Neurological Emergencies in Pregnancy

Koushik Pan¹, Shyamal Kumar Das²

Abstract
On one side, pregnancy is a bliss, a beautiful journey for most women while on the other, it increases the risk of several diseases which may cause considerable morbidity and mortality in young women in the most productive period of their lives. Neurological emergencies in pregnancy often have grave prognosis and so, must be promptly diagnosed and treated. This article reviews the clinical features and management of some of the common severe neurological emergencies in pregnancy.

Introduction
Neurological complications of pregnancy may turn out emergent.¹ However, several diseases have increased prevalence during pregnancy.

Table 1: Neurological emergencies in pregnancy

<table>
<thead>
<tr>
<th>Headache</th>
<th>Migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>Posterior reversible encephalopathy syndrome</td>
</tr>
<tr>
<td></td>
<td>Reversible cerebral vasospasm syndrome</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
</tr>
<tr>
<td>Neurovascular</td>
<td>Postpartum neuropathy</td>
</tr>
<tr>
<td></td>
<td>Guillain Barre syndrome</td>
</tr>
<tr>
<td></td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Cranial neuropathy</td>
<td>Bell’s Palsy</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>Pituitary apoplexy</td>
</tr>
<tr>
<td>Movement disorder</td>
<td>Chorea gravidarum</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Wernicke’s encephalopathy</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Seizure</td>
</tr>
</tbody>
</table>

or postpartum period. These diseases may either be unique to the pregnant/postpartum state like preeclampsia and delivery-associated neuropathies else may be indirectly related to pregnancy, such as cerebral venous thrombosis, ischemic stroke, and intracerebral hemorrhage. Hence, it is vital for the treating clinician to have a sound diagnostic approach towards these neurological emergencies. Moreover, being the health issue of young individuals, social, epidemiological and medico-legal impact of pregnancy related adverse outcomes is often high. This article intends to review those serious neurological diseases which are commonly seen during pregnancy and the postpartum period² (Table 1).

Migraine
Migraine is commonly prevalent among women of childbearing age and often can be severe enough in pregnancy. Severe migraine may present as ‘status migrainosus’ (headache beyond 72 hrs at a stretch). Infrequently, migraine may occur for the first time during pregnancy. However, migraine incidence usually more common in first trimester appears to be reduced during the second and third trimesters, new onset aura may appear during that time trimester of pregnancy.³,⁴ Migraine doesn’t significantly affect fertility or pregnancy outcomes, but it is associated with a risk of preeclampsia or stroke.⁵,⁶

Medical therapy usually include analgesics such as acetaminophen, steroids, and if necessary, opiate medications.⁷ Antiemetic therapy may include metoclopramide, ondansetron and sedating agents such as promethazine and chlorpromazine.⁸ Triptans, are probably safe in pregnancy but may slightly affect preterm labor rates.⁹ However, given the limited safety data available, triptan therapy cannot be recommended.¹⁰

Stroke in pregnancy
Pregnancy contributes to the risk of a cerebrovascular event.¹¹ Pregnancy is a hypercoagulable state because of increased platelet aggregability,
fibrinogen levels and factors VIII, IX and X. Fibrinolytic activity is decreased with a reduction in the levels of endogenous anticoagulants, like protein S and antithrombin III. These changes persist into the early postpartum period. Consequently, majority of the ischemic strokes occur late in pregnancy and particularly in the postpartum period.\(^{11,12}\) Hypertension, which is associated with ischemic as well as hemorrhagic strokes, is a primary feature of preeclampsia. Pregnancy, in itself, is a state of induced hypercoagulability which may facilitate the development of venous thromboemboli in a susceptible individual.\(^{13}\) Paradoxical embolism related to the presence of a patent foramen ovale (PFO) sometimes gets triggered by both the coagulation profile changes and by the hemodynamic changes such as increased venous stasis.\(^{13}\) Peripartum cardiomyopathy is a rare complication of pregnancy but may cause cardioembolic stroke and severe progressive cardiac failure requiring transplant.\(^{13}\) Etiologies of stroke unique to pregnancy include choriocarcinoma, postpartum cerebral angiopathy and postpartum cardiomyopathy. Stroke during labor or soon after vaginal delivery may result from an amniotic fluid embolus. Abortions and obstetric procedures performed outside medical standards may cause vaginal air insufflations, thus resulting air embolus to the heart, with subsequent generalized and focal cerebral ischemia.\(^{14}\)

