

Haemorrhagic Stroke in Pregnancy

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Stroke in pregnancy is rare, with a reported incidence of 8.9 to 67.1 per 100 000 deliveries. With significant improvements in antenatal and intrapartum care, stroke has become the leading non-obstetric cause of maternal mortality in high-income countries such as Canada, United States, United Kingdom, and Japan. Strokes are classified as ischaemic (arterial or venous) or haemorrhagic (subarachnoid or intracerebral). Asians have more haemorrhagic strokes than ischaemic strokes in pregnancy than Caucasians. We report three patients who had haemorrhagic stroke in pregnancy with various causes, symptoms, treatments, and outcomes, and then review the literature on haemorrhagic stroke in pregnancy.

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Case Series

Patient 1

In September 2017, a 25-year-old, parity 0, woman with good past health and uneventful antenatal care was diagnosed with gestational diabetes at 25 weeks. While awaiting an appointment with a dietitian, she was admitted to the United Christian Hospital at 25+3 weeks of gestation for sudden onset of severe headache and vomiting. She was noted by her husband to be drowsy with reduced responsiveness. She had no history of illicit drug use or head injury.

Her Glasgow Coma Scale (GCS) score was 14/15 (E4V5M5). Her blood pressure was 106/67 mm Hg, and urinalysis was positive for albumin. Her bilateral lower limb power had decreased to grade 4/5, but reflexes were normal. The cardiotocogram was reactive. Blood tests showed a haemoglobin level of 10.1 g/dl, but the platelet count, clotting profile, liver and renal function tests were normal. Ultrasonography showed normal fetal parameters and liquor volume and normal umbilical artery Doppler indices. Urgent computed tomography (CT) of the brain showed diffuse subarachnoid haemorrhage (SAH) with mild hydrocephalus (Figure 1a). The patient was transferred to the Queen Elizabeth Hospital (QEH) for neurosurgical treatment. CT angiography showed a 7x4 mm fusiform aneurysm arising from the right posterior cerebral artery, suggestive of a dissecting aneurysm (Figure 1b). The patient underwent endovascular occlusion of the intracranial vessel by coiling (Figure 1c). A course of dexamethasone was given to enhance fetal lung maturity in case of maternal deterioration and consequent need for urgent delivery.

Two days later, the patient complained of headache. CT of the brain revealed an infarct over the territory of the posterior cerebral artery. She developed weakness of the left side 7 days after coiling. Repeat CT showed a new right parietal infarct. Emergency classical Caesarean section was performed at 26+4 weeks owing to maternal deterioration with a progressive and enlarging maternal brain infarct. A baby with birthweight of 860 g was born with Apgar scores of 5 at 1 min and 8 at 5 mins. Cord arterial pH was 7.33. The patient subsequently recovered gradually and was discharged 25 days after coiling. She could walk unaided with normal limb power and had no neurological deficits on follow-up.

Patient 2

In April 2011, a 33-year-old, parity 2, woman presented to the United Christian Hospital with spontaneous onset of labour at 39 weeks of gestation. Her first pregnancy had been complicated by transient postpartum convulsion at the time of episiotomy repair following vaginal delivery; it was suspected to be an episode of eclampsia. Results of subsequent examinations by CT of the brain and electroencephalography were normal, and she was lost to follow-up. Eight years later, her second pregnancy was uneventful, with a normal vaginal delivery without pre-eclampsia or eclampsia.

