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Neurological disorders in pregnancy

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INTRODUCTION

Neurological disorders are a significant cause of morbidity and mortality in pregnancy. In the UK between 2003 and 2005, women with neurological conditions accounted for 37 out of a total 87 'indirect' maternal deaths (those not arising from pregnancy or birth), with stroke ($n = 24$) and epilepsy ($n = 11$)¹ accounting for the majority of deaths from neurological causes².

Neurological assessment can distinguish between neurological symptoms that are common in pregnancy (such as dizziness, pain and urinary frequency) and those that might indicate a more significant disorder. Neurological conditions can arise from 'organic' disorders, which are usually associated with clear-cut abnormalities with neurological investigations, but may also result from less well understood 'functional' problems, typically causing pain, fatigue or even alteration in levels of consciousness. All neurological conditions may present both medical and obstetric challenges to clinicians unfamiliar with their management within the context of pregnancy.

Fortunately, the natural history of key neurological conditions has been observed during pregnancy, providing a useful basis on which to counsel women and organize services. Less information is available about the safety of neurological treatments or investigations during pregnancy or obstetric and neonatal outcomes for these women. Therefore, many decisions rely on applying key obstetric and

neurological principles to situations where published data are not available.

This chapter outlines neurological assessment and investigation in pregnancy before considering the most common and important neurological presentations – multiple sclerosis, stroke, epilepsy and pain. These conditions arise from different pathologies, but their management allows the basic principles of management of other neurological conditions to be described. Overall women with pre-existing neurological conditions, or women who present with neurological symptoms during pregnancy rely on good communication between their obstetrician, neurologist, physician, neonatologist and anesthetist to achieve optimal obstetric and neonatal outcomes.

NEUROLOGICAL ASSESSMENT (CLINICAL EXAMINATION AND INVESTIGATIONS)

Neurological assessment in pregnancy is undertaken in the usual way with clinical history and examination guiding use of investigations.

Even when a number of neurological symptoms may be attributed to pregnancy, as when considering neurological symptoms in the non-pregnant woman, much can be established by careful emphasis on the onset, progression and associated features.

Neurological examination should consider higher mental function, cranial nerves and

neurological assessment of the trunk and limbs. In later pregnancy, small mechanical changes in gait and ability to participate in tests of hip power may be noted, but, in general, changes in the key markers of tone, power, co-ordination, sensation or reflexes should not be attributed to pregnancy itself. Similarly, inspection should not reveal any changes in muscle bulk or symmetry.

Neurological investigation may cause more concern in pregnancy, although in most cases anxieties are unfounded and tests may be undertaken as in the non-pregnant woman.

For example, neurophysiologic assessment such as electroencephalography (EEG), nerve conduction studies and electromyography (EMG) may be uncomfortable but are non-invasive and safe.

Cerebrospinal fluid is obtained by the standard method of lumbar puncture, although access may be difficult in later pregnancy and should be undertaken by suitably skilled practitioners. Spinal fluid can show evidence of a wide range of central nervous system disorders including infection, inflammation, demyelination or, with cytological analysis, presence of neoplasia. Lumbar puncture is relatively invasive and standard relative and absolute contraindications should be considered. In particular, consideration of any coagulation disorders should be made, and lumbar puncture should not be undertaken in suspected raised intracranial pressure, as brain stem herniation may occur. If there is any doubt, clotting studies and neuroimaging should precede this investigation.

Neuroimaging is often an integral part of patient assessment. The ionizing radiation associated with computerized tomography (CT) neuroimaging leads to obvious concern on the parts of both clinicians and patients when imaging the pregnant woman. Nevertheless, CT of the head involves a fetal radiation dose exposure of less than 0.0005 rad and the impact of fetal exposure is likely to be small³.

Uterine shields are routinely employed and reduce fetal exposure further. In some cases the advantages that CT imaging of the head offers – it can usually be obtained promptly and interpreted with ease – particularly when cerebral hemorrhage is suspected – may outweigh any putative risk of exposure to ionizing radiation to mother and fetus.

Nevertheless, in most cases magnetic resonance imaging (MRI) offers greater resolution and extent than CT and therefore is likely to be more clinically valuable. It does not involve ionizing radiation and thus avoids any issues related to fetal radiation exposure in pregnancy. However, although there is no evidence of fetal harm in humans after 20 years of widespread use of this technology many guidelines recommend that, when possible, MRI be delayed until the end of the first trimester and particularly when high-field (3 Tesla) magnets are proposed. However, even in the first trimester, the advantages may on occasion outweigh any theoretical risks.

It should be noted that in contrast to CT, which may be acquired in a few minutes, MR images are significantly more time-consuming to obtain. Depending on the technology being used, MR scanning of more than two areas of the neuroaxis (for example, head and cervical spine) may take in excess of 60 minutes. This may not be appropriate when an individual's condition is unstable, or the woman is confused.

In later pregnancy, even with shorter duration MRI, women may have difficulty lying supine as compression of the inferior vena cava by the gravid uterus impairs venous return, leading to hypotension and ultimately fetal hypoxia. MR radiographers will be familiar with methods by which this can be overcome, such as use of a lateral wedge or tilt. The size of a heavily pregnant woman may occasionally preclude the use of some CT or MRI scanners and claustrophobia may be more of an issue than usual.

Iodinated contrast agents can be used in pregnancy and lactation but the intravenous contrast agents used in MR (e.g. gadolinium) should not⁴.

Certain clinical situations may indicate the use of other ionizing radiological techniques such as digital subtraction angiography – typically used to visualize the intracranial cerebral vessels or spinal vessels in suspected vascular malformations such as aneurysms or arteriovenous malformations. The expected radiation dose depends on the procedure. For example, this may be low with head imaging, but higher for spinal procedures. Clinicians should balance the risks of not fully investigating a patient against potential harm to the fetus.

NEUROLOGICAL CONDITIONS: EPIDEMIOLOGY AND DEMOGRAPHY

In many cases, women with neurological disorders are aware of their condition before conception. But neurological illness may change or even present for the first time during pregnancy, presenting a very wide range of clinical and obstetric challenges to those involved in their care.

Nevertheless, it is self-evident that the majority of neurological conditions seen by obstetric services reflect those disorders that typically present among women of childbearing age. Thus obstetric-neurology clinics or other forms of neurology-obstetric liaison services will be dominated by the four disparate conditions of multiple sclerosis, stroke, epilepsy and pain syndromes – typically headache. Consequently, this chapter focuses on these four disorders. Nevertheless, the descriptions of the neurological impairments that arise in these conditions and their management can be applied to other rarer conditions. It is very unusual for women with neurodegenerative conditions such as Parkinson's disease or dementia to be pregnant, and these disorders are mentioned only in passing.

MULTIPLE SCLEROSIS

Definition and incidence

Multiple sclerosis (MS) is a disease of the central nervous system (brain and spinal cord) that is characterized by both neuroinflammation and neurodegeneration. Incidence is 3.6 cases per 100,000 person years (95% CI 3.0–4.2) in women and is higher in northern latitudes, although this trend seems to be reducing⁵. The disease can have many clinical manifestations (with sensory loss in the limbs, visual loss, subacute motor loss, double vision and gait disturbance being most common) and a highly variable pace of progression (relapsing remitting, secondary progressive, primary progressive and progressive relapsing). The median survival from onset of symptoms is 38 years. MS is usually diagnosed between 20 and 50 years old, and so women with MS will therefore become pregnant relatively early in the course of their illness and usually have correspondingly little associated disability. Nevertheless the issues of symptom management and counseling are relevant at all stages throughout pregnancy.

Preconception

Preconceptional counseling offers the opportunity to discuss the potential effect that pregnancy may have on MS, the effect that MS-related neurological impairment may have on pregnancy and delivery, and the use of disease modifying or symptomatic treatments in both pregnancy and postpartum.

Many people with relapsing and remitting MS are treated with disease modifying drugs (DMDs). These include beta-interferons and a synthetic polypeptide, glatiramer acetate. These treatments are administered by subcutaneous or intramuscular injection at least twice weekly and have been shown to have a modest but significant effect on reducing

relapse rate (approximately 30% per year) and to some extent long-term disability.

The safety of these treatments in pregnancy has not been established. The US Food and Drug Administration (FDA) have assigned glatiramer acetate to pregnancy safety category B (i.e. appears to be safe for pregnancy in animal studies but not adequately studied in pregnant humans)⁶. It has not been shown to be a teratogen in animal studies and its large molecular weight (4700–11,000) suggests that if it crosses the placenta, it does not do so by simple diffusion. The interferons are US FDA pregnancy safety category C (i.e. human studies are lacking and animal studies are either positive for fetal risk or lacking as well). In high doses, interferons appear to be abortifacients, but not teratogens.

Current advice is that in most cases women should stop treatment with DMDs if they are planning to become pregnant – or find themselves unexpectedly pregnant. Although stopping treatment may expose the pregnant woman to increased risk of relapse, in absolute terms the risk is relatively low (an ‘extra’ 0.2 relapse/year)⁷. This risk is further modified by the beneficial effect of pregnancy itself (see below). It should be noted that some experts would offer women with MS the option of continuing agents for which there are limited reassuring pregnancy data, such as glatiramer acetate.

Women with MS may also be taking other drugs, such as antimuscarinics for bladder disorders (e.g. oxybutinin), antispasmodics (e.g. baclofen or diazepam) and antidepressants (e.g. tricyclic antidepressants). Antimuscarinics, benzodiazepines or tricyclic antidepressants have low teratogenic potential.

Rarely, patients with MS or other conditions that cause spasticity have implantable devices delivering an antispasmodic agent, typically baclofen, intrathecally. These pumps are sited extraperitoneally within the abdominal wall. Although the local infusion of baclofen intrathecally presents a significant theoretical advantage in terms of significantly reduced serum levels (and therefore transplacental

transfer) of drug compared with oral treatment, there are practical concerns regarding ‘kinking’ and blockage of treatment catheters. Nevertheless, case reports have reported successful obstetric outcome⁸.

Genetics of multiple sclerosis

The inheritance of MS is poorly understood and is likely to involve a complex interaction between genetic and environmental factors. Nevertheless, in general, the child of a mother with MS has an approximately 2–3% chance of developing MS, compared with 0.1% prevalence in the general population⁹, although the mother should be counseled that should MS occur, symptoms are unlikely to present until the third decade or later. The risk is increased further if both parents are affected.

Effect of pregnancy on relapse rate

Women with MS who are considering pregnancy will seek to establish whether pregnancy will affect the number of relapses they suffer and the overall course of their condition. In the past, the relatively high number of relapses observed postpartum led to the false conclusion that pregnancy might lead to a long-term poorer outcome when compared with non-pregnant women who have not been pregnant. More reassuring evidence has been obtained from a large, prospective study (‘PRegnancy In MS’/PRIMS), which has continued to monitor enrolled mothers many years after enrolment into the study¹⁰. This study showed that, although risk of relapse postpartum was increased by a factor of two for approximately 3 months’ postpartum, this was equally balanced by the observation of significantly fewer relapses during pregnancy. Thus, overall no difference is observed in the long-term number of relapses and disability of women who become pregnant.

Relapse management

Although the risk of relapse is reduced during pregnancy, this ‘protective’ effect is less pronounced during the first and second trimesters. Should relapse occur, management is the same as for non-pregnant women. Mild relapses require no treatment, but are likely to warrant assessment by occupational or physiotherapists – as levels of disability may be increased for several weeks. High-dose corticosteroids (for example a total of 1 g of methyl-prednisolone administered intravenously or orally for 3–5 days) may be used to speed up remission. Steroids present well known risks including reduced bone density, infection, mood alteration and adverse gastrointestinal effects. Nevertheless, where standard precautions and pretreatment assessment are applied, steroids may avoid the need for hospitalization or reduce considerably the length of stay.

Occasionally, relapses are severe and progressive. In the non-pregnant woman these may be managed with more aggressive treatment, such as mitoxantrone (a chemotherapeutic agent) or natalizumab (a monoclonal antibody, which reduces white cell traffic into the CNS). These treatments are either clearly teratogenic and embryotoxic or have no evidence to support their safety in pregnancy. Their use should consider the advantages and risks to both mother and fetus on a case-by-case basis, taking into account the mother’s condition and the gestation. Intravenous immunoglobulin (IVIG)¹¹ or possibly hemodialysis may pose less risk to the fetus, but there is less evidence to support their efficacy in reducing MS progression.

Management of other symptoms

Women with MS may suffer from a range of symptoms during pregnancy including fatigue, restless lower limbs and urinary symptoms.

Non-pharmacological advice to improve quality of sleep (‘sleep hygiene’) should be offered. These include examination of an individual’s sleep routine and the sleeping environment. Women should be encouraged to avoid psychologically stimulating activities in the evenings and intake of pharmacological stimulants such as caffeine should be minimized. Drug treatments such as amantadine or modafanil, which are sometimes used to reduce MS-related fatigue, cannot be recommended, as there is no evidence to support their safety in pregnancy.

A sense of restlessness in the lower limbs is common in pregnant women, but women with MS may also have a degree of spasticity manifest as painful or irritating spasm. Neurological examination can be useful to demonstrate spasticity and localize relevant muscle groups. Physiotherapy advice and possibly use of benzodiazepines, which are regarded to be relatively safe in pregnancy may be warranted.

Urinary symptoms should be carefully evaluated as impaired bladder emptying in women with MS predisposes to infection. Baclofen to treat bladder spasm is a reasonable option in pregnancy. Women with pre-existing urinary problems may be concerned that vaginal delivery will exacerbate urinary symptoms postpartum, and this may be a matter of understandable concern to the individual. In such cases, individualized advice should be given.

Immobility in pregnancy increases the risk of thromboembolism, so there should be a low threshold for the use of thromboprophylactic measures, such as graduated compression stockings or low molecular weight heparin in women with impaired mobility due to MS.

Third trimester and delivery

In most cases, the third trimester and the peripartum period are not different between women with MS and the non-MS population. Specifically, obstetric and neonatal outcomes

do not differ – with similar rates of induction, instrumentation, cesarