Stroke in pregnancy and the puerperium

S D Treadwell,[1] B Thanvi,[2] T G Robinson[3]

[1] Department of Integrated Medicine, University Hospitals of Leicester NHS Trust, Leicester Royal Infirmary, Leicester, UK; [2] South Warwickshire Hospital, Warwick, UK; [3] Department of Medicine for the Elderly, University Hospitals of Leicester NHS Trust, Leicester General Hospital, Leicester, UK

Correspondence to:
Dr S D Treadwell, Department of Integrated Medicine, University Hospitals of Leicester NHS Trust, Leicester Royal Infirmary, Leicester LE1 5WW, UK;
seantreadwell@hotmail.com

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ABSTRACT

Stroke is a recognised complication of pregnancy, contributing to more than 12% of all maternal deaths. Estimated incidence rates vary considerably from 4.3 to 210 strokes per 100 000 deliveries. Atherosclerosis is rare in young adults, and so other causes of stroke become increasingly likely. Aetiological factors important in pregnancy include hypercoagulability due to maternal physiological changes, pre-eclampsia and eclampsia, cerebral venous thrombosis, paradoxical embolism, postpartum cerebral angiopathy and peripartum cardiomyopathy. Management of patients with pregnancy-related stroke should generally proceed as for non-pregnant patients, although there are a number of important areas specific to pregnancy which will be considered here.

Stroke in young adults aged 15–35 years is more common in women than in men,[1] and women also have poorer outcomes in terms of disability and dependency.[2] There has been growing interest in the role of oestrogens in stroke,[3] and risk factors unique to women include pregnancy, use of oral contraceptives, and postmenopausal hormone therapy. Stroke associated with pregnancy has been recognised for many years, and is an uncommon but feared complication contributing to more than 12% of all maternal deaths.[4 5] The declining incidence of direct causes of maternal death has led to an increased awareness of non-obstetric factors such as stroke. Clearly, any recognised cause of stroke in young patients may also occur coincidentally during pregnancy, although there are a number of factors associated with pregnancy that have an important aetiological role, and these will be considered here. We will also consider the current scope of the problem, and focus on relevant areas unique to pregnancy, including issues surrounding investigation and treatment options.

INCIDENCE

Stroke in pregnancy is relatively rare, and the exact risk and the increased risk above that of age-matched non-pregnant women is therefore difficult to establish. Very large population bases are required for reliable estimation, and reported incidence rates vary considerably. This variation reflects small sample sizes, inadequate consideration of referral bias, differences in study designs, and variations in definitions of patient subgroups. For example, when ischaemic stroke has been examined, venous infarction has been grouped separately,[6] alongside arterial occlusion,[4] or not at all.[7]

The incidence of stroke in non-pregnant women aged 15–44 years has been reported to be 10.7 per 100 000 women-years.[8] This compares to pregnancy-related stroke, with incidence rates of 4.3–210 strokes per 100 000 deliveries.[9–11] Recently, a large population-based study in the USA used the Nationwide Inpatient Sample to examine data from ~1000 hospitals[12]: 2850 cases of pregnancy-related stroke were identified with a rate of 34.2 per 100 000 deliveries. Data from non-pregnant women were not analysed, but on comparing with other studies, the authors estimated a threefold increase in incidence of stroke in pregnant than in non-pregnant women. An earlier study by Wiebers and Whisnant[13] reported a much higher (13-fold) increased risk.

It has previously been assumed that most strokes in pregnancy are secondary to cerebral vein thrombosis (CVT), and a study in Mexico City found that over half of the cases of CVT were associated with pregnancy.[14] However, although pregnancy clearly increases the risk of venous thrombosis, most cerebral infarctions are due to arterial occlusion.[6 15] Ischaemic and haemorrhagic strokes have been reported in roughly equal proportions,[7 11] although Jaigobin and Silver[6] found a much higher incidence of ischaemic stroke (18 vs 8 per 100 000 deliveries). As mentioned above, these observed differences may be attributable to patient subgroup selection, as stroke due to CVT was not included in some of the studies.

Most pregnancy-related strokes occur in the third trimester or puerperium, and this is especially true of venous infarction. Jaigobin and Silver[6] identified eight women with venous infarctions, seven of which occurred post partum, and a study in Taiwan showed that 73% of CVTs occurred in the puerperium.[16] Considering all stroke subtypes, data from the Nationwide Inpatient Sample showed that 89% of pregnancy-related strokes occurred either at the time of delivery or post partum. Lanska and Kryscio[9] found that just 0.6% occurred antepartum, although the timing of the stroke was not specified in a number of these cases. Kittner *et al*[10] found no increased risk of ischaemic stroke during pregnancy, but an 8.7-fold increase post partum, and the risk of haemorrhagic stroke was increased 2.5-fold during pregnancy and 23.8-fold post partum.

CAUSES OF STROKE IN PREGNANCY

Risk factors that have been reported for pregnancy-related stroke include age more than 35 years, black ethnicity, hypertension, heart disease, smoking, diabetes, lupus, sickle cell disease, migraine headaches, alcohol and substance abuse, caesarean delivery, fluid and electrolyte disorders, thrombophilia, multiple gestation, greater parity and postpartum infection.[12]

Extensive physiological, biochemical and anatomical changes occur throughout pregnancy affecting

all major organ systems. Coagulation and fibrinolytic systems undergo major alterations during pregnancy so that the overall balance leans towards hypercoagulability, representing physiological preparation for delivery. These changes contribute to the pathogenesis of complications in pregnancy such as venous thromboembolism and stroke.

Hypercoagulability, venous stasis and vascular endothelial injury are a triad of risk factors described by Virchow for the development of venous thromboembolism.[17] All may occur during the course of normal pregnancy, and factors responsible are outlined in box 1. Throughout pregnancy there are increased concentrations of most coagulation factors, especially von Willebrand factor, factor VIII and fibrinogen. In addition, there is progressive resistance to protein C activity and a decrease in protein S.[18] Fibrinolysis is also affected in normal pregnancy because of raised concentrations of plasminogen activator inhibitors 1 and 2. Physiological increases in prolactin concentrations during pregnancy prepare for delivery and breast feeding, and hyperprolactinaemia has been shown to cause increased platelet aggregation through ADP stimulation both in vitro and in vivo.[19]

Anatomical changes in pregnancy lead to venous stasis, which is likely to be a consequence of iliac vein compression by the gravid uterus. Ultrasound studies of the venous system throughout pregnancy have shown decreased flow velocity and increased vessel diameter of the deep leg veins, with flow velocity in the femoral vein at term a third of that recorded in the first trimester.[20] Instrumental delivery and caesarean section may result in prolonged bed rest, reducing blood flow in the legs and contributing to venous stasis. Infection and dehydration secondary to blood loss after delivery may also worsen this prothrombotic state.

Although normal pregnancy itself is not associated with endothelial injury, some degree of damage to pelvic vessels may occur during the course of vaginal or abdominal delivery, which may contribute to the physiological changes outlined above and increase the risk of developing venous and arterial thromboembolism.

Atherosclerosis is less common in young patients, and so other causes of stroke become increasingly important in this age group. There are numerous causes of stroke in young adults, which have been detailed elsewhere,[21 22] and are outside the scope of this article. Any of these causes may occur in young women of childbearing age during pregnancy, and often difficulties arise in establishing whether stroke is due to pregnancy or is coincidental. Here we shall consider just those factors that are either specific to pregnancy or become increasingly important as a result of pregnancy, and therefore warrant special consideration when assessing this group of patients.

Box 1 Physiological changes in pregnancy predisposing to thrombosis

Hypercoagulability

- Increased von Willebrand factor
- Increased factor VIII
- Increased fibrinogen
- Protein C resistance
- Reduced protein S concentrations
- Increased plasminogen activator inhibitors 1 and 2
- Platelet aggregation secondary to hyperprolactinaemia

Venous stasis

- Compression of pelvic vessels by gravid uterus
- Reduced mobility

Endothelial injury

- Trauma during delivery

SPECIFIC STROKE SYNDROMES IN PREGNANCY

Pre-eclampsia and eclampsia

Pre-eclampsia is a pregnancy-specific multi-system disorder affecting 2–10% of pregnancies,[23] and is defined as new onset of raised blood pressure with proteinuria after 20 weeks' gestation. Eclampsia is characterised by the new onset of seizures in a woman with pre-eclampsia. The association between eclampsia and cerebral haemorrhage has been recognised since 1881,[24] and this is reported to be the most common cause of death in patients with eclampsia.[25] Sharshar *et al*[7] found eclampsia to be associated with both cerebral haemorrhage and non-haemorrhagic stroke, and, since then, several studies have reported an increased risk of stroke associated with both pre-eclampsia and eclampsia.[12 26 27] The proportion of patients with pregnancy-related stroke who have pre-eclampsia or eclampsia is 25–45%.[7 10] The risk of ischaemic stroke associated with pre-eclampsia appears to persist even beyond pregnancy and the puerperium, and data from the Stroke Prevention in Young Women Study suggest that women with a history of pre-eclampsia are 60% more likely to have a non-pregnancy-related ischaemic stroke.[28]

It is unlikely that raised blood pressure alone is responsible for the observed increased risk of stroke, as cerebral haemorrhage is relatively rare in women with pre-eclampsia, even with sustained severe hypertension. Also, a recent case series presented by James *et al*[29] showed that 80% of patients with stroke related to pre-eclampsia did not exhibit sustained diastolic pressures of more than 105 mm Hg before stroke.

The exact pathophysiology of pre-eclampsia remains unclear, although endothelial dysfunction appears to play a significant role,[30] suggesting parallels between pre-eclampsia and atherosclerosis. The initiating event is thought to represent abnormal cytotrophoblast invasion of spiral arterioles.[31] The ischaemic placenta secretes soluble factors into the maternal vasculature inducing endothelial dysfunction.[32] Some 4–14% of women with pre-eclampsia present with haemolysis, raised liver enzyme activities, low platelets (HELLP syndrome, which is a severe form associated with multi-organ failure resulting from endothelial damage), fibrin deposition and platelet aggregation. Stroke is the most common cause of death in women with HELLP,[33] supporting the role of endothelial dysfunction in stroke related to pre-eclampsia. A family history of heart disease or stroke is associated with an increased risk of developing pre-eclampsia,[34] suggesting possible genetic risk factors common to both this and atherosclerosis.

Cerebral autoregulation is usually maintained over a mean arterial pressure range of 60–150 mm Hg,[35] which may be altered in pregnancy as a result of chronic hyperventilation. Disturbance of cerebral autoregulation resulting in higher cerebral perfusion pressures has been reported in association with pre-eclampsia and eclampsia,[36 37] which may result in barotrauma and vessel damage. In pre-eclampsia, haemoconcentration due to third spacing of intravascular fluids,[38] and activation of the coagulation cascade with micro-thrombi formation,[39] may also contribute to the overall picture of hypoperfusion and increased stroke risk.

Box 2 Learning points for the clinician

- Pregnancy is associated with an increased risk of both ischaemic and haemorrhagic stroke, the majority occurring in the third trimester or puerperium.
- Stroke accounts for more than 12% of all maternal deaths.
- Stroke can present in a similar way to other more common complications of pregnancy, such as eclampsia, and should therefore be considered in all cases of neurological deterioration.
- Investigation should proceed as in the non-pregnant state, with special consideration of the pregnancy-specific causes outlined.

The only definitive treatment for pre-eclampsia and eclampsia is delivery of the fetus and placenta, and drug therapy focuses on the treatment of hypertension and prophylaxis against seizures. Hydralazine is the antihypertensive agent of choice, and magnesium sulphate is the first-line therapy for seizures, as it prevents vascular spasm.

Postpartum cerebral angiopathy (PCA)

PCA belongs to a group of disorders termed reversible cerebral vasoconstriction syndromes. These are characterised by reversible multifocal vasoconstriction of the cerebral arteries and occur in a variety of clinical settings including pregnancy and the puerperium,[40–43] drug exposure,[44] migraine,[45] mechanical trauma,[46] hypercalcaemia[47] and idiopathic causes with no obvious precipitating factor.

PCA usually occurs a few days after delivery, and although a similar syndrome has been described with eclampsia,[48] most patients have a history of uncomplicated pregnancy and delivery. Presenting features include sudden (thunderclap) headache, photosensitivity, vomiting, altered consciousness, seizures and transient or permanent focal neurological symptoms. Vasoconstriction can cause a variety of focal deficits due to transient ischaemia, cerebral infarction and intracranial haemorrhage, all of which have been reported.[40–43 49] Differential diagnoses to consider in this clinical setting include aneurysmal subarachnoid haemorrhage (SAH), carotid or vertebral artery dissection, cerebral vasculitis, cerebral venous sinus thrombosis, intracranial infection and pituitary apoplexy.

The pathophysiology of PCA remains unclear, and a similar syndrome has been described with eclampsia[48] leading many authorities to believe that these both represent the same condition, although PCA appears to be isolated to the nervous system and most patients have a history of uncomplicated pregnancy and delivery. A disturbance in the control of vascular tone is likely to play a central part, and factors known to be responsible for SAH-related vasospasm may be responsible.[50] Some cases of PCA have occurred in association with the use of vasospastic drugs such as ergonovine[51] and bromocriptine[44] during pregnancy.

Radiological features include multifocal segmental narrowing of the cerebral arteries, with reversibility and complete resolution 4–6 weeks later. Diagnostic uncertainty may arise because of overlapping clinical and angiographic features with cerebral vasculitis. Examination of the cerebrospinal fluid may be helpful, as this is often normal in PCA, and is also critical to rule out SAH. Occasionally brain biopsy may be necessary when uncertainty exists, as the distinction between PCA and vasculitis has important therapeutic and prognostic implications.

Treatment of PCA is guided by observational data, and, although vasodilators and glucocorticoids have been used, the process is usually self-limiting. Although it generally runs a benign course with complete resolution of symptoms and angiographic findings, cerebral haemorrhage,[49] maternal death[52] and recurrence in subsequent pregnancies[49] have all been reported.

Cerebral aneurysm rupture and SAH

SAH is the third leading cause of non-obstetric-related maternal death.[53] Most cases of SAH are due to ruptured cerebral aneurysms, and typically present with thunderclap headache, vomiting, seizures or reduced level of conscious. Presentation in pregnancy may be confused with eclampsia, and the diagnosis should be confirmed with neuroimaging or cerebrospinal fluid analysis. The quoted incidence of SAH from aneurysmal rupture in pregnancy ranges from 3 to 11 per 100 000 pregnancies.[7 10] The relative risk of intracerebral haemorrhage during pregnancy and 6 weeks post partum has been reported to be 5.6 times that of the non-pregnant patient,[10] and 50% of all aneurysmal ruptures in women below the age of 40 years are pregnancy-related.[54] Aneurysms are most likely to rupture in the later stages of pregnancy, and up to 6 weeks post partum,[5 10 55] and mortality is higher than in non-pregnant patients.[56]

Haemodynamic changes related to pregnancy are likely to contribute to aneurysm instability and the increased risk of SAH. Blood volume increases by more than 50% by the third trimester, with an associated increase in cardiac output, placing further stress on potentially weakened vessel walls. Pregnancy is also associated with hyperplasia of arterial wall smooth muscle and loss of the normal elastic fibre alignment[57] contributing to weakness of the vessel wall. Metabolic and endocrine factors have also been implicated.[58] Non-aneurysmal SAH has been reported in the context of pregnancy-induced hypertension and eclampsia.[59]

Surgical treatment after aneurysmal SAH during pregnancy improves both maternal and fetal outcome,[60] and the management should generally follow the same course as for the non-pregnant population, which has been well described elsewhere.[61] Endovascular techniques have been successfully demonstrated during pregnancy.[62] The route of delivery has been reported to have no effect on the rate of maternal complications,[63] and once the aneurysm has been treated, the pregnancy can generally proceed to term. Most clinicians favour vaginal delivery unless the aneurysm is diagnosed at term, there has been neurosurgical intervention within the week before delivery, or other maternal factors indicate caesarean delivery.

CVT

CVT is characterised by a variety of clinical manifestations depending on the site involved. Occlusion of the cerebral cortical veins can result in venous infarction with associated focal neurological symptoms and signs. Occlusion of the major venous sinuses usually results in the development of intracranial hypertension from increased venous pressure and impaired absorption of cerebrospinal fluid, leading to headache, vomiting and papilloedema. Cavernous sinus thrombosis may also lead to a painful eye and sometimes exophthalmos.

As previously mentioned, pregnancy induces several changes in the coagulation system, which persist into the puerperium resulting in a prothrombotic state. These have all been regarded

as important factors contributing to the risk of CVT in pregnancy and the puerperium. The first description of puerperal CVT was in 1828,[64] and since then the relationship of CVT to pregnancy and the puerperium has been well documented.[65] The likelihood that stroke is of venous origin is greater in pregnant than in non-pregnant women of similar reproductive age,[66] and it has long been assumed that most strokes associated with pregnancy are secondary to CVT. However, many of these studies used data collected before the advent of newer neuroimaging techniques, and did not have pathological or angiographic documentation. This concept was challenged by Cross *et al*[15] in 1968, who found that, in a series of 31 patients with pregnancy-related stroke, only one was attributable to venous thrombosis. Despite this, subsequent studies have reported a higher incidence of CVT,[14 67] although it should be noted that most pregnancy-related infarctions are still attributable to arterial occlusion.[6]

The risk of pregnancy-related venous infarction is significantly higher in the puerperium. Data from the Healthcare Cost and Utilization Project[9] estimated a risk of 11.6 cases of peripartum CVT per 100 000 deliveries. Jaigobin and Silver[6] identified 21 cases of cerebral infarction associated with pregnancy over a 17-year period, 13 of which were arterial and eight of which were of venous origin. Seven of the eight venous infarctions occurred post partum. More recently, a study in Taiwanese women reported 11 cases of pregnancy-related CVT, 73% of which occurred during the puerperium.[16] Most of these patients had a pre-existing hereditary coagulopathy. Of 113 cases of CVT identified in Mexico City, 73 were related to pregnancy, 61 of which occurred post partum,[14] and, in a study in India, 20% of cases of stroke in young patients were due to postpartum CVT.[67]

The risk of peripartum CVT increases with hypertension, advancing maternal age, caesarean delivery, associated infections and excess vomiting during pregnancy.[9] The rate of death from all-cause CVT is 2–10%,[14 68 69] although mortality is significantly less for pregnancy-associated CVT.[14] When maternal deaths occur, they usually result from secondary intracranial haemorrhage,[4 13] although one analysis reported the most common cause of death to be transtentorial herniation.[70]

Treatment of CVT in pregnancy is complicated by uncertainty about the most appropriate use of antithrombotic agents in particular circumstances. Recent guidance from the American College of Chest Physicians[71] suggests that low-dose aspirin appears to be safe after the first trimester, and, although warfarin may be safe for the fetus after 12 weeks, it is not usually recommended during pregnancy because of uncertainty surrounding the risks. On the basis of this guidance, the American Heart Association/American Stroke Association have recommended a number of options for pregnant women with ischaemic stroke and high-risk thromboembolic conditions: adjusted-dose unfractionated heparin (UFH) throughout pregnancy with activated partial thromboplastin time monitoring; adjusted-dose low-molecular-weight heparin (LMWH) with factor Xa monitoring; or UFH or LMWH until week 13 followed by warfarin until the middle of the third trimester, when UFH or LMWH is reinstituted until delivery.[72]

Paradoxical embolism

Patent foramen ovale (PFO) is an inter-atrial communication present in about 27% of adults,[73] and increasing availability of diagnostic techniques such as transcranial Doppler has led to higher rates of detection of this anomaly. There is a well-established link between cryptogenic stroke in the young and the presence of PFO, which is present in over half of these patients.[74 75] Paradoxical embolism is likely to represent the most important pathophysiological mechanism, where the presence of PFO permits right-to-left shunting of venous emboli into the arterial circulation. Thrombus formation due to stagnant blood flow may also occur within the PFO, and susceptibility to atrial arrhythmias provides further potential mechanisms for cardioembolism.[76]

The presence of PFO in pregnancy-related stroke has been well described.[77 78] However, this aetiological link should be interpreted with caution in view of the relatively high incidence of PFO in the general population. As outlined earlier, pregnancy is associated with a hypercoagulable state with an increased risk of venous thromboembolism. The presence of PFO during pregnancy therefore provides an additional risk factor for ischaemic stroke because of the possibility of paradoxical embolism. Straining associated with delivery may invert the pressure gradient across the heart, facilitating right-to-left shunting of emboli.