Stroke patients usually present with abrupt onset of focal neurological deficits (hemiparesis, hemianaesthesia, ataxia, blindness). However, at times, patients may present with non-focal symptoms like headache, seizures and altered consciousness. These symptoms are more frequently observed in patients with venous thrombosis and resulting venous infarctions.\(^{15,16}\)

The primary treatment for acute ischemic stroke is intravenous thrombolyis with tissue plasminogen activator (tPA). However, pregnant patients were not included in tPA clinical trials. There have been concerns regarding the adverse effects of tPA on the pregnant mother and fetus like placental abruption, abortion, uterine hemorrhage and preterm delivery as well as hemorrhage including intracerebral hemorrhage. However, with scientific data available, preterm delivery and fetal loss are infrequent.\(^{17-19}\)

**Hemorrhagic stroke is of lower incidence in pregnancy as compared to ischemic stroke and occurs mostly during late pregnancy and the puerperium. Intracerebral hemorrhage has a higher maternal mortality rate, nearly accounting for 5% to 12% of overall maternal mortality in pregnancy.\(^{11}\)** Hemorrhage is often associated with preeclampsia / eclampsia, arteriovenous malformations (AVM,) and aneurysmal rupture.\(^{20}\) In case of an unruptured AVM, risk of first hemorrhagic event during pregnancy is about 3.5%, no higher than over a similar period outside pregnancy.\(^{21}\) Aneurysmal rupture is more likely in the second and third trimesters (30% and 55% of ruptures respectively), as compared with first trimester or puerperium (6% and 9% respectively).\(^{22}\) The possible etiology for the heightened risk of intracerebral hemorrhage (ICH) during pregnancy may relate to the physiological changes of pregnancy including increased blood volume, rising blood pressure, and changes in vascular tone. The physical stress of delivery and labor may also contribute to the risk of aneurysmal rupture, and patients with known aneurysms and AVMs are often delivered by scheduled C-section. Treatment include antihypertensives and antiseizure medications including magnesium, with close monitoring.\(^{13,24,25}\)

**Eclampsia**

**Worldwide, the incidence of preeclampsia ranges between 2% and 10% of pregnancies. The incidence of preeclampsia, the precursor to eclampsia, varies greatly worldwide. WHO estimates the incidence of preeclampsia to be seven times higher in developing countries (2.8% of live births) than in developed countries (0.4%).\(^{23}\)** Preeclampsia is defined by proteinuria and gestational hypertension which usually occurs after the 20th week of pregnancy. Severe cases may manifest with headache, visual changes, other signs of raised intracranial pressure and reduced fetal growth.\(^{26,27}\) The underlying etiology for preeclampsia and eclampsia remain unknown, but abnormal immunological interactions between foetal and maternal tissues appear to be involved.\(^{28}\)

Eclampsia may complicate with diffuse cerebral oedema, subarachnoid haemorrhage, cerebral haemorrhage and microinfarctions.\(^{29}\)

Eclampsia is conventionally characterized by the new onset seizures and/or coma during the pregnancy, labor, or puerperium in the background of preeclampsia.

Recently researchers found favor with the opinion that seizures usually occur without the pre-existing setting of preeclampsia, particularly in late postpartum eclampsia.\(^{30}\)

In severe pre-eclampsia and eclampsia, prompt delivery is the immediate goal.\(^{29}\) Thus, treatment strategies include control of arterial blood pressure, reduction of cerebral oedema, and rapid control and prevention of seizures. Magnesium sulphate is being commonly used in pre-eclampsia and eclampsia. Ongoing seizures should be aborted with intravenous diazepam 5-10 mg or lorazepam 2-4 mg given as slow intravenous bolus, while phenytoin may prevent recurrent seizures. Chlormethiazole is not commonly used nowadays.

