The management of cryptogenic stroke in pregnancy

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Summary: Cerebrovascular accidents (CVAs) during pregnancy are uncommon but can have devastating consequences. The causes of CVA in both the pregnant and the non-pregnant state are diverse and require thorough investigation. Recent studies have indicated that embolic stroke in young adults may be caused by paradoxical emboli through a patent foramen ovale (PFO), suggesting that the presence of a PFO should be specifically sought in pregnant or postpartum women presenting with CVA. This review will outline the causes of CVAs in pregnancy and the role of paradoxical emboli, with a focus on PFO.

Keywords: cardiac, cardiology, cardiovascular, neurology

CAUSES OF CEREBROVASCULAR ACCIDENT IN PREGNANCY

The risk of cerebrovascular accident (CVA) in pregnancy is between 3.8 and 34.2 in 100,000 pregnancies, with a substantial mortality rate of between 8% and 15%,^{1,2} so prevention of CVA is paramount. CVAs can occur at any stage of pregnancy or the puerperium. In one study of 2850 pregnant patients presenting with a stroke, 11% presented antepartum, 41% at time of delivery and 48% presented postpartum.¹ Thus, the puerperium is associated with the highest risk of CVA. Several studies have investigated the causes of CVA in pregnancy, and although there are differences in classification of causes of CVAs, Table 1 lists the causes and incidence of CVAs in pregnancy.

There are specific pregnancy-related cerebrovascular events such as amniotic fluid embolism, preeclampsia or postpartum angiopathy, which in some studies are not classified separately.^{1,3,4}

HAEMODYNAMIC AND THROMBOTIC CHANGES IN PREGNANCY

During pregnancy, there are profound changes in both the haemodynamics and the coagulation system, leading to a hypercoagulable state that may predispose to the development of venous thrombosis. Circulating blood volume increases by 50%, due to retention of fluid with a relative enlargement of plasma volume. Peripheral vascular resistance also decreases in early pregnancy, which can cause an increase in either right to left or left to right intracardiac shunts.⁹ These haemodynamic changes are thought to be due to increased levels of oestrogens and progesterones; however, the mechanism by which this occurs is unknown.¹⁰ Plasma levels of fibrinogen, factors VII, VIII and X, and thrombin increase, while the level of protein S decreases due to increased levels of its binding protein C4b, leading to a prothrombotic state,¹¹ presumably

as an adaptation to reduce postpartum haemorrhage. These elevated coagulation factor levels drop rapidly after delivery to reach normal values at about two weeks postpartum. The fibrinolytic system is also altered: plasminogen activator inhibitor types 1 and 2 dramatically increase during pregnancy especially in the third trimester.¹² These levels can remain elevated for up to eight weeks postpartum, thus increasing the risk of venous thrombosis in this period.

CRYPTOGENIC CVA

This refers to an ischaemic cerebrovascular accident (CVA), which occurs in the absence of an identifiable cause or of risk factors associated with ischaemic CVAs. An episode of altered neurological state needs to be thoroughly investigated in pregnancy. History and examination are paramount, with magnetic resonance imaging and magnetic resonance angiography being the modality of choice to image the brain and neurovascular system. Other tests include haematological investigation for thrombophilia, including

- Lupus anticoagulant;
- Anticardiolipin antibodies;
- Anti-B2 glycoprotein I antibodies;
- Activated protein C resistance with Factor V Leiden;
- Prothrombin G20210A polymorphism;
- Proteins C and S;
- Antithrombin III.

Up to 40% of ischaemic CVAs in patients under 55 have no identifiable cause,¹³ despite investigation of a possible embolic source. However, recent evidence suggests that thromboembolism across a patent foramen ovale (PFO) may be an important cause of cryptogenic CVA in pregnancy.

TpA has been used in the treatment of acute arterial ischaemic stroke in pregnancy successfully;¹⁴ however, no randomized trial has evaluated its efficacy in this setting.

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Table 1 Incidence and types of cerebrovascular accidents found in pregnancy

Causes	James <i>et al.</i> ¹	Lanska <i>et al.</i> ³	Sharshar <i>et al.</i> ⁵	Jaigobin <i>et al.</i> ²	Kittner <i>et al.</i> ⁶	Jeng <i>et al.</i> ⁷	Liang <i>et al.</i> ⁸
N =	2850	353	31	34	31	49	32
Ischaemic (%)	27	52	48	38	55	33	25
Haemorrhagic (%)	25	48	52	38	45	45	65
Cerebral venous thrombosis (%)	2	NA	NA	24	NA	22	10
Pregnancy related CVAs (%)	46	NA	NA	NA	NA	NA	NA

CVA = cerebrovascular accident; NA = not applicable

PATENT FORAMEN OVALE

A PFO is an embryological anomaly caused by lack of fusion of primum and secundum septum that normally occurs after birth, when left atrial pressure rises above right atrial pressure. In contrast to atrial septal defects, in PFO there is no structural defect in the tissue of the atrial septum, and since left atrial pressure normally remains higher than right atrial pressure, the foramen ovale remains closed. However, transient increases in right atrial pressure, as occur during the Valsava manoeuvre, can lead to right to left shunting if the foramen ovale remains patent. In the presence of venous thrombosis that occurs at an increased rate in pregnancy, spontaneous right to left shunting may allow paradoxical embolism of venous thrombus, which can present as a cryptogenic CVA.