Three years later, she had her third pregnancy, and the antenatal course was uneventful. On admission, her

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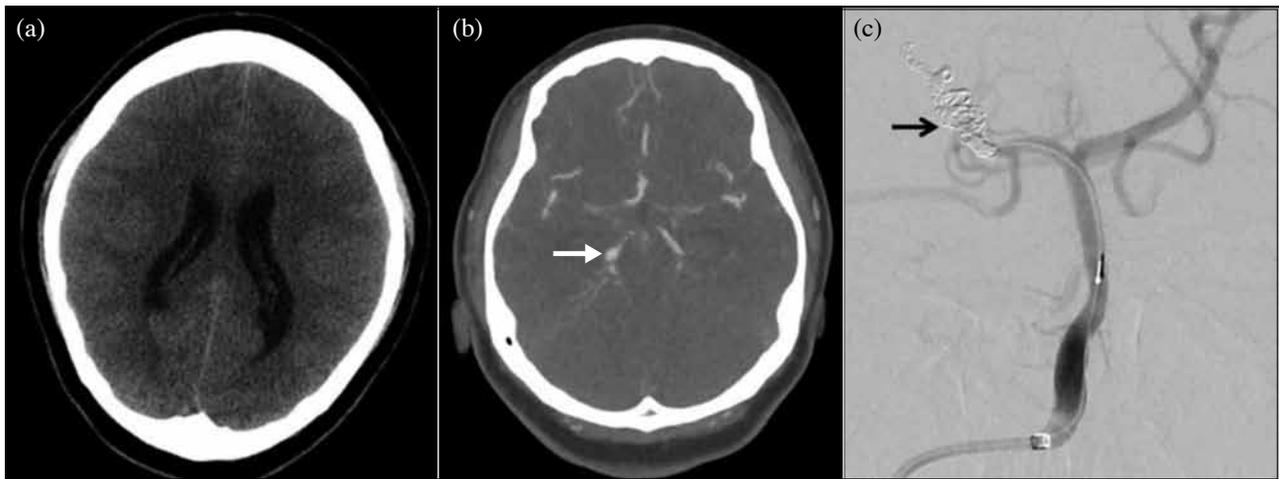


Figure 1. Patient 1: (a) A computed tomography scan showing diffuse subarachnoid haemorrhage with bilateral sulcal spaces effaced. (b) A computed tomography angiogram showing a cerebral aneurysm (arrow) arising from the right posterior cerebral artery. (c) A digital subtraction angiogram showing endovascular coiling (arrow) of an intracranial vessel

blood pressure was 160/80 mm Hg and urinalysis revealed proteinuria. Neurological examination was normal. Her haemoglobin level was 9.3 g/dl, but the platelet count, clotting profile, liver and renal function tests were normal. Three hours after admission, she was noted to be drowsy. Neurological examination showed increased tone on the left side of her body. Magnesium sulphate was given in view of possible eclampsia. Twenty minutes later, she had a tonic-clonic convulsion and transient fetal bradycardia. Emergency Caesarean section was performed and the baby was born in good condition. The patient was transferred to the intensive care unit (ICU) and had two more episodes of seizure despite the magnesium sulphate treatment. Phenytoin was given. Urgent CT of the brain showed a left intracranial haemorrhage and intraventricular haemorrhage with blood in the fourth ventricle with mass effect (Figure 2).

Two hours after delivery, the patient was transferred to QEHS and immediately underwent left craniotomy. Large blood clots were evacuated from the left basal ganglia, but bleeding tendency continued. Platelet and fresh frozen plasma transfusion was commenced. The operative blood loss was 2000 ml. One hour later, her intracranial pressure increased again. CT revealed a large haematoma (5 cm) over the left cerebral hemisphere and the left basal ganglia, with midline shift to the right side. Four hours later, decompression was performed. The brain was found herniating out after the scalp was opened. Frontal lobectomy was performed anterior to the Sylvian vein and the blood clots were evacuated. The operative blood loss was 3000 ml.

On day 6, CT showed cerebral oedema and further



Figure 2. Patient 2: a computed tomography scan showing left intracranial and intraventricular haemorrhage (arrow)

intracerebral haemorrhage. She underwent decompression and evacuation of the necrotic brain tissue and haematoma and partial left temporal lobectomy. On day 16, the patient was transferred to the general ward. Cranioplasty was performed 2 months after delivery, but was subsequently removed 5 weeks later owing to infection. Six months later, the patient developed hydrocephalus, and a ventriculo-peritoneal shunt was inserted. The patient stayed at QEHS for 1 year and was transferred to the Kowloon Hospital for rehabilitation, with a GCS score of 11/15 (E4V2M5). She had right hemiparesis and receptive and expressive

dysphasia. She underwent physiotherapy and training for 3 years and was finally discharged home with a GCS score of 13/15 (E4V3M6). She could walk a few steps with the aid of a walking frame and could speak a few single words. Cranioplasty was performed 6 years after delivery.

Patient 3

In October 2015, a 35-year-old, parity 2, woman with two uneventful normal vaginal deliveries was scheduled for morphology scanning in our antenatal clinic at 19+4 weeks of gestation. Incidentally, she presented to the United Christian Hospital in a wheelchair with severe dizziness for 1 week and headache and neck pain that were not improved by paracetamol. She also had nausea and vomiting. Morphology scan was normal. Her blood pressure was normal and urinalysis was negative for albumin. Neurological examination was normal. Her haemoglobin level was 12.3 g/dl, and the platelet count, clotting profile, liver and renal function tests were normal. Urgent CT of the brain revealed haemorrhage in the right basal ganglia (Figure 3a), and the patient was transferred to QEH for further management.

A ruptured arteriovenous malformation (AVM) was suspected, but the patient declined magnetic resonance angiography. Her headache subsequently improved and there was no immediate need for neurosurgical intervention. She was counselled by joint neurosurgery and obstetrics teams and the risk of acute rupture of AVM was explained. Nonetheless, the patient refused any neuroimaging and surgical intervention during pregnancy. The agreed plan was to undergo emergency Caesarean section followed by neurosurgical operation if there was re-rupture of the AVM. Otherwise, delivery was planned at 34 weeks of gestation by elective Caesarean section to avoid the risk of rupture during labour. Neuroimaging and surgical intervention would then be performed after delivery.

The patient's dizziness gradually improved. She had one course of steroid injections to enhance fetal lung maturity. Lower-segment Caesarean section was performed at 34 weeks and the baby was born in good condition. Two days after delivery, CT of the brain showed a 2-cm AVM at the right medial frontal lobe. Digital subtraction angiography (DSA) and magnetic resonance angiography showed a right frontal lobe AVM and a 2-mm-wide aneurysm at the junction of the left anterior cerebral artery and anterior communicating artery (Figure 3b). The neurovascular team at QEH suggested embolisation of the AVM followed by surgery or radiosurgery. The patient sought a second opinion from the neurosurgical team at

Queen Mary Hospital and was offered radiosurgery instead of embolisation. She underwent radiosurgery at Queen Mary Hospital 11 months after Caesarean section. Seven weeks later, CT and magnetic resonance imaging (MRI) of the brain showed no cerebral oedema. 11 months later, the patient presented to Queen Mary Hospital with left lower limb weakness and unbalanced gait. CT of the brain revealed right parietal oedema. Dexamethasone was given and her limb power improved. She was discharged in good condition, pending repeat MRI later.

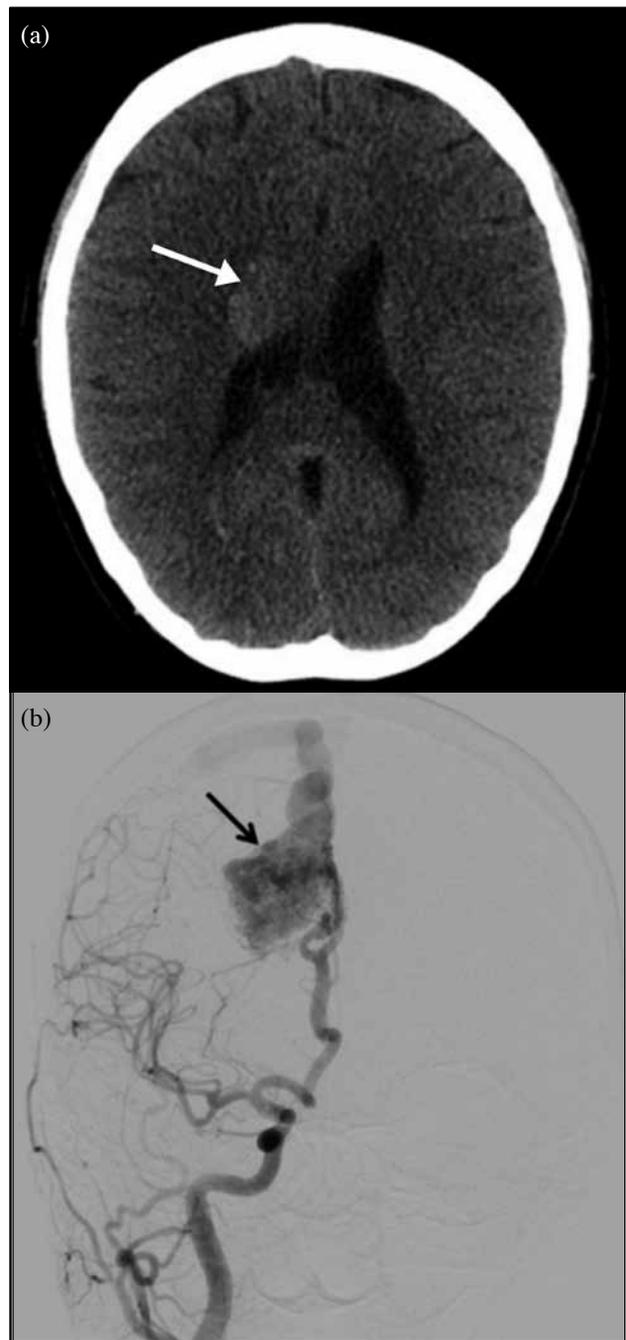


Figure 3. Patient 3: (a) a computed tomography scan showing haemorrhage in the right basal ganglia (arrow). (b) A digital subtraction angiogram showing a right frontal lobe arteriovenous malformation (arrow)

Discussion

Haemorrhagic strokes account for 29% to 46% of all strokes in pregnancy among Caucasians and 43% to 74% among Taiwanese and Japanese¹⁻⁵. Japanese have a 2.8-fold increased risk of aneurysm rupture. Non-white people including Asians have a 3.09-fold increased risk in rupture of AVM than white people¹. In a Hong Kong study of 49 368 deliveries from 1952 to 1994, five patients were diagnosed with a haemorrhagic stroke, accounting for an incidence of 10 per 100 000 deliveries⁶. In pregnant women, haemorrhagic stroke is associated with higher maternal mortality and morbidity than ischaemic stroke; the average maternal mortality has been reported to be 13.8% and 3.9%, respectively⁵.

Subarachnoid Haemorrhage

The most common cause of SAH in pregnancy is rupture of cerebral aneurysms. Other causes include rupture of AVM, eclampsia, coagulopathy, and vasculopathy such as connective tissue disorders⁷. The incidence of SAH is higher in pregnant patients than non-pregnant patients^{7,8}. The postulated causes include an increased plasma volume during pregnancy, pregnancy-induced hypertension, and pregnancy-related hormonal changes that lead to remodelling of arterial and venous intima and media of vessel walls^{7,9}. Aneurysmal rupture may occur in any trimester of pregnancy², with the highest incidence in the third trimester¹⁰⁻¹². The risk of aneurysmal rupture increases because of gross haemodynamic fluctuations during the intrapartum period, particularly in association with the Valsalva manoeuvre during delivery. However, one study reported that 90% of the aneurysmal ruptures occur in the antepartum period, and only 2% in the intrapartum period and 8% in the puerperium¹³. Hypertension is associated with 10% to 20% of SAH in pregnancy and is the most important risk factor. Pre-eclampsia or eclampsia is present in 14% to 40% of intracranial haemorrhages in pregnancy. Other risk factors include use of anticoagulants and cigarette smoking⁷⁻¹⁰.

