and Coppage, 2004) and the reported incidence of pregnancy-related stroke is 3.8 to 26 per 100 000 (Jeng et al, 2004). This wide range in reported incidence may be explained by small study sizes, referral bias, difference in study designs and incorporation of different subgroups of patients. Additionally, it is reported that cerebral infarctions account for between 48% and 62% of cerebrovascular events in pregnancy (Sharshar et al, 1995).

Pregnancy and the risk of stroke

While it is reported that the incidence of stroke is increased in pregnancy, there is no consensus regarding the magnitude of the increased risk. A 13-fold increase in the risk of stroke during pregnancy compared with the non-pregnant state is the highest quoted risk (Wiebers, 1985).

The timing of stroke associated with pregnancy is also controversial. It has been reported that the risk is greater later in pregnancy and in the postpartum period (Walker, 2003). Kittner et al (1996) found the relative risk of cerebral infarction was 0.7 during pregnancy, increasing to 8.7 for the puerperium (following live birth or stillbirth).

Causes of stroke in pregnancy

The relative frequencies of different causes of stroke in pregnancy and the puerperium remain unknown because of the small numbers of patients and the lack of detailed investigation relating to the aetiology.

The underlying aetiologies of ischaemic stroke can be divided into pregnancy-specific and non-pregnancy-specific causes (*Table 1*). Three conditions are specific to pregnancy: eclampsia, choriocarcinoma and amniotic fluid embolism. Postpartum cerebral angiopathy and peripartum cardiomyopathy were initially thought to be pregnancy-specific causes, but have been reported apart from pregnancy.

Of the non-pregnancy-specific causes, uncertainty remains as to whether pregnancy plays a causative role in the occurrence of the stroke, or whether it is coincidental in these cases. For example, it is well known that pregnancy results in increased risk of recurrence of rheumatic heart disease.

There are a number of known genetic causes of stroke in pregnancy (e.g. factor V Leiden mutation) and research is ongoing in this area. In one study of pregnant women where no identifiable cause was found, a mutation in the methylenetetrahydrofolate reductase gene that has been associated with atherothrombotic disease, could have contributed to stroke pathogenesis (Korn-Lubetzki et al, 2001). Acquired thrombophilic states, e.g. antiphospholipid syndrome, may also contribute to stroke incidence (Quenby et al, 2005).

Despite detailed investigation, it is reported that the cause of stroke in pregnancy and the puerperium remains uncertain in 23–32% of reported cases (Jaigobin and Silver, 2000). This makes the optimum management of these patients particularly challenging.

Risk factors for stroke in pregnancy

The hypercoagulable state, increased venous stasis and fluctuating blood pressure in pregnancy have all been postulated as mechanisms that increase the risk of stroke. Pregnancy is known to cause a significant reduction in protein S levels and protein C resistance may occur in up to one third of women. Procoagulant factors are increased (except for factors XI and XIII), and changes in thrombin and adhesiveness of platelets are thought to take place. Oestrogens and some progesterones also increase blood coagulability. The haematocrit in pregnant females may

Table 1. Causes of stroke in pregnancy and the puerperium

Cardiac disorders	Paradoxical embolus
	Peripartum cardiomyopathy
Thrombophilias	Protein C or S deficiency
	Factor V Leiden mutation
Haematological disorders	Thrombotic thrombocytopenic purpura
	Disseminated intravascular coagulation
Vascular	Arterial dissection
	Cerebral venous thrombosis
Other causes	Eclampsia
	Metastatic choriocarcinoma

From Mas and Lamy (1998); Sibai and Coppage (2004)

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fluctuate as a result of changes in plasma volume and red blood cell mass, resulting in blood hyperviscosity. However, as only a very small number of women who are pregnant experience a stroke, there must be other factors that determine the risk.

A number of common risk factors for stroke are present in pregnant patients as they are in non-pregnant patients with stroke, including hypertension, smoking and premature atherosclerosis (Clark and Greer, 2003). Some researchers have focused on exploring risk factors in an attempt to identify patients at risk from pregnancy-related stroke. Higher parity, advanced maternal age, non-white race and multiple pregnancies are thought to be associated with a higher risk of stroke, as is the presence of infections, anaemia, diabetes, metabolic disorders (electrolyte, fluid and acid-base disorders), and as mentioned previously, eclampsia (Lanska and Kryscio, 2000).

However, according to data from the Maryland Behavioural Risk Factor Survey, the presence of hypertension, diabetes and current smoking was lower among pregnant women with stroke than among non-pregnant women with stroke (Rohr et al, 1996). This suggests that neither the pregnancy itself, nor the risk factors, although important to identify, should be presumed in isolation to be the cause of the stroke. It has also been reported that in the majority of women the factors that predispose patients to stroke are usually not apparent before pregnancy, with little to suggest that medical intervention could prevent these strokes (Mas and Lamy, 1998).

Uncertainty about the mechanism of stroke in the postpartum period is also apparent. It has been suggested that postpartum stroke may be the indirect result of a significant reduction in blood volume or secondary to hormonal changes, and is also thought to be related to caesarean delivery and pregnancy-related hypertension (Kittner et al, 1996).

Investigation of stroke in pregnancy

When assessing a patient with stroke, both risk factors and the altered physiology during pregnancy should be considered, with a thorough investigation for the causes of stroke in young people, as well as the rarer pregnancy-specific causes already mentioned.

Investigation should include computed tomography (CT) scanning or magnetic resonance imaging (MRI) to locate the infarct and to rule out associated cerebral haemorrhage: pregnancy should not be a contraindication to radiological procedures if they are required (Clark and Greer, 2003). Abdominal shielding should be used to limit fetal radiation exposure during CT scanning. Although data are lacking on the long-term safety of MRI in pregnancy, it does not appear to have any associated risk.

Laboratory testing should include a full blood count, metabolic profile, erythrocyte sedimentation rate, fasting lipids and triglycerides, urine drug screen, anti-nuclear antibody screen and coagulation profile (Sibai and Coppage, 2004). Thrombophilia studies are extremely important since transient cerebral ischaemia during pregnancy is thought to be associated with a high rate of inherited thrombophilia.

Other investigations should be used as deemed necessary, including echocardiography, carotid Doppler studies, magnetic resonance angiography and lumbar puncture.

Management of stoke in pregnancy

The aim of treatment in the pregnant patient is to minimize damage to brain tissue without extreme risk to mother and fetus. Management of stroke includes acute treatment and stroke prevention, as it does for non-pregnant patients. However, there are added complications in the management of labour and delivery.

Acute stroke treatment in pregnancy encompasses basic medical management in addition to specific intervention. Thrombolytic therapy may be beneficial if the patient presents within 3 hours of symptom onset. Unfortunately, data are scarce as most major trials exclude pregnant women, and there are no guidelines on this in the latest updates on acute stroke management. According to a review undertaken in 2002, where thrombolysis (tissue plasminogen activator (tPA)) was used for a variety of indications in pregnant women, the maternal bleeding rate was found to range from 1–6%, similar to that seen in non-pregnant patients (Dapprich and Boessenecker, 2002). There have been two reported cases of tPA use in pregnant females for acute stroke since, without adverse maternal outcome (Ahearn et al, 2002). The continuing debate regarding haemorrhagic complications following delivery, the effect on the fetus and possible excretion of thrombolytics into breast milk, suggest that it should be used only if the potential benefits outweigh the risk.

Although there remains no consensus on the risk–benefit ratio of antithrombotic treatment to prevent recurrent ischaemic stroke during pregnancy, it is recommended that aspirin should be started as soon as possible after the onset of stroke if a diagnosis of primary haemorrhage has been excluded. Guidelines from the Royal College of Obstetricians state that aspirin is safe in pregnancy (Collaborative Low-dose Aspirin Study in Pregnancy, 1994). Patients with a single transient ischaemic attack can be managed with low dose aspirin, but if these attacks increase in frequency and duration, heparin at therapeutic levels should be started (Waddy and Stern, 2003).

Clearly an understanding of the underlying aetiology of the stroke is vital in the subsequent management. If the event is an infarction where the cause remains unknown, low-dose aspirin or another antithrombotic agent should be used. If there is a clearly identified aetiology, with a specific clinical indication, unfractionated heparin, or preferably, low molecular weight heparin, should be used. Warfarin passes into the placenta easily, and can cause serious adverse effects to the fetus in early pregnancy. In cases where heparin is contraindicated, warfarin may be used after week 13 until the middle of the third trimester (Waddy and Stern, 2003).

The optimal management of labour and delivery in women who have had an ischaemic stroke during pregnancy is unclear. In most cases, vaginal-assisted delivery is probably adequate and there appears to be no indication to recommend caesarean section delivery. A prolonged second stage of labour should be avoided and close monitoring of blood pressure is mandatory.

Many questions about the subsequent management of patients who have had a stroke in pregnancy remain unanswered. As mentioned previously, many of the risk factors that predispose women to stroke are not apparent before pregnancy, and this makes the prevention of strokes extremely challenging. The only prognostic factor that has been found to be significant appears to be an initial stroke of definitive cause (Lamy et al 2000). Vascular risk factors and antithrombotic treatment at the time of discharge do not appear to influence the risk of recurrence, thus the need for long-term antiplatelet treatment remains unanswered.

Recurrence of stroke in pregnancy

Few data are available on the influence of pregnancy on the risk of recurrent stroke or whether a stroke in pregnancy carries the same risk of recurrence as for the general population. Very few studies have looked at the recurrence risk of stroke during pregnancy. This is clearly of great importance to women who are considering future pregnancy, with reasons for not having subsequent pregnancies including concern about recurrent stroke during pregnancy, medical advice against pregnancy and residual deficit.