The prevalence of PFOs in the general population is up to 35%.¹⁵ Many studies have reported an association between cryptogenic CVA and PFO. In a study by Lamy *et al.*¹⁶ of 581 patients <55 years of age presenting with a cryptogenic stroke, the prevalence of PFO was reported as 46%. However data demonstrating an increased recurrence rate of cryptogenic CVA in patients found to have a PFO have not been adequately demonstrated.^{17,18} PFOs have been linked to migraine, and improvement in migraines with and without aura has been demonstrated post PFO closure.¹⁹ However other studies have refuted this including the MIST trial.^{20,21} Interestingly in one large review of the incidence and risk factors for stroke in pregnancy and the puerperium, it was found that the strongest association for stroke was migrainous headaches; however in this study the incidence of migraines was reported as <1% in all patients, which is far less than the overall incidence in women.¹ Treatment with antiplatelet agents and warfarin has been shown to reduce the recurrence rate of CVAs but data on percutaneous closure of PFOs tend to favour percutaneous closure but the data are non-randomized and further trials are awaited.²²

DIAGNOSIS OF CRYPTOGENIC CVA IN PREGNANCY

If an obvious cause for a CVA is not apparent, further investigation for an origin of an embolus should be undertaken. These include a thrombophilia screen, and an ultrasound scan of the venous system of the legs, to look for pelvic clots. If this is negative then magnetic resonance venography should be undertaken. An intracardiac source of thrombus or an intracardiac shunt to allow systemic venous clot to embolize to the cerebral arterial tree needs to be investigated. The first line of imaging is a transthoracic echo cardiogram, which allows visualization of most cardiac structures and is safe and easy to perform in pregnancy. Depending on fetal gestation it can be difficult to image the intra-atrial septum from a transthoracic

echo subcostal view and therefore a contrast echocardiogram should be performed (Figure 1) from the cardiac apex. This involves the use of agitated saline and a Valsalva manoeuvre to demonstrate an intra-atrial shunt. A transcranial Doppler can also be used as a screening tool for intracardiac shunts. Microbubbles are injected into a peripheral vein and are subsequently visualized with Doppler in the middle cerebral artery; if a patient has a right to left shunt a Doppler signal of bubbles will be produced (Figure 2). Transcranial and transthoracic echo with contrast are relatively safe techniques but there have been reports of CVAs/transient ischaemic attacks occurring immediately post procedure.²³ A positive bubble study is very sensitive but not specific, as a pulmonary arterio-venous malformation may also produce a positive result.²⁴ In a non-pregnant patient transoesophageal echocardiography should be performed if there is any uncertainty about the diagnosis, as it is the gold standard technique to demonstrate a PFO. The intra-atrial septum is visualized in the bicaval 110 view or short axis 50 view (Figure 3). The ability to perform a Valsalva manoeuvre may be compromised somewhat and if this is not possible, careful abdominal palpation and release is an acceptable alternative. In pregnancy transoesophageal echocardiography can be performed safely, but due to the need for sedation transthoracic echo with transcranial Doppler are often used in first instance with transoesophageal echocardiogram (TOE) and sedation being undertaken if there is any diagnostic uncertainty.

MANAGEMENT OF CRYPTOGENIC CVA

Conventional therapy for the management of cryptogenic CVA in the non-pregnant state would include antiplatelet agents and/or anticoagulants. The antiplatelet agent with most data to support its use is aspirin, which is known to be safe in pregnancy.²⁵ Newer antiplatelet agents including clopidogrel have been used but there are few data on their effects in pregnancy.²⁶

In pregnancy anticoagulation with warfarin is problematic due to increased risk of miscarriage, teratogenic effects in the first trimester and risk of bleeding to both fetus and mother. Heparin in the fractionated form is the preferred anticoagulant, but has the disadvantage of parenteral administration, risk of inducing reduced bone density and of heparin-induced thrombocytopenia.