**Myasthenia Gravis**

Myasthenia gravis (MG) is a chronic disease which affects the neuromuscular transmission resulting in fatigable weakness of the skeletal muscles. Women are more commonly affected with the disorder (2:1).\(^{31}\) The course of MG during pregnancy is variable and varies with subsequent pregnancies.\(^{32}\) Exacerbations occur in nearly 40% of pregnancies with the remainder of patients having stable disease or remission of symptoms.\(^{33}\) The neuromuscular blockade occurs due to an autoimmune mechanism, and anti-acetylcholine receptor (AChR) antibody is detectable in 90% of affected patients.\(^{34}\) Antistriated muscle antibody is often associated with an underlying thymoma.

In the pre-thymectomy era, one third of myasthenic patients deteriorated during their pregnancies, one third had their health unchanged, and one third improved.\(^{35}\) Thymectomy is indicated for thymoma and is recommended in all young myasthenic patients who have a deteriorating response to an anticholinesterase drug.\(^{35}\) The thymoma should be resected prior to a planned pregnancy;
Steroid-sparing immunosuppressant drugs such as azathioprine should be discontinued prior to pregnancy owing to the risk of teratogenicity.35 Corticosteroid therapy also poses a risk to the mother and the foetus. The oral or intramuscular administration of pyridostigmine and neostigmine is safe as there is little passage through the placenta. Azathioprine can induce fetal leukopenia but is often maintained for severe disease.

The management of preeclampsia in myasthenic patients presents a challenge as magnesium sulfate is contraindicated. Phenytoin can be a suitable alternative to manage seizures.31 Vaginal delivery is not contraindicated but a myasthenic patient may not be able to tolerate full labor due to fatigue.31 Following the delivery, infant must be evaluated for neonatal MG which may occur in nearly 10% to 20% of deliveries via placental transmission of acetylcholine antibodies.36 Neonatal MG responds well to anticholinesterase medications.37 Pregnancy does not worsen the long-term prognosis of MG.38

**Guillain-Barre syndrome (GBS)**

GBS represents a heterogeneous group of immune mediated peripheral neuropathies. GBS must be kept under consideration in any pregnant woman complaining of muscle weakness, tingling of the fingers, and difficulty in breathing.37,38

Presentation: Rapidly progressive symmetric areflexic weakness.

Timing: Any trimester and postpartum period but is more frequent in third trimester and initial 2 weeks after delivery.

Course: Worsen in post partum period due to delayed type of hypersensitivity.39 Nearly 20% disability and a maternal mortality of approximately 7% has been documented while GBS without pregnancy has a mortality rate of less than 5%.40

**T**reatment: **I**ntravenous immunoglobulins (IVIG) or plasmapheresis, along with ventilatory support whenever needed. Plasmapheresis and IVIG significantly improve patients’ outcome with complete recovery in almost 70-80% of the cases.39,41

Obstetric Precaution: Delivery must be actively coordinated with anesthesiologist as autonomic instability in some patients may complicate anesthetic care.43 Additionally, there are reports of succinylcholine administration precipitating hyperkalemia and use should be avoided.42,43

**Idiopathic Facial Nerve Palsy**

Bell’s palsy occur in approximately 17/100,000 women of child bearing age per year.44 Overall, Bell’s palsy is more frequent in females (2:4:1) and incidence may rise up to 6 times more in pregnancy as compared to non-pregnant women, although some of the studies have found no increase in incidence.45-47 Bell’s palsy presents mostly during the third trimester and peripartum.46,47 There appears to be an association with pre-eclampsia.47,48 Almost 15% of pregnant women with acute lower motor neuron facial paralysis may have secondary etiologies.49 Plasma volume expansion in pregnancy may result in increased interstitial fluid which may lead to mechanical compression of the facial nerve in fallopian canal. Based on this hypothesis, Bell’s palsy apparently has maximum incidence in third trimester because of the peak increase in interstitial fluid volume during third trimester.46,50 Besides, some researchers have proposed another hypothesis that hypercoagulable state in pregnancy may predispose to thrombosis of vasa nervosum of the facial nerve, thus leading to devascularization and ischemic nerve injury.52

**Neuropathies**

Postpartum neuropathies are relatively uncommon. Intrinsic obstetric palsies may result from delivery or labor process, the most commonly occurring of which is lateral femoral neuropathy. Other neuropathies known to occur are femoral, obturator, sciatic, common peroneal nerve, and lumbosacral plexus in descending order of frequency.53 The most apparent cause of these neuropathies is mechanical stretch in dorsal lithotomy position. However, nulliparity and prolonged second stage of labor have been reported as important risk factors.53

**Cerebral Venous Thrombosis**

A rare cause of stroke overall, cerebral venous thrombosis (CVT) is an important consideration in pregnancy and postpartum state.54-57 A spike in incidence in the first trimester might be attributable to women who become pregnant with an underlying thrombophilia.39 However, more than 75% of cases of CVT are post partum.59 The main risk factors are caesarean section, traumatic delivery, dehydration, anaemia, increased serum homocysteine and low CSF pressure due to dural puncture from a neuraxial anaesthetic.59,60 Pregnancy in itself is a hypercoagulable state, and thus a risk factor for thrombotic events.11,13 Other genetic causes of hypercoagulability including antiphospholipid syndrome, prothrombin gene mutations, and factor V Leiden / MHTFR deficiency are predisposing factors for the development of CVT.61 Oral contraceptive pills (OCP) use is often associated with CVT and must be enquired for, especially in young women presenting with acute headache and visual changes.52

Superior sagittal and transverse sinuses are most commonly involved and may manifest with headache, seizures, papilledema and other signs of raised intracranial tension. The cavernous sinus is infrequently involved and when thrombosed, may present with proptosis, cranial nerve deficits and painful ophthalmoplegia due to raised pressure inside the sinus and orbit. CT of brain is often negative, but 30% of cases might show a clot or signs of infarction.53 Ischaemic infarcts often undergo haemorrhagic transformation. MR venography-along with gradient echo (GRE) sequences is usually diagnostic and often, the imaging study of choice.53

Anticoagulation with warfarin is generally avoided in pregnancy complicated with CVT, especially in first trimester due to risk of teratogenicity. However, the American Heart Association (AHA) recommendations say that warfarin therapy is safe in second and third trimester while it should be discontinued in later stage of pregnancy.64 Low-dose aspirin is felt to be safe, particularly after the first trimester, according to the American College of Chest Physicians 2008 guidelines.65 Additionally, both groups suggest that unfractionated heparin or low-molecular weight heparin can be utilized in pregnancy either as a bridge to warfarin therapy or as a stand-alone treatment.64,65 Following delivery, warfarin can be utilized for anticoagulation which is generally continued for a 3- to 6-month period
Seizures in pregnant or post-partum stage can be classified into three categories: first, and most common, are women with established epilepsy prior to pregnancy; second group comprises of non-pregnancy related seizures, like new onset seizure from an structural brain lesions or hypoglycemia; and lastly, the third group comprises of pregnancy related new onset seizures (caused by eclampsia, cerebral venous thrombosis, reversible cerebral vasoconstriction syndrome, posterior reversible encephalopathy syndrome, intracerebral hemorrhage or thrombotic thrombocytopenic purpura).

Maternal seizures and antiepileptic drugs can accentuate the risk of fetal malformation approximately two to three times. The conventional anticonvulsants drugs (phenytoin, valproate, and carbamazepine) carry almost similar overall risk. Valproate and Carbamazepine are associated with a higher risk of spina bifida (about 1% for carbamazepine and 2% for valproate). Polytherapy appears to increase the risk of fetal malformations. Folate supplementation is vital to reduce the risk of spina bifida.

Generalised tonic-clonic seizures can lead to profound fetal bradycardia.

Status epilepticus may be associated with poor prognosis and death of the child or mother, have both been reported as a consequence. Treatment protocol for status epilepticus in pregnancy remains the same as in general cases. Mothers who are kept on antiepileptic enzyme inducing drugs should be given 20 mg oral vitamin K1 daily for a week prior to delivery. If the exact date of delivery is not known in advance which is a usual situation, it seems sensible to start K1 a month before the expected delivery date. Alternatively, the mother can be given 10 mg K1 parenterally during labour. Administration of vitamin K1 to the newborn is recommended in these circumstances. Most of the anticonvulsants drugs apparently pass into breast milk, albeit in very low concentrations, which is not likely to have any adverse effect on infant. Breast feeding can therefore be encouraged.

Reversible Cerebral Vasoconstriction Syndrome

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by abrupt onset of thunderclap headaches and multifocal, reversible cerebral vasoconstriction.

Timing: Within 1 week of a normal delivery associated with a normal pregnancy.

Clinical Features: Recurring daily thunderclap headaches in several weeks after a single thunderclap headache are nearly pathognomonic. Headache episodes are often associated with vomiting, confusion, photophobia, and blurred vision. When seizures or focal neurological deficits develop, they nearly always follow the headache.

Course: Symptoms usually subside over 2-3 months.

Complications: Cerebral infarction, edema, and death.

Association: Cervicocranial arterial dissections.

CSF Study: Normal but can show small numbers of lymphocytes and a mild rise in protein concentrations.

CT Scan: Normal if there is no associated hemorrhage.

Angiography: Multifocal segmental arterial constriction and can detect arterial dissections.

Treatment: Analgesics including opiates. Glucocorticoids, magnesium sulfate, calcium channel blockers and cytotoxic agents have tried to boost patient’s recovery. Steroids and immunosuppressive agents are considered in cases of suspected underlying vasculitis or inflammatory process.

Differential: Anurysmal subarachnoid hemorrhage (SAH), pituitary apoplexy, ICH and venous sinus thrombosis

Posterior Reversible Encephalopathy Syndrome

Posterior Reversible Encephalopathy Syndrome (PRES) commonly presents with headache, seizures, encephalopathy, and visual disturbances.

Clinical Setting: Acute hypertension, pre-eclampsia or eclampsia, renal disease, sepsis, and other conditions and in those exposed to immunosuppressant and other drugs.

Clinical Features: Nearly 90% of seizures might be focal to start along with secondary generalization, and generally precede visual changes or headache, which is generally dull, bilateral, and not thunderclap. Confusion is common and may progress to more significant degrees of altered awareness including stupor or coma. 40% of cases have visual symptoms such as visual hallucinations, blurred vision, scotomata, and diplopia. Nearly, 1-15% of patients have transient cortical blindness.

Etiopathogenesis: Impairment in underlying cerebral autoregulation and/or endothelial dysfunction.

Course: Symptoms often develop without a prodrome and progress rapidly over 12-48 hours. Visual symptoms often resolve completely in hours to days while the resolution of oedema on imaging lags behind.

CT Finding: Vasogenic oedema mostly involves occipital lobe

MRI Finding: Focal oedema, in the parieto-occipital lobes. Unlike posterior cerebral artery lesions, the occipital lesions spare the medial occipital lobe and calcarine cortex.

Treatment: Emergent delivery if feasible and appropriate. Magnesium sulfate is commonly used for seizure control.

Differential Diagnosis: The distribution of the lesions usually involves multiple vascular territories that help to distinguish the changes from ischemic stroke.

Conclusions

Pregnant and post-partum patients who present with new acute neurological symptoms need a thorough diagnostic evaluation that targets a range of pathological conditions that are either unique to or arise more frequently in this population. Appropriate management, preferably under the joint care of obstetricians, neurologists, neurosurgeons, and paediatricians in established centres, will ensure successful foetal and maternal outcomes.

References
