Neurological disease in pregnancy

Felicity Coad
Catherine Nelson–Piercy

Abstract

Neurological disease encompasses a broad spectrum of conditions which may be affected by pregnancy, present *de novo* in pregnancy, or are caused by the pregnancy itself. In the UK, 9.8 women in 100,000 died during pregnancy or up to 42 days after delivery (Mothers and Babies Reducing Risk through Confidential Enquiry (MBRRACE) report 2018). Neurological diseases, including epilepsy and stroke, continues to be the second leading indirect cause of maternal mortality and the numbers have not changed since reporting began in 1985, despite the availability of easily accessible Green-top Guidelines on the management of epilepsy through the Royal College of Obstetricians and Gynaecologists (RCOG). It is important than any women of child-bearing age with a neurological condition receive appropriate pre-pregnancy counselling and that during pregnancy they are managed by an experienced multi-disciplinary team including a neurologist, specialist nurse or midwife, maternal medicine obstetrician or obstetric physician and obstetric anaesthetist. Additional benefits in care will come with improving awareness in the general public and community doctors so that appropriate support is provided to enable the safest possible pregnancy.

Keywords Anti-epileptic drugs; epilepsy; headache; migraine; neurological disease; neuropathy; pre-pregnancy counselling; pregnancy; stroke

Epilepsy

Classification

Epilepsy affects approximately 0.5–1% of women of childbearing age and is the commonest neurological disorder seen in pregnancy. An estimated 2500 infants are born to women with epilepsy (WWE) every year in the UK. Epilepsy is the third most frequent cause of indirect maternal deaths and the risk of death is increased ten-fold in pregnant WWE. The majority of deaths in WWE have been attributed to SUDEP (sudden unexplained death in epilepsy). The challenge of managing WWE is combining optimal seizure control with lowest effective dose of AEDs (anti-epileptic drugs) in order to minimise *in utero* exposure to the fetus and the associated risks of neurodevelopmental delay and structural defects.

Classifying epilepsy is important as it guides the neurologist in choosing appropriate AEDs (anti-epileptic drugs) and counselling about prognosis during pregnancy. Epilepsy is classified according to the clinical type of seizure or specific encephalographic (EEG) features.

Seizures can be focal (previously simple partial –conscious, or complex partial -consciousness impaired) or generalised (petit-mal or grand-mal). A specific type of focal seizure is temporal lobe epilepsy, often associated with an aura, a duration of one or more minutes, and confusion after the event. Generalised tonic-clonic seizures are associated with variable periods of hypoxia in the mother and fetus. This seizure-type carries the highest risk of SUDEP.

About one-third of patients with epilepsy have a positive family history of epilepsy, although most cases are idiopathic, with no underlying cause found. Secondary epilepsy may occur in patients who have had previous brain surgery or trauma, an intracranial mass lesion or antiphospholipid syndrome. Table 1 lists other causes of seizures in pregnancy.

The diagnosis of epilepsy and epileptiform seizures should be made by a physician, usually a neurologist, with expertise in epilepsy. *De novo* seizures in women in the second half of their pregnancy should not be assumed to be epilepsy, and the pre-eclampsia pathway should be initiated until further neurological assessment can be made. Investigation including MRI or CT imaging should not be withheld because the woman is pregnant. The diagnosis of non-epileptic attack disorder can be difficult and should be made when other causes of seizure have been excluded (see Table 1). They often co-exist in women with epilepsy.

WWE require specific care throughout their pregnancy. Guidelines have been developed by the Royal College of Obstetrician and Gynaecologists (RCOG) and were published in June 2016 to help improve the care of WWE who are or wish to become pregnant.

Preconception care

Women with epilepsy should be referred to a neurologist before getting pregnant. A re-evaluation of the need for AED treatment should include whether the diagnosis is correct and whether the epilepsy has spontaneously remitted. As part of pre-pregnancy counselling, women should be given information on the following:

1. The impact of AEDs on the fetus including structural and neurodevelopmental effects
2. The change in metabolism of AEDs during pregnancy and potential changes in seizure frequency
3. The importance of good pre-conception seizure control and pregnancy planning including taking high dose folic acid (5 mg) for at least three months prior to conception.

Anti-epileptic medication

AEDs cross the placenta and are teratogenic. The benefits of seizure control (i.e. the reduction of seizure-related harm, including SUDEP) need to be balanced against the detrimental effects of AEDs (i.e. teratogenesis and neurodevelopmental delay). Major congenital malformations (MCM) include neural tube defects, orofacial clefts, congenital heart defects and hypospadias. Minor malformations include dysmorphic features, hypertelorism, hypoplastic nails and distal digits and midface hypoplasia. WWE not exposed to AEDs during pregnancy have a similar incidence of MCM to the background population.