The most quoted study regarding recurrence risk is that of Lamy et al (2000), who studied 125 women with a history of ischaemic stroke in 187 subsequent pregnancies. They found that only two of the 13 recurrent strokes occurred during subsequent pregnancies or the puerperium, with a recurrence risk of 1% within 1 year and 2.3% within 5 years. The relative risk of recurrence was actually higher in the postpartum period, which corresponds with data available for a first ischaemic stroke. Of particular interest, they found that no woman who had their first stroke during pregnancy had a recurrent stroke during subsequent pregnancies, and in strokes occurring outside of pregnancy the absolute risk of recurrence was found to be 0.5%.

A large study by Coppage et al (2004) also gives data similar to this with no overall risk of recurrence in women with a prior history of ischaemic stroke.

Conclusions

Stroke in pregnancy remains a challenge to manage, principally reflecting the lack of evidence-based guidance available. Women who suffer a stroke in pregnancy should be investigated in a similar way to any young patient with stroke. Furthermore, women with a previous history of ischaemic stroke can be reassured that there is a very low risk of recurrent stroke in pregnancy, that the overall outcome of pregnancy is similar to that of the general population, and that a prior stroke is not a contraindication to future pregnancies. **BJHM**

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Ahearn GS, Hadjiliasdis D, Govert JA, Tapson VF (2002) Massive pulmonary embolism during pregnancy successfully treated with recombinant tissue plasminogen activator: a case report and review of the treatment options. *Arch Intern Med* **162:** 1221–7

Clark P, Greer IA (2003) Prevention and treatment of arterial thrombosis in pregnancy. *Semin Thrombos Haemost* **2:** 155–63

Collaborative Low-dose Aspirin Study in Pregnancy (CLASP) (1994) A randomised trial of low dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. *Lancet* **343:** 619–29

Coppage KH, Hinton AC, Moldenhauer J, Kovilam O, Barton JR, Sibai BM (2004) Maternal and perinatal outcome in women with a history of stroke. *Am J Obstet Gynecol* **190:** 1331–4

Dapprich M, Boessenecker W (2002) Fibrinolysis with alteplase in pregnant women with stroke. *Cerebrovasc Dis* **13:** 290

Jaigobin C, Silver FL (2000) Stroke and pregnancy. *Stroke* **31:** 2948–51

Jeng JS, Tang SC, Yip PK (2004) Incidence and etiologies of stroke during pregnancy and puerperium as evidenced in Taiwanese women. *Cerebrovasc Dis* **18:** 290–5

Kittner SJ, Stern BJ, Feeser BR et al (1996) Pregnancy and the risk of stroke. *N Engl J Med* **335:** 768–74

Korn-Lubetzki I, Gillis S, Steiner I (2001) Mutation in the methylenetetrahydrofolate reductase gene may be a risk factor for cerebrovascular disease in peripartum and under oral contraceptive use. *Eur Neurol* **45:** 171–3

Lamy C, Hamon JB, Coste MD, Mas JL (2000) Ischaemic stroke in young women: risk of recurrence during subsequent pregnancies. *Neurology* **55:** 269–74

Lanska DJ, Kryscio RJ (2000) Risk factors for peripartum and postpartum stroke and intracranial venous thrombosis. *Stroke* **31:** 1274–82

Mas JL, Lamy C (1998) Stroke in pregnancy and the puerperium. *J Neurol* **245:** 305–13

Quenby S, Farquharson RG, Dawood F, Hughes AM, Topping J (2005) Recurrent miscarriage and long-term thrombosis risk: a case–control study. *Hum Reprod* **20**(6): 1729–32

Rohr J, Kittner SJ, Feeser BR et al (1996) Traditional risk factors and stroke in young adults: the Baltimore-Washington Cooperative Young Stroke Study. *Arch Neurol* **53:** 603–7

Sharshar T, Lamy C, Mas JL (1995) Incidence and causes of strokes associated with pregnancy and puerperium: a study in public hospitals of Ille de France. *Stroke* **26:** 930–6

Sibai BM, Coppage KH (2004) Diagnosis and management of women with stroke during pregnancy/postpartum. *Clin Perinatol* **31:** 853–68

Waddy S, Stern BJ (2003) Cerebrovascular disease in pregnancy. *Curr Treat Options Cardiovasc Med* **5**(3): 241–9

Walker ID (2003) Arterial thromboembolism in pregnancy. *Best Pract Res Clin Haematol* **16**(2): 297–310

Wiebers DO (1985) Ischaemic cerebrovascular complications of pregnancy. *Arch Neurol* **24:** 1106–13

KEY POINTS

- There is a large variability in the reported incidence of stroke in pregnancy.
- The majority of cases of stroke in pregnancy are the result of cerebral infarction.
- Causes of ischaemic stroke in pregnancy may be pregnancy-specific, e.g. eclampsia.
- Non-pregnancy specific causes include cardiac disorders, thrombophilias, haematological disorders, vascular and other miscellaneous causes.
- Women with stroke in pregnancy should be investigated in a similar way to any young patient with stroke, commenced on low-dose aspirin in the majority of cases and reassured that the risk of recurrence is low.