Treatment options for secondary prevention in patients with cryptogenic stroke and PFO include medical therapy, in the form of warfarin or antiplatelet agents, and percutaneous transcatheter closure. Recent American Stroke Association guidelines[72] suggest the use of aspirin for secondary prevention, with warfarin reserved for high-risk patients. Consideration of PFO closure is recommended for patients with recurrent cryptogenic stroke despite optimal medical therapy, although current knowledge on treatment options is based primarily on observational studies. Transcatheter closure has been increasingly used in recent years, although stroke recurrence may still occur.[79] As mentioned, warfarin is relatively contraindicated in pregnancy, although percutaneous device closure of PFO during pregnancy has been successfully performed under echocardiographic guidance with trivial fetal radiation exposure.[78]

Peripartum cardiomyopathy (PPCM)

Cardiomyopathy is an established risk factor for cardioembolic stroke.[80] PPCM is a disorder of unknown cause occurring in the peripartum period, characterised by symptoms of heart failure due to left ventricular systolic dysfunction in women without pre-existing heart disease.[81] PPCM was first described as a distinct entity in the 1930s,[82] and diagnostic criteria initially established in 1971[81] have more recently been reviewed.[83] PPCM remains a diagnosis of exclusion, and factors required to fulfil diagnostic criteria include the following: development of congestive heart failure due to decreased left ventricular systolic function in the last month of pregnancy or within the 5 months after delivery; the absence of pre-existing cardiac dysfunction; and the absence of a determinable cause of the cardiomyopathy.[83]

The true incidence of PPCM is unknown and there is wide geographical variation, although this has been estimated at 1 in every 3000–4000 live births.[84] The cause and pathogenesis of PPCM remains unclear, although a number of aetiological factors have been proposed, including myocarditis,[85] nutritional deficiency,[86] abnormal immune response,[87] stress-activated cytokines[88] and viral antigen persistence.[89] The presence of left ventricular thrombus is common in PPCM,[88] and peripheral embolisation may occur, resulting in ischaemic bowel,[90] myocardial infarction,[91] acute limb ischaemia[92] and cerebral infarction.[7 93]

Treatment follows that of heart failure unrelated to pregnancy, with agents such as diuretics and angiotensin-converting enzyme inhibitors. The use of antithrombotic agents in pregnancy for high-risk thromboembolic conditions has been

detailed previously.[59] Mortalities of 18–56% have been reported for PPCM,[81 94] and prognosis appears to depend on normalisation of left ventricular size and function within 6 months of delivery.

Other causes

Other aetiological factors related to pregnancy that have been reported include: arterial dissection,[95] which may occur as a consequence of straining during labour; cerebral haemorrhage resulting from disseminated intravascular coagulation due to obstetric complications such as amniotic fluid embolism;[6 7] middle cerebral artery thrombosis complicating ovarian hyperstimulation syndrome due to fertility drugs;[96] and stroke related to the use of drugs in pregnancy including bromocriptine[71] and conduction anaesthesia.[97]

MANAGEMENT

Although initial assessment should include consideration of the pregnancy-specific causes of stroke outlined above, it should be recognised that all other aetiological factors in young patients may also occur coincidentally during pregnancy and should not be overlooked. The assessment and treatment of patients with pregnancy-related stroke should generally proceed as in the non-pregnant state. Management guidelines have been previously well described,[48 59] and are outside the scope of this article. There are, however, a number of issues that deserve additional consideration during pregnancy because of concerns over the risks to the fetus, and these will be outlined here.

Investigation

Investigations such as head CT, which involve exposure to ionising radiation, may cause considerable anxiety in view of the potential hazard to the developing fetus. The potential effects of ionising radiation on the fetus include death, malformation, growth retardation, mental retardation and cancer induction. Risk is assessed on the basis of dose, and absorbed dose is measured in rad or gray, Gy (100 rad = 1 Gy). Risk estimates are derived from the survivors of high-radiation doses from atomic explosions in Hiroshima and Nagasaki, using linear extrapolation to low levels of radiation exposure. The maximum estimated fetal absorbed dose of ionising radiation is ~50 mrad for a head CT, 10 mrad for cerebral angiography, and 1.0 mrad for a chest radiograph.[98 99] To put this into context, natural background exposure at sea level is about 300 mrad per year. Estimation of the excess risk of cancer up until the age of 15 is 1 in 17 000 per 100 mrad of fetal exposure.[100] The estimated increase in lifetime risk of developing cancer after fetal exposure from a head CT is 0.07%. As approximately 1 in 4 people will develop cancer at some time in their life, this excess risk is extremely small. Up until 10 weeks of pregnancy, the threshold for detecting an increased risk of congenital malformation is above 5000 mrad. It should be emphasised that there is no direct evidence that fetal exposure to ionising radiation used in diagnostic imaging causes cancer or birth defects. Analysis suggests that pregnant women exposed to less than 5000 mrad have no additional risk to the fetus compared with women receiving background radiation alone.

MRI does not involve ionising radiation, and no adverse effects on the developing fetus have been documented, although any long-term effects are yet to be determined. Recent guidance from the American College of Radiology suggests that pregnant patients can undergo MRI scans, provided that the potential risk/benefit ratio warrants the study, the information cannot be acquired by other non-ionising means (eg, ultrasonography), and the information cannot wait until the patient is no longer pregnant.[101] MR contrast agents cross the blood–placenta barrier easily, and no data exist to assess the rate of clearance of contrast agents from the amniotic fluid cycle, or the potentially toxic effects to the fetus. Guidelines suggest that administration of gadolinium-based MR contrast agent should be avoided unless overwhelming potential benefit to the patient or fetus that outweighs the theoretical risks can be demonstrated.[101]

Treatment

Specific treatment options relating to individual causes of stroke including the use of antithrombotic agents have been outlined above under the relevant sections. Here we shall focus on general issues surrounding the role of thrombolytic therapy during pregnancy.

The benefit of intravenous and intra-arterial thrombolysis in acute ischaemic stroke is well established.[102] Arterial occlusion is the most common cause of pregnancy-related stroke,[6] although historically the use of thrombolytic agents during pregnancy has been relatively contraindicated because of concerns about fetal and maternal complications. Potential risks include preterm labour, placental abruption, fetal death, postpartum haemorrhage and possible teratogenicity. For these reasons there are currently no data from randomised controlled trials in pregnant patients, and only case reports and case series have been published.

There are more than 200 reports in the literature of pregnant patients who have received thrombolytic therapy for various indications including myocardial infarction,[103] pulmonary embolus,[104] superior vena cava syndrome[105] and, more recently, ischaemic stroke.[106] Murugappan *et al*[107] reported a case series in 2006 including eight pregnant patients who had been treated with thrombolytic therapy for acute ischaemic stroke. Seven mothers made a good recovery, and one died from arterial dissection complicating angiography, although this was not attributed directly to thrombolysis. Three patients had therapeutic abortions, there were two spontaneous abortions, and two babies were delivered healthy. Johnson *et al*[108] reported on a patient with right middle cerebral artery occlusion presenting late on in pregnancy. She was successfully treated with recombinant tissue plasminogen activator, and delivered a healthy baby just 3 days later.

Approximately half of patients who survive a pregnancy-related stroke are left with a residual neurological deficit.[109] The benefits of thrombolytic therapy in reducing maternal disability

Box 3 Current research questions

- The role of oestrogens in stroke is complex and not yet fully understood. In addition to the associated increased risk of stroke, oestrogens may have a neuroprotective role, although the underlying mechanism remains unclear.
- The risk of stroke recurrence in subsequent pregnancy, and the association between hypertensive diseases of pregnancy and stroke later in life, needs further evaluation.
- Factors that predispose a woman to develop risk factors for pregnancy-associated stroke such as pre-eclampsia are incompletely understood.
- Although initial results on the use of thrombolysis in pregnancy have been encouraging, further evaluation with regard to maternal and fetal risk is warranted.

need to be weighed against potential maternal and fetal risks. The use of thrombolytic agents in pregnancy is not without its consequences, although the overall maternal mortality and fetal loss is relatively low at 1% and 6%, respectively.[104] Available data suggest that the use of thrombolytic therapy for acute ischaemic stroke in pregnancy should at least be considered in appropriate patients, and limited case series have so far shown favourable outcomes.

PROGNOSIS

Mortality from pregnancy-related stroke typically results from intracranial haemorrhage or malignant hypertension.[7 110] Maternal deaths associated with ischaemic events are uncommon, and when they do occur usually result from secondary haemorrhage.[111 112] Sharshar *et al*[7] reported 31 cases of pregnancy-related stroke in a study in Ile de France. From the 15 patients with ischaemic stroke, there were no maternal deaths. Five patients were left with mild to moderate deficit, and there were two stillbirths and four premature deliveries. Of the 16 patients with intracranial haemorrhage, four died (three of which had eclampsia), and eight of the survivors had mild to moderate deficit. There were two stillbirths and seven premature deliveries in this group. This study confirmed the poor maternal prognosis associated with eclampsia complicated by intracranial haemorrhage.

Data from the Nationwide Inpatient Sample[12] reported an estimated overall case fatality rate for pregnancy-related stroke of 4.1%. As expected, this is significantly lower than the case fatality rate of 24% for all strokes,[113] but is also lower than the reported mortality of 4.5–24% for all-cause strokes in young adults.[18 114–116]

There are no data supporting the relationship between childbearing and the risk of recurrent stroke. Lamy *et al*[117] reported on 489 women aged 15–40 years with a first ever ischaemic stroke. Thirteen patients had a recurrent event, and only two of these occurred during a pregnancy. None of the women whose initial stroke occurred in pregnancy had a recurrent stroke during subsequent pregnancies, and this low recurrence rate suggests that a previous ischaemic stroke should not be a contraindication to further pregnancies. There does, however, appear to be an association between a history of pre-eclampsia and the risk of subsequent ischaemic stroke remote from pregnancy.[28]

SUMMARY

Stroke occurring in pregnancy can be devastating not only because of maternal mortality and disability occurring during childbearing years, but also because of potential risks to the fetus. An understanding of particular aetiological factors that may occur more commonly in pregnancy is essential when assessing this group of patients. Identification of underlying precipitating factors will clearly have different therapeutic implications—for instance, the use of anticoagulation in CVT and conditions that carry a high risk of cardioembolism, such as PPCM. Identification and closure of PFO has also been successfully demonstrated during pregnancy. Despite the lack of randomised data, there have been encouraging results on the use of thrombolytic therapy in pregnancy, and this should be considered in appropriate patients.

Despite fears surrounding this serious complication, it should be remembered that stroke in pregnancy is relatively rare and carries more favourable mortality data than other causes of stroke in young adults, and patients should be reassured that there does not appear to be any increased risk of recurrence in subsequent pregnancies.

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SELF ASSESSMENT QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AFTER THE REFERENCES)

1. The majority of strokes occurring in pregnancy are due to cerebral haemorrhage.
2. Cerebral vein thrombosis related to pregnancy occurs more commonly in the postpartum period than during pregnancy itself.
3. Increased concentrations of coagulation factors occur physiologically throughout normal pregnancy.
4. Peripartum cardiomyopathy is characterised by symptoms of worsening heart failure in the peripartum period in women with pre-existing cardiac dysfunction.
5. Cerebral haemorrhage is the most common cause of maternal mortality in patients with eclampsia.

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Answers

1. F (most strokes in pregnancy are ischaemic and secondary to arterial occlusion); 2. T; 3. T; 4. F (the absence of pre-existing heart disease is required to fulfil diagnostic criteria for peripartum cardiomyopathy); 5. T