Felicity Coad *BSc MBBS MRCP is a Medical Registrar in Acute Medicine at Guy's and St Thomas' Hospital working as a Clinical Fellow in Obstetric Medicine, UK. Conflicts of interest: none.*

Catherine Nelson-Piercy *MA FRCP FRCOG is Professor of Obstetric Medicine at Guy's and St Thomas' Hospitals NHS Foundation Trust, London, UK. Conflict of interest: none.*

Seizures in pregnancy

Other causes of seizure	Potential distinguishing features
Eclampsia	High blood pressure; proteinuria;
Thrombotic Thrombocytopenic purpura (TTP)	fever, low platelets, microangiopathic haemolytic anaemia, thrombosis causing renal and neurological impairment ADAMTS13 - < 5–10%
Cerebrovascular accident	On-going neurological impairment and CT/MRI evidence of an infarct or haemorrhage
Cerebral Venous or Sinus thrombosis	Identified on CT venogram; often a history of severe headache
Hypoglycaemia	Neurological impairment should resolve once glucose corrected although this may depend on the period of hypoglycaemia
Electrolyte Imbalances	Typically hyponatraemia and hypocalcaemia
Posterior reversible leukoencephalopathy syndrome	Associated visual symptoms. Can be associated with high blood pressure; identified on MRI and symptoms usually resolve 1–2 weeks later
Reversible cerebral vasoconstriction syndrome	Typical history of thunder-clap headache; identified on CT/MR angiography; presents post-partum, symptoms usually resolve within 3 weeks
Space-occupying lesion (SOL)	Possible focal neurological deficit depending on site of SOL; CT/MRI will identify

Table 1

The risk of major congenital malformations

A 15-year prospective observational study looking at the MCM risk of AED monotherapies in pregnancy in UK and Ireland, showed that the MCM risk with valproate monotherapy was 6.7%, compared to 2.6% with carbamazepine and 2.3% with lamotrigine. A significant dose effect was seen with valproate and carbamazepine-exposed pregnancies. High dose lamotrigine (>400 mg daily) was associated with fewer MCMs than low dose (<600 mg daily) valproate.

A recently published pregnancy cohort study looked at women taking topiramate and the risk of oral clefts in the fetus. It found that WWE taking higher doses of topiramate as monotherapy (>100 mg) during the first trimester had a relative risk of 5.16 of cleft lip versus a 1.64 in the lower dose group (<100 mg). The UK and Ireland Epilepsy and Pregnancy Register from 2013 showed that levetiracetam as monotherapy was relatively low-risk for MCM in fetuses exposed from the first trimester, but when used in combination with another AED conferred an increased risk of a MCM. Levetiracetam and lamotrigine given together were lower risk for MCM compared with levetiracetam and sodium valproate.

Data taken from the North American AED Pregnancy Registry showed that among infants exposed to carbamazepine as polytherapy, the risk of MCM was 15.4% for carbamazepine plus valproate, and 2.5% for carbamazepine plus any other AED. The risk of MCM in infants exposed to lamotrigine plus valproate was 9.1%, and 2.9% for lamotrigine plus any other AED.

These studies suggest that appropriate counselling should be based on the specific AED combinations, and monotherapy is preferable where possible. Table 2 summarises data from four Epilepsy in Pregnancy registries, showing the percentage of MCM in fetuses born to women taking different AEDs.

Long-term neurodevelopmental outcomes

A study looking at the cognitive function at six years of age after fetal exposure to AEDs showed a statistically significant decrease in IQ scores of children whose mothers were exposed to valproate *in utero* compared to carbamazepine and lamotrigine. These data support the need to avoid valproate in pregnancy where possible. Valproate must no longer be prescribed to women or girls of childbearing potential unless they are on the pregnancy prevention programme (PPP). Peri-conception folic acid has, for a number of years, been known to reduce the incidence of NTDs, but recently it has also been shown to increase IQ at six years of age in children whose mothers took folic acid, compared to those children whose mothers did not.

A Cochrane review in 2014 demonstrated no significant differences in neurological development in children exposed to carbamazepine, lamotrigine and phenytoin AEDs versus children born to epileptic mothers not on AED or the general non-epileptic population. *In utero* exposure to carbamazepine and lamotrigine does not appear to adversely affect neurodevelopment of the children, but this is based on limited data. There is also little evidence for levetiracetam and phenytoin so parents should be aware of the limitations on advising the use of these agents.

Measures to minimise risk to mother and fetus

Discontinuation of AEDs in seizure-free women should be discussed before conception although women with juvenile myoclonic epilepsy should not discontinue their medication. The aim is to treat with one AED at the lowest effective dose. 5mg folic acid should be commenced three months before conception and should be continued throughout pregnancy. The risk of the child developing epilepsy (4–5% if either parent has epilepsy, with maternal epilepsy associated with a higher risk) should also be discussed with the woman.

Antenatal management

Once pregnancy is confirmed, WWE should book early so they can be referred to an obstetrician, obstetric physician or ideally a joint obstetric epilepsy clinic. WWE should be provided with information about the UK Epilepsy and Pregnancy Register and encouraged to participate. Any unplanned pregnancies in WWE warrant urgent referral to a neurologist. These women should be discouraged from abruptly stopping or changing their medications until they see a neurologist and have an informed discussion of the risks and benefits.

In addition to regular antenatal care and first trimester ultrasound screening, a detailed anomaly scan at 18–20 weeks, including fetal echocardiography should be performed. WWE taking AEDs have an increased risk of small-for-gestational-age

babies and therefore require serial growth scans from 28 weeks of gestation.

Effect of pregnancy on seizures

A review of seizure control in pregnancy from the EURAP (International Registry of Anti-epileptic Drugs and Pregnancy) database shows that seizure frequency 1 year prior to pregnancy is the best predictor of seizure frequency during pregnancy. A meta-analysis showed that freedom from seizures for nine months to one year prior to pregnancy is associated with a 72 −92% likelihood of remaining seizure-free during pregnancy.