The most common symptom of SAH is severe and sudden onset of headache. It is commonly described as 'an explosion within the head' and 'the worst headache of my life'. The headache is usually sub-occipital or frontal, and associated with nausea and vomiting. There may be blurring of vision and other focal neurological deficits⁷. The most common sign of SAH is neck stiffness, which is present in 90% of patients, but it may not develop until hours after SAH. Intraocular bleeding, which is seen as unilateral or bilateral subhyaloid haemorrhage on ophthalmoscopy, is present in 25% of patients. Seizures are found in 15%

of patients¹⁴. It is sometimes difficult to distinguish SAH from severe pre-eclampsia or eclampsia, as both result in headache, blurring of vision, seizures, and neurological deficits. Blood pressure may be transiently elevated following aneurysmal rupture due to raised intracranial pressure or increased catecholamine release. In addition, proteinuria can be detected in up to 30% of patients⁷.

A prompt diagnosis and treatment are important to achieve good maternal outcomes¹⁵. CT is the first choice for diagnosing intracranial haemorrhage, as it is quick to perform and available 24 hours a day in most clinical settings. Nonetheless, MRI has lower radiation risks to the fetus⁷ and should be the first choice for diagnosis if the pregnancy is <10 weeks of gestation, which is the time for fetal organogenesis and most susceptible to radiation. Precautions to limit radiation exposure to the fetus by abdominal shielding should be adopted. Diagnosis of intracranial haemorrhage can be made by CT, MRI, intra-arterial DSA (a fluoroscopy technique to visualise blood vessels), or CT-angiography (a contrast angiogram visualised by CT) to determine the cause of bleeding such as ruptured aneurysms and AVM^{7,10}. Magnetic resonance angiography may be used to detect cerebral aneurysms but its specificity is lower than DSA⁷.

The risk of re-bleeding is 4% over the first 24 hours following aneurysmal rupture and increases to 10% to 20% in the first month. Re-bleeding occurs in 33% to 50% of untreated ruptured aneurysms within 4 to 6 weeks⁷. Up to 33% of SAH patients have cerebral vasospasm that leads to delayed cerebral ischaemia¹⁶. The maternal mortality due to rupture of cerebral aneurysm ranges from 13% to 35%¹⁷. It is the third leading cause of maternal death from non-obstetric causes, accounting for 5% to 12% of total mortality during pregnancy in United States¹⁰.

As there is a risk of re-bleeding after ruptured aneurysm, a conservative approach is associated with a maternal mortality of 63% and a fetal mortality of 27%; early surgery can lower these mortalities to 11% and 5%, respectively⁹. Therefore, early surgery is recommended for aneurysmal rupture during pregnancy. Traditional surgery for aneurysmal rupture involves craniotomy and clipping of the aneurysm. In 1990, a detachable platinum coil was introduced to exclude aneurysm from the parent vessel by exciting thrombosis within the sac¹⁸. It was initially used in aneurysms in the posterior part of the Circle of Willis or in the cavernous segment where surgical clipping was technically difficult. Subsequently, endovascular coiling was widely performed for aneurysms in both anterior and

posterior parts of the circulation. Since the publication of the International Subarachnoid Aneurysm Trial (ISAT) in Europe in 2002, endovascular coiling has become the first-line treatment for cerebral aneurysm¹⁹. Patients treated by coiling have been reported to have significantly better survival and less disabilities at 1-year follow-up than those treated by surgical clipping¹⁹. The risk of death or severe disability after coiling is 22.6% lower than that after surgical clipping at 1-year follow-up¹⁹.

Nonetheless, not all patients are suitable for endovascular coiling. Patients with middle cerebral artery aneurysms where terminal branches frequently arise from the sac itself are not appropriate candidates²⁰. Presence of cerebral vasospasm may obstruct endovascular access. Aneurysms with an excessive dome-to-neck ratio are not suitable for coiling as the coil may prolapse back into the parent lumen. Endovascular coiling is more likely to succeed in aneurysms with a dome-to-neck ratio of >1.6 and with a neck size of <4 mm, and is more likely to fail in aneurysms with a dome-to-neck ratio of <1.2²⁰.

Endovascular coiling has been a successful treatment for ruptured aneurysm in pregnancy^{21,22}. Nonetheless, studies to compare endovascular coiling with surgical clipping for cerebral aneurysms in pregnant patients are limited. There are concerns about whether the ISAT trial results can be extrapolated to pregnant patients^{23,24}. Endovascular coiling in pregnancy has the disadvantages of prolonged fetal radiation exposure under DSA and full systemic heparinisation throughout the procedure. Heparinisation carries risks of haemorrhage if pre-term labour or delivery is needed in case of fetal distress or maternal deterioration. It is difficult to have concurrent fetal monitoring in the DSA suite and to arrange immediate Caesarean section in case of fetal distress during the procedure^{7,10,17,23}. The ISAT trial showed that endovascular coiling is inferior to surgical clipping in terms of subtotal occlusion rate or residual aneurysmal neck; two patients had re-bleeding after endovascular coiling but none after surgical clipping¹⁹. Incomplete obliteration of the aneurysm by coiling may result in regrowth of the remnant aneurysm and risk of re-bleeding²⁴.

Surgical clipping has additional advantages, as craniotomy enables direct vision for aneurysm exclusion and concurrent treatment of other associated neurosurgical conditions such as obstructive hydrocephalus and intracerebral haematoma. In addition, intra-procedural rupture, which occasionally occurs during coiling⁷, can be avoided or salvaged.

The choice of treatment should be individualised according to the gestational age, patient condition, and expertise and experience of the neurosurgeon. Surgical clipping is preferred for gestational age of <10 weeks to avoid prolonged fetal radiation exposure. Endovascular coiling requires an experienced radiologist who may not be available in some units. Multidisciplinary assessment involving obstetricians, neurosurgeons, radiologists, anaesthetists, paediatricians, and intensivists should be conducted to provide best management.

Delivery by emergency Caesarean section should be considered if the maternal status is life-threatening and the pregnancy exceeds the gestation for viability (≥ 24 weeks gestation)¹⁰. In patient 1, emergency Caesarean section was performed because of maternal deterioration with a repeated and enlarging cerebral infarct. When the maternal condition is stable and the gestational age exceeds 34 weeks, delivery can be considered, as the risk from prematurity is small and the concern about radiation risks of subsequent imaging and endovascular procedures is less after delivery. In addition, surgical clipping can be performed simultaneously with Caesarean section in the same operation theatre after the baby is delivered. When the gestation is <34 weeks, treatment of the aneurysm should be proceeded while the pregnancy is allowed to continue⁷. There is no contraindication for vaginal delivery after aneurysm occlusion. Adequate pain relief by epidural analgesia and use of instrumental delivery to shorten the second stage is advised⁷. Caesarean section is preferable if labour occurs shortly after treatment of the aneurysm or if there is incomplete occlusion of the aneurysm¹⁰.

Intracerebral Haemorrhage

The most common cause of intracerebral haemorrhage in pregnancy is ruptured AVM. Other causes include trauma and brain tumour. In patient 2, although ruptured AVM was not identified intraoperatively, it was postulated that her intracerebral haemorrhage was likely due to a ruptured AVM. She had an episode of an eclamptic fit during her first delivery that may have been due to a mild rupture of her AVM. During her third pregnancy, her AVM could have severely ruptured and no longer be identified intraoperatively, with the presence of massive bleeding.

The prevalence of AVM has been reported to be 0.01% to 0.5% in the general population, and most patients have symptoms at 20 to 40 years of age²⁵. The risk of haemorrhagic cerebral AVM during pregnancy has been reported to be 3.5%, similar to the 3.1% in non-pregnant populations²⁶. Rupture of AVM may occur in any trimester,

Table. Spetzler-Martin grading system for cerebral arteriovenous malformation

Features	Score
Size of nidus (cm)	
<3 (small)	1
3-6 (medium)	2
>6 (large)	3
Location	
Non-eloquent brain (frontal and temporal lobe or cerebellar hemispheres)	0
Eloquent brain (sensorimotor, language, visual cortex, hypothalamus, thalamus, brainstem, cerebellar nuclei, or regions immediately adjacent to these structures)	1
Venous drainage	
Superficial only	0
Deep	1

with the highest incidence in the second trimester^{1,2,27}. More than 50% of patients with AVM present as intracranial haemorrhage. Intracerebral haemorrhage occurs more commonly than SAH and intraventricular haemorrhage. 20% of patients present with generalised or focal seizure.

After diagnosing intracerebral haemorrhage by CT or MRI, the gold standard for diagnosing AVM is by DSA, which can delineate its size, location, feeding artery, flow rate, arteriovenous fistula, coexisting aneurysm, venous drainage, and ectasia of drainage veins²⁵.

Rupture of AVM is associated with high maternal mortality of 35% to 83%²⁸, and is responsible for 5% to 12% of maternal deaths during pregnancy and 17% of fetal mortality²⁹.

Urgent operations (emergent nidus resection, ventricular drainage, and haematoma removal) are necessary for pregnant patients with ruptured AVM and worsening neurological symptoms or signs of impending cerebral herniation^{25,27}. If bleeding of the AVM is stopped and the patient is stable, conservative management can be adopted²⁹. The risk of re-bleeding from ruptured AVM during pregnancy is 26%⁹. The operative outcomes for cerebral AVM depend on its grade according to the Spetzler-Martin system (Table) that takes account of the size, location, and drainage of the AVM. Higher grades indicate poorer prognosis. Grade 1 or 2 AVMs are usually treated by surgical excision; grade 3 lesions should be treated by embolisation followed by surgical excision; and grade 4 or 5 lesions should be treated conservatively because of high surgical risk²⁷. Recent advances in radiosurgery enable treatment for small deeply seated AVMs that carry high operative risks²⁷. Stereotactic radiosurgery focuses a narrow X-ray beam on the AVM such that a high dose is concentrated on the AVM and a much lower dose to the rest

of the brain. It induces thickening in the walls of the AVM and then closes the AVM. It has successfully closed AVMs in around 80% of patients over a period of 2 to 3 years. Nonetheless, it is suitable only for small AVMs, and 3% to 5% of patients may develop long-term side-effects such as limb weakness or numbness. Patients have a 4% chance of bleeding from the AVM yearly until the AVM is completely closed³⁰. There is no randomised controlled trial to compare different treatment options (surgery, radiosurgery, embolisation, and a combination of these). In the largest systematic review that compared outcomes of different treatments for AVM, results were inconclusive because of differences in patient conditions and AVM characteristics (size and location) among different studies³¹. Therefore, the treatment choice for AVM depends on the experience and expertise of the neurosurgeons and interventional radiologists. The timing of delivery for ruptured cerebral AVMs should be similar to that for ruptured aneurysms. There is no contraindication to vaginal delivery for a completely excised AVM²⁵. There is no consensus as to whether vaginal delivery increases the risk of rupture for an intact AVM, but Caesarean section is recommended for patients with ruptured AVM³².

Conclusion

Haemorrhagic stroke is rare in pregnancy. Its symptoms are sometimes similar to severe pre-eclampsia or eclampsia. A high index of suspicion, early diagnosis, and prompt management are crucial to improve maternal and neonatal outcomes. A multidisciplinary approach involving different specialties and expertise to provide the most optimal management is essential.

Declaration

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