The prevention of a further CVA is paramount in this group as data have shown that in pregnancy CVAs are associated with significant morbidity with 22% of CVA survivors requiring sufficient rehabilitation to necessitate discharge to a facility other than home.¹

Medical therapy in non-pregnant patients with either antiplatelet agents and anticoagulants has still resulted in a recurrent

Figure 1 Contrast transthoracic echocardiogram of inter-atrial septum

Following injection of agitated saline into an antecubital fossa vein, contrast is initially seen to light up the right atrium and ventricle, and then with a Valsalva manoeuvre the left atrium and ventricle, having passed through a patent foramen ovale

Figure 2 Transcranial Doppler

Ultrasound probe is placed on middle cerebral artery at rest (panel 1), with injection of contrast (agitated saline) (panel 2), and with injection of contrast and a Valsalva manoeuvre (panel 3)

CVA rate as high as 25% depending on the case series^{16,27-30} with no benefit demonstrated between therapies, but these studies included heterogeneous patient populations. For these reasons interest has grown in devising a device that could prevent thromboembolic phenomena passing into the systemic

circulation. In the early 1990s, devices that were originally designed for the closure of intracardiac defects in congenital heart disease were used to close PFOs in patients with recurrent cryptogenic CVAs. This percutaneous closure device leads to a reduction in subsequent CVAs.³¹ Since then these devices have been further developed and are now widely used for closing PFOs; these include Amplatzer, Helex, Starflex and Cardioseal devices. They are made up of a nitinol wire frame which has memory and can be inserted into a sheath and reformed *in situ* across the atrial septum. There are few studies comparing the efficacy of these various devices. However, one study found that the cardioseal device was more prone to thrombus formation at 30 days than either the Helex or Amplatzer devices and assessment of shunting through the device found smaller residual shunts with the Amplatzer device.³²

If patients present with a CVA during the first trimester of pregnancy and are found to have a PFO, they are normally managed with aspirin and subcutaneous low molecular

Figure 3 Transoesophageal echocardiogram
 Panel 1. From a 50 degree view, following injection of agitated saline into an antecubital fossa vein, contrast is seen crossing the PFO from right atrium to left atrium.
 Panel 2. From a 50 degree view, colour flow Doppler mapping of the atrial septum demonstrating a PFO with colour flow across it.

weight heparin. This may be continued throughout pregnancy. After the first trimester, however, it is feasible to contemplate closure of the PFO percutaneously. Radiation exposure during the first trimester is avoided as this is when organogenesis is occurring. In patients with recurrent CVAs, contraindications to anticoagulation percutaneous closure should be considered. During percutaneous closure catheters are inserted via the femoral veins under both fluoroscopic and ultrasound guidance into the left atrium across the PFO. In our practice the use of intracardiac echo is the preferred ultrasound imaging of choice as it negates the need for general anaesthesia or heavy sedation for a TOE (Figure 4). The use of low frame rate imaging, as low as two frames per second, small collimated beam sizes, long sheaths for venous access which bypass the pelvis and short

Figure 4 Percutaneous closure of a PFO
 Panel 1. Fluoroscopy demonstrating balloon sizing of a PFO. The balloon (B) is passed on a guide wire across the PFO, and the size of the PFO can therefore be measured and appropriate device chosen. Intracardiac echo transducer is marked with arrow
 Panel 2. Amplatzer device placed across the PFO on fluoroscopy, the intracardiac echo transducer is again marked with an arrow
 Panel 3. Amplatzer device placed across PFO on intracardiac echo
 PFO = patent foramen ovale

screening times reduces the total fluoroscopic dose to the fetus. Concern has been raised regarding the use of ionizing radiation in pregnancy. With judicious use fluoroscopic

doses can be kept to as low as 0.04 mSv per patient or 19 cGy/cm², thereby minimizing the risk to fetus.³³

There are no data to support either closing or not closing a PFO in pregnant women presenting with a cryptogenic stroke, due to the small numbers of patients involved. There are two randomized control trials underway reviewing the recurrence rate of cryptogenic CVA in patients treated with either antiplatelet agents or anticoagulants and percutaneous closure devices. There are case reports describing percutaneous closure either during pregnancy, after the first trimester or in the immediate postpartum period to prevent further cryptogenic CVAs,^{33,34} as women with a previous diagnosis of CVA are at an increased risk during pregnancy.³⁵

CONCLUSION

Pregnancy and the puerperium are associated with an increased risk of CVAs, due to changes in haemodynamics and coagulation. CVAs are associated with major risk of mortality and long-term morbidity. Paradoxical thromboembolism through a PFO is an important cause of pregnancy-associated CVA and justifies specific diagnosis or exclusion. Management in this group of patients is complicated by both maternal and fetal needs and careful discussion needs to occur between all members of a multidisciplinary team before decisions are made on management.

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