In a cohort study (n = 3784), 66.6% of the women were seizure-free during their pregnancies. Worsening seizure control in the second and third trimester was more common in women taking lamotrigine than those taking carbamazepine or valproate. Several studies have documented an increase in plasma clearance of levetiracetam and lamotrigine during pregnancy. A study in 2013 found that in a cohort of 115 pregnancies, WWE showed a peak clearance increase of 207% for levetiracetam and 191% for lamotrigine. Interestingly, in this same cohort, women undergoing subsequent pregnancies did not necessarily follow the same pattern of plasma clearance making it difficult to predict drug dosing. Routine serum AED levels are not currently recommended by the RCOG due to paucity of evidence about whether levels improve seizure control. Data from the EMPiRE study (2018) have suggested that regular therapeutic drug monitoring (TDM) does not improve seizure control or alter maternal or fetal outcomes. However, we still use TDM in selected patients, for example those women in whom we are concerned about adherence, toxicity or increased seizure frequency. Seizure deterioration during pregnancy may be a result of increased plasma clearance but other causes include poor adherence (often due to fears of teratogenesis), vomiting or lack of gastrointestinal absorption and lack of sleep.

Green Top RCOG guidelines recommend that babies born to mothers taking enzyme-inducing AEDs should be offered 1 mg of intramuscular vitamin K to help prevent haemorrhagic disease of the newborn. There is insufficient evidence to support giving routine oral vitamin K to women antenatally to prevent haemorrhagic disease of the newborn.

RCOG guidelines suggest that women with epilepsy who are not considered to have a high risk of unprovoked seizures can be managed as low-risk women in pregnancy.

Intrapartum management

Most women with epilepsy have normal vaginal deliveries and caesarean section is only required for obstetric reasons or if there are recurrent generalised seizures in late pregnancy or labour. The risk of seizures increases around the time of delivery so women with major convulsive seizures should deliver in hospital. Women should not stop their oral AEDs during labour. An early epidural can be offered in order to limit the risk of precipitating a seizure because of pain and anxiety. For women with poor seizure control, such as those with recent convulsive seizures or recent stress/sleep-deprivation provoked seizures or a history of seizure during labour, long-acting benzodiazepines such as clobazam can be initiated prophylactically during the peripartum period. The risk of neonatal respiratory

Table 2 Rates of major congenital malformations in four different epilepsy registries. (Adapted from a review article by Kevat and Mackillop, 2013.)

	Carba-mazepine	Clonazepam	Lamotrigine	Leve-tiracetam	Pheno-barbital	Phenytoin	Topiramate	Sodium Valproate
International Lamotrigine Pregnancy Registry (2011)	–	–	2.2% (of 1558)	–	–	–	–	–
UK Pregnancy and Epilepsy Register (2014)	2.6% (of 1718)	–	2.3% (of 2198)	–	–	–	–	6.7% (of 1290)
North American AED Pregnancy Registry (2018)	2.78% (of 1080)	2.00% (of 100)	2.05% (of 2143)	2.00% (of 999)	6.12% (of 201)	2.58% (of 427)	5.34% (of 468)	8.18% (of 341)
International registry of antiepileptic drugs and pregnancy (EURAP) (2018)	5·5% (of 1957)	–	2·9% (of 2514)	2·8% (of 599)	6·5% (of 294)	6·4% (of 125)	3·9% (of 152)	10·3% (of 1381)

Data show the total number of women exposed to monotherapy AED and the percentage of these who have a baby with a MCM.

depression must be balanced against the benefit of seizure prevention. In the event of a seizure, which is not self-limiting, facial oxygen and intravenous lorazepam, or rectal or intravenous diazepam should be administered.

A recent systematic review identified 38 studies looking at pregnancy in WWE and outcomes. There was a small but statistically significant increase in obstetric risk including spontaneous miscarriage, antepartum haemorrhage, hypertensive disorders, induction of labour, caesarean section and postpartum haemorrhage. Babies born to WWE on AEDs were more likely to require neonatal intensive care.

A population-based cohort study in Denmark looked at pregnancies between 1997 and 2008 and identified WWE. 4700 women used AEDs during pregnancy and compared to non-AED using WWE, they had no statistically significant increased incidence of spontaneous miscarriage or still birth.

Postpartum care

The risk of having a seizure in the first 24 h after delivery is approximately 1–2% so women should not be left unattended. Sleep deprivation during the postpartum period lowers seizure threshold so additional support is advised during this time. To minimise the risk to the baby in the event of a major convulsive seizure, strategies including changing nappies on the floor, and bathing the baby in very shallow water or under supervision should be employed.

The neonate should be given 1 mg of intramuscular Vitamin K to prevent haemorrhagic disease of the newborn. Women with epilepsy should be encouraged to breastfeed as most AEDs only cross into the breast milk in minimal amounts (3–5% of maternal levels). However, women taking lamotrigine or phenobarbitone should breastfeed prior to taking their medication in order to minimise neonatal exposure, as these drugs cross into breast milk in much larger amounts (30–50%). If the mother's dose of AED was increased during pregnancy, the AED dose should be reviewed within 10 days of delivery to avoid postpartum toxicity.

Headache

Headache accounts for one-third of all neurological problems in pregnancy. A careful history and neurological examination should be performed in order to distinguish between the different causes and exclude focal signs, papilloedema and neck stiffness. Primary headache disorders include migraine and tension headache. Other acute causes of headache include CNS infections e.g. meningitis, encephalitis, vascular disease e.g. subarachnoid and other intracranial haemorrhage, cerebral venous sinus thrombosis and arterial dissection, and other intracranial disease e.g. raised and reduced intracranial pressure and pituitary apoplexy. Obstetric causes include pre-eclampsia and post-dural puncture headache. It is also important not to forget some drug side-effects, for example, vasodilators such as nifedipine and hydralazine, as well as analgesia overuse, can cause headaches.

Migraine

Migraine is common in women of childbearing age. It may present *de novo* in pregnancy and may be difficult to differentiate from a tension headache, as migraine may present with or without aura. Migraine is thought to be caused by vasodilatation of cerebral blood vessels, possibly related to platelet aggregation and serotonin release with stimulation of nociceptors. MRI during a migraine attack shows episodic cerebral oedema, dilatation of intracerebral vessels and reduced water diffusion not respecting vascular territories, so the primary event may be neurological, rather than vascular.

Migraine with aura (classical) and without aura (non-classical) may represent separate clinical entities. In pregnancy, 50–90% of women with pre-existing classical migraine improve with a reduction in frequency and severity of attacks. Improvement is most marked in the second and third trimesters, and in those with premenstrual and non-classical migraine.

A careful history is essential and features of headache that make migraine a likely diagnosis include a throbbing, unilateral severe headache which may be made worse by movement, light (photophobia) or sound (phonophobia). There may be associated nausea and vomiting, and episodes generally last from 4 to 72 h. Aura occur in around 20% of patients and consist of visual disturbances (e.g. flashes of lights or zigzag lines in front of the eyes), paraesthesia or other neurological symptoms. Hemiplegic migraine may mimic a transient ischaemic attack, particularly if there is no headache. In the absence of known hemiplegic migraine, the presence of focal neurological signs should be urgently investigated with cerebral imaging. Pre-existing migraine is associated with an increased risk of gestational hypertension or pre-eclampsia, predominantly in women whose headaches do not improve in pregnancy.

The mainstay of the management of migraines in pregnancy includes the avoidance of triggers, treatment of acute attacks and prevention of future attacks. Non-pharmacological measures to avoid migraine such as adequate sleep and stress management may be of benefit. In an acute attack, simple analgesics may be used with anti-emetics e.g. buclizine or cyclizine. Non-steroidal anti-inflammatory agents such as ibuprofen are effective but should not be used in the third trimester due to the risk of premature closure of the ductus arteriosus and oligohydramnios. Many women who experience severe migraine have been managed at one time or another with 5-HT_1 agonists (triptans, e.g. sumatriptan, naritriptan), which are useful in treating acute attacks but are of limited benefit in preventing further migraines. Triptans bind to 5-HT receptors, causing vasoconstriction and inhibition of neuronal inflammation. Recent data from an international registry suggest no teratogenic effects; only minimal amounts of triptans have been measured in breast milk and they are therefore considered to be safe during breastfeeding.

If frequent migraine attacks occur (two or more attacks per month), 75 mg aspirin daily should be used as a first-line agent. β-blockers (propranolol) are effective in more than 80% of cases and can be used in patients without contraindications if aspirin is ineffective. Tricyclic anti-depressants (amitriptyline 25–50 mg at night), calcium channel blockers (verapamil 40–80 mg at night), and cyproheptadine (2–4 mg at night) are safe in pregnancy and may be useful in resistant cases. There are insufficient data regarding safety of pizotifen (a serotonin antagonist) for prevention of migraine in pregnancy, however, its use is justified after the first trimester if first- and second-line prophylactic agents are ineffective. Topiramate is avoided where possible due to increased risk of MCM (see epilepsy section).

Cerebral vein thrombosis

Cerebral vein thrombosis (CVT) has an incidence of 1 in 10,000, but if untreated carries a high mortality rate. The majority of cases are seen in pregnant or puerperal women. The pathogenesis relates to the hypercoagulable pregnant state exacerbated by dehydration or maternal sepsis, although underlying thrombophilias may contribute. Possible trauma to the endothelial lining of cerebral sinuses and veins during labour may also play a role. Common presentations include headache, vomiting, seizures, photophobia and signs of raised intracranial pressure, along with focal signs such as hemiparesis. Maternal pyrexia and leucocytosis may be present.

Diagnosis is made using CT or MR venous angiography. The differential diagnosis includes subarachnoid haemorrhage, herpes encephalitis and eclampsia. Management includes rehydration, anticoagulation and anticonvulsants (if seizures are present).

Other causes of headache

Pre-eclampsia: may also present with a headache which may be associated with visual scintillations, visual loss or jitteriness. Headache in this condition is thought to be secondary to vasoconstriction and/or cerebral oedema. Severe headache in a woman with pre-eclampsia suggests the possibility of intracerebral haemorrhage especially if the blood pressure is very high.

Subarachnoid haemorrhage (SAH): occurs in 20 per 100,000 pregnancies; this is two-to three-fold higher than non-pregnant rates. It may occur due to rupture of an arterial (berry) aneurysm or an arterio-venous malformation (AVM). The patient may present with a sudden-onset severe 'thunderclap' headache, with nausea and vomiting. There may be altered consciousness, neck stiffness, papilloedema and focal neurological signs. Clipping and endovascular treatment of aneurysms has been successful during all stages of pregnancy. The risk of re-bleeding from an AVM in the remainder of the pregnancy may be 50% with the greatest risk in the post-haemorrhagic period.

Postpartum angiopathy: is a member of a group of reversible cerebral vasoconstriction syndromes (RCVS) with similar clinical and radiologic features that are characterized by 'thunderclap' headache and diffuse, segmental, reversible vasospasm. It usually presents in the first week postpartum after a previously uncomplicated pregnancy, with a severe 'thunderclap-type' headache with or without focal neurological signs. 50–70% of cases are associated with the patient being given ergot derivatives. There may be associated seizures and the presentation may mimic a subarachnoid haemorrhage or transient ischaemic attack. It is associated with atypical SAH. The diagnosis is by CT angiography or MR angiography, which shows smooth narrowing and dilatation of multiple segments of intracranial arteries (string of beads appearance). It is important to note, however, that the imaging may be normal if done early. Treatment includes analgesia and nimodipine. There is usually complete resolution within months.

Posterior reversible encephalopathy syndrome (PRES): is a transient neurological disturbance causing occipital lobe-related symptoms commonly headache, seizures and cortical blindness of acute or subacute onset. In pregnant patients, it is usually related to pre-eclampsia or eclampsia and there is severe impairment of vision limited to distinguishing light and dark with normal optic fundi and a normal pupillary reflex. Blurred vision, photophobia and nausea and vomiting can also be present, with symptoms and signs recovering relatively rapidly. It is thought to be caused by vasogenic brain oedema. MRI shows characteristic bilateral involvement of white and grey matter in the posterior regions of cerebral hemispheres.

Idiopathic intracranial hypertension (IIH): often presents with a retro-orbital headache worse after laying flat (e.g. first thing in the morning). Other symptoms include visual obscuration and intracranial noises such as tinnitus. Classically, it is associated with obesity or women who have had recent rapid weight gain and can form part of an obesity hypoventilation syndrome with associated sleep apnoea. The diagnosis of IIH is made from the combination of papilloedema and raised intracranial pressure without CT or MRI evidence of hydrocephalus or a space-occupying lesion. A lumbar puncture should be performed to measure the cerebrospinal fluid (CSF) opening pressure (>25 cm H_2O). Pre-existing IIH tends to worsen in pregnancy, and is seen more commonly in the second trimester. Management of IIH includes limitation of weight gain. Acetazolamide can be used from the second trimester onwards, and thiazide diuretics can be administered, although should be avoided in the third trimester, as they can cause neonatal thrombocytopenia. Repeated lumbar punctures over a period of time may be needed to reduce the CSF pressure. Women with IIH should fill out an Epworth Sleepiness Scale questionnaire and be referred for overnight pulse oximetry testing.

Post-dural puncture headache (PDPH): arises due to loss of CSF and a reduction in cerebrospinal pressure. Up to 38% of PDPH can arise after a seemingly uneventful procedure. It is commonly associated with a dural tap (most common with epidural but may occur after a spinal). Onset is usually within 24 h (but can be up to 72 h) after epidural/spinal anaesthesia/analgesia and often presents as a fronto-occipital throbbing headache which occurs abruptly on standing and improves almost immediately on lying flat again. Associated features include nausea and vomiting, visual symptoms and rarely seizures. An anaesthetic review is required and effective treatment includes an epidural blood patch, which can cure in approximately 50%.

Cerebrovascular disorders

Stroke is an important cause of severe maternal morbidity and mortality in the UK. The increasing age of women at childbirth, along with the physiological changes of pregnancy such as thromboembolic, immunological and connective tissue changes, may lead to an increase in the incidence of haemorrhagic stroke associated with pregnancy and all strokes during the puerperium. The incidence of stroke in non-pregnant women aged between 15 and 49 is approximately 25.0 per 100,000. This becomes 9-fold higher in the peripartum and 3-fold higher in early postpartum, so although the background risk in this population is low, pregnancy significantly increases the relative risk. Stroke contributes to more than 12% of maternal deaths, with pre-eclampsia and eclampsia associated with 25–45% of pregnancy-related stroke, including haemorrhagic and non-haemorrhagic causes.

Ischaemic (non-haemorrhagic) stroke

Most strokes associated with pregnancy occur in the distribution of the middle cerebral arteries and the majority of pregnancy-related strokes occur in the third trimester or postpartum. The common risk factors for stroke outwith pregnancy, including hypertension, diabetes and smoking are less common in pregnancy, so rarer causes, for example, cardiac causes of arterial emboli or arrhythmias, mitral valve disease, paradoxical embolus through an atrial septal defect or patent foramen ovale, antiphospholipid syndrome or an underlying vasculitis need to be considered. MRI or CT with angiography is appropriate to confirm stroke and differentiate haemorrhage from infarction. If the stroke is ischaemic, an echocardiogram and carotid Doppler studies are indicated. Management depends on the underlying cause, and includes 75 mg aspirin daily, which should be continued postpartum. Some patients require anticoagulation. Thrombolysis or thrombectomy should not be withheld because of pregnancy and multi-disciplinary discussion about optimal timing of delivery should take into consideration stabilisation of the mother and minimising bleeding risk.

Haemorrhagic stroke

Haemorrhagic stroke is rare in women of child-bearing age outside pregnancy but is as common as ischaemic stroke during pregnancy. Management of haemorrhagic stroke is similar to non-pregnant women and often involves neurosurgical intervention, including clipping or endovascular treatment. These interventions have been performed in all trimesters of pregnancy and are associated with low fetal and maternal mortality. With regards to delivery, epidural is contraindicated only if the intracranial pressure is elevated and caesarean section should only be performed for obstetric indications. The most pressing need is to treat hypertension (especially systolic hypertension) quickly and effectively to prevent haemorrhagic stroke.

Multiple sclerosis

Multiple sclerosis (MS) is an inflammatory demyelinating disorder of the central nervous system, which typically presents in the second or third decade of life and is twice as common in females as in males. Three main clinical subtypes are recognised which are relapsing-remitting, primary progressive or secondary progressive. There are Revised McDonald Criteria for diagnosing multiple sclerosis which involve a combination of clinical and radiological signs suggesting at least two separate episodes of demyelination. The pathogenesis of MS is incompletely understood but involves a maladaptive T-cell-mediated immune response to an unknown antigen. Common presentations include optic neuritis, diplopia, sensory symptoms or weakness of the limbs.

Consensus guidelines have been published regarding the management of women with multiple sclerosis. MS does not affect fertility, so appropriate contraception and a planned pregnancy after pre-pregnancy counselling are advised. Key points to cover during such counselling include:

1. Do not defer disease modifying drug treatment because of a wish to have children in the future
2. Pregnancy does not increase the risk of worsening long-term disability although some symptoms may worsen such as fatigue, balance and bladder symptoms.

Women with advanced MS may experience deterioration in their mobility and worsening spasticity as pregnancy advances, which may be due to increasing weight and an altered centre of gravity. Patients with a pre-existing neuropathic bladder are at increased risk of recurrent urinary tract infections, which require prompt treatment with antibiotics, or more frequent self-catheterizations. Drugs used to relieve spasticity (baclofen), paroxysmal pain or dysaesthesiae (carbamazepine and gabapentin) may also be used.

3. Whilst relapses during pregnancy are felt to reduce in frequency, a postpartum relapse in subsequent 3 months is not uncommon (25%).
4. The Pregnancy in Multiple Sclerosis (PRIMS) study reported a reduction in MS relapse during pregnancy, particularly in the third trimester (70% reduction), and an increase in relapse rates in the first 3 months postpartum (40% relapse rate), with a subsequent decline in relapse rates to pre-pregnancy levels by 10 months postpartum.

Despite the increased risk of relapse post-partum there is no evidence to suggest that pre-emptive methylprednisolone or immunoglobulin therapy will prevent this. Relapses should be treated with corticosteroids as per the non-pregnant population.

Severe, acute relapses may warrant treatment with high dose corticosteroids during pregnancy and breastfeeding.

5. Medication should not be stopped abruptly should a woman become pregnant – urgent referral to the MS team is advised to discuss the risks and benefits of each medication.

There are now many options available to reduce the relapse rate of multiple sclerosis. There are data available regarding the safe use of interferon B and glatiramer acetate (e.g. Copaxone) and they should be continued at least until conception. Copaxone is licenced for use in pregnancy. Some women will need to continue these treatments throughout pregnancy and as yet there is no evidence of harm to the fetus.

Natalizumab (Tysabri) is licenced for women with rapidly evolving severe MS. These women are less likely to benefit from the relatively immunosuppressed state of pregnancy and may need to continue this treatment during pregnancy. Natalizumab does not cross the placenta in the first trimester, but it does cross the placenta in the second and third trimester. The recommendations to minimise fetal exposure suggest taking a last dose around 34 weeks. Breast feeding is possible with natalizumab as oral bioavailability is felt to be negligible.

Fingolimod should be taken with contraception and stopped 2 months prior to conceiving. In an unplanned pregnancy fingolimod should be stopped and referral for fetal medicine scanning made. There are no data regarding safety in breast feeding and it should be avoided.

Teriflunomide is teratogenic and women taking this medication should be on a reliable form of contraception. Unplanned pregnancy requires urgent referral to an obstetrician and neurologist and accelerated clearance of this medication.

Dimethylfumarate (Tecfidera) has limited data but has been continued in pregnancy where benefit outweighs the risk, but ideally a medication switch should be arranged. Women on this medication should not breastfeed due to paucity of data about breast milk excretion.

6. Vitamin D supplementation of 4000 IU (100 μg) vitamin D per day is advised to all MS patients regardless of pregnancy status.

MS is not a contraindication to vaginal delivery or epidural anaesthesia, however, careful documentation of pre-existing neurological deficit in the legs is necessary to avoid any postpartum MS exacerbation being wrongly attributed to the regional block.

Women with MS should be encouraged to breast feed. A recent meta-analysis of 12 studies showed that women who did not breastfeed were almost twice as likely to have at least one postpartum relapse compared to those women who exclusively breastfed although it remains uncertain whether exclusive breastfeeding can truly reduce post-partum relapse rate.

There is evidence of an increased risk of post-partum depression in both men and women with MS, and therefore the local MS team and midwives must monitor carefully for this and offer appropriate support if required.

Myasthenia gravis

Myasthenia gravis (MG) is a rare autoimmune condition caused by antibodies against the nicotinic acetylcholine receptor (AChR) and other postsynaptic antigens, for example muscle specific kinase (MuSK). There is a female to male preponderance of 2:1 with onset usually in the second and third decades. Clinical features include fatigable painless muscle weakness leading to diplopia, ptosis and dysphagia, and in severe cases, respiratory muscle weakness. Diagnosis is confirmed by serum autoantibody analysis and EMG evidence of disordered neuromuscular transmission.

Forty per cent of women with MG have an exacerbation in pregnancy; in 30% there is no change in symptoms and 30% go into remission. Exacerbation in pregnancy is less likely if the woman has undergone previous thymectomy, as 10% have an associated thymoma. Postpartum exacerbations occur in 30% of women. Pyridostigmine (a long-acting anticholinesterase drug) is the mainstay of treatment, and larger or more frequent doses may be required as the pregnancy advances. When MG symptoms are not satisfactorily controlled, corticosteroids, azathioprine and in some cases intravenous immunoglobulin or plasmapheresis have been used. Respiratory insufficiency may occur during pregnancy or postpartum so close monitoring by a multidisciplinary team is necessary.

A UK multispecialty working group recommend that pre-pregnancy counselling should be offered to all women of childbearing age with MG, and specific advice about the safety of different therapies in pregnancy should be offered with clear instructions not to discontinue safe immunosuppressive agents or pyridostigmine in pregnancy.

Initial evaluation of pregnant woman with MG should include pulmonary function tests, a baseline ECG and thyroid function tests (due to the association with other autoimmune conditions). MG women with dyspnoea or cough could be promptly evaluated for the possibility of a myasthenic flare with diaphragm and respiratory muscle weakness. Infections should be treated promptly as they can also precipitate MG flares.

Monitoring of fetal movements should be encouraged because transplacental passage of AChR antibodies may rarely cause arthrogryposis multiplex congenita, where the fetus develops contractures due to lack of movement. There is a high incidence of preterm delivery and intrauterine growth restriction (40%). Since the uterus has smooth muscle, the first stage of labour is unaffected by MG, however, the second stage which utilises maternal voluntary striated muscle may be impaired.

Referral to an obstetric anaesthetist should be made early in the pregnancy, to plan for all delivery eventualities and regional/general anaesthesia. Certain drugs should be avoided or used with caution in women with MG including magnesium sulphate for eclampsia prophylaxis (which may precipitate a crisis), depolarising muscle relaxants such as suxamethonium, and drugs that impair or block neuromuscular transmission such as gentamicin and β-blockers, particularly propranolol.

Up to 10% of neonates born to mothers with MG may be affected by neonatal myasthenia due to transplacental passage of IgG antibodies. This is characterised by difficulty feeding, crying, a floppy baby and respiratory difficulties and is usually apparent in the first 48 h after birth. Newborn babies should have rapid access to neonatal high-dependency support in the event they have transient myasthenic weakness. This resolves within two months corresponding to the disappearance of maternal antibodies in the neonate and is treated with anticholinesterase drugs.

Cerebral tumours

Cerebral tumours are uncommon in pregnant patients, however, primary tumours of the central nervous system and metastatic cancer may present during pregnancy with signs and symptoms including headache, nausea and vomiting, and visual symptoms that are often unremitting. The headache is generally exacerbated by manoeuvres that increase intracranial pressure, such as coughing. Other symptoms depend on the site and size of the tumour and may include an altered mental state, focal neurological deficits or seizures. Meningiomas and pituitary tumours are more common among women and tumour size may be influenced by the vascular and hormonal changes that accompany pregnancy. Neuroimaging will aid diagnosis and guide further investigations.

Myotonic dystrophy

Myotonic dystrophy (MD) is a rare degenerative neuromuscular and neuroendocrine disease. The most common form is myotonic dystrophy type I which is inherited in an autosomal dominant pattern. It is a trinucleotide repeat disorder with the affected gene located on chromosome 19, making the condition amenable to pre-implantation genetic diagnosis (PGD) to avoid bearing an affected child. The characteristic features include a progressive muscular dystrophy, muscle weakness and myotonia. Cataracts, cognitive impairment, cardiac conduction defects, dysphagia, and respiratory compromise may become evident later in life.

In pregnancy, MD can worsen, particularly in the third trimester with the associated extra weight and diaphragmatic splinting from a gravid uterus. However, symptoms improve rapidly after delivery. There are a number of pregnancy-related complications associated with MD including increased risk of miscarriage, polyhydramnios (which may lead to premature labour), dysfunctional labour, intra-partum and postpartum haemorrhage which can be managed with uterotonics. These complications are more likely when the baby has congenital myotonic dystrophy.

Congenital MD occurs in some pregnancies and is characterized by severe generalized hypotonia and weakness of the neonate, difficulties in breathing, sucking and swallowing, talipes and neurodevelopmental problems.

Women with MD should be referred to an obstetric anaesthetist experienced in managing these patients. When required, caesarean sections can be performed under either regional or general anaesthesia, but the drugs used for the latter can cause complications in these patients and women should be counselled regarding this.

Bell's palsy

This is a unilateral lower motor neurone lesion of the facial (VIIth cranial) nerve which causes a unilateral facial weakness. Involvement of frontalis muscle on the affected side distinguishes this from an upper motor neurone lesion. The incidence of Bell's palsy is approximately 45 in 100,000 pregnancies with the condition having a 10-fold increase compared to the non-pregnant state. Most cases in pregnancy occur around term, either in the two weeks before or after delivery. Peripartum Bell's palsy may be related to swelling of the facial nerve within the petrous temporal bone, which may be related to oedema. Ramsay Hunt syndrome (herpes zoster of the geniculate ganglion) should be excluded in women presenting with Bell's palsy, in which herpetic vesicles may be visualized in the external auditory meatus or soft palate. Bell's palsy resolves spontaneously in most cases but recovery may take several months. If the patient presents within 72 h of onset of symptoms, a seven-day course of 60–80 mg of prednisolone once a day is associated with reduced risk of unfavourable recovery. There is limited evidence that combined antiviral and glucocorticoid treatment achieves improved outcomes. Aciclovir, ideally within 72 h of symptoms, is used for Ramsay Hunt syndrome instead of steroids.

Entrapment neuropathies

Carpal tunnel syndrome affects 2–3% of pregnant women and arises due to median nerve compression at the flexor retinaculum. It presents in later pregnancy with paraesthesia and numbness of the thumb and lateral two and a half fingers, and can sometimes be painful. More severe symptoms can occur at night and in the dominant hand, and motor loss of the median nerve can occur, resulting in wasting of the thenar eminence. Relief can occur by vigorous shaking of the affected hand. Wrist splints and physiotherapy may offer symptomatic relief during pregnancy and carpal tunnel syndrome usually improves after delivery.

Nerves arising from the lumbosacral plexus may become damaged during delivery, particularly following a long second stage, due to fetal head compression. Foot drop due to compression of the sciatic nerve (L4-S3), the lumbosacral trunk (L4-5) or the common peroneal nerve (L4-5) is the commonest presentation. The latter occurs due to pressure on the common perineal nerve at the neck of the fibula, usually with the woman in the lithotomy or squatting position. Numbness or pain in the anterolateral aspect of the thigh, in the distribution of the lateral cutaneous nerve of the thigh, may arise in pregnancy due to nerve compression at the lateral aspect of the inguinal ligament. It is more common in obese patients and resolves spontaneously following delivery. ◆

FURTHER READING

Allais G, Gabellari IC, Borgogno P, de Lorenzo C, Benedetto C. The risks of women with migraine during pregnancy. *Neurol Sci* 2010; **31:** S59–61.

Campbell E, Kennedy F, Russell A, et al. Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers. *J Neurol Neurosurg Psychiatry*, 2014 Feb 3; https://doi.org/10.1136/jnnp-2013-306318 [Epub ahead of print].

Dobson R, Dassan P, Roberts M, et al. UK consensus on pregnancy in multiple sclerosis: 'Association of British Neurologists' guidelines. *Pract Neurol* 2019; **19:** 106–14.

Ephross SA, Sinclair SM. Final results from the 16-year sumatriptan, naratriptan, and treximet pregnancy registry. *Headache J Head Face Pain*, 2014.

Hernandez-Diaz S, Huybrechts KF, Desai RJ, et al. Topiramate use early in pregnancy and the risk of oral clefts. *Neurology*, 2017; https://doi.org/10.1212//WNL.0000000000004857.

Holmes LB, Mittendorf R, Shen A, Smith CR, Hernandez-Diaz S. Fetal effects of anticonvulsant polytherapies: different risks from different drug combinations. *Arch Neurol* 2011; **68:** 1275–81.

Kevat D, Mackillop L. Neurological diseases in pregnancy. *J R Coll Phys Edinb* 2013; **43:** 49–58.

KJ1 Meador, Baker GA, Browning N, et al. NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol* 2013; **12:** 244–52.

Royal College of Obstetrician and Gynaecology Green Top Guidelines No.68 epilepsy in pregnancy, June 2016.

Thangaratinam S, Marlin N, Newton S, et al. AntiEpileptic drug Monitoring in PREgnancy (EMPiRE): a double-blind randomised trial on effectiveness and acceptability of monitoring strategies. *Health Technol Assess* 2018; **22**.

Vossler DG. Comparative risk of major congenital malformations with 8 different antiepileptic drugs: a prospective cohort study of the EURAP registry. *Epilepsy Curr* 2019; **19:** 83–5.

Vukusic S, Hutchinson M, Hours M, Moreau T, Cortinovis-Tourniaire P, Adeleine P. Confavreux C, and the Pregnancy in Multiple Sclerosis Group. Pregnancy and multiple sclerosis (the PRIMS study): clinical predictors of post-partum relapse. *Brain* 2004; **127:** 1353–60.

Practice points

- A thorough history and physical examination of the patient should be performed, and specialist advice sought early when looking after pregnant women with neurological disease
- Women should be managed by a multidisciplinary team, ideally including a neurologist with expertise in pregnancy or an obstetric physician, specialist nurse or midwife, maternal medicine obstetrician and an obstetric anaesthetist.
- The risks and benefits of continuing medication in pregnancy need to be discussed with the patient and an informed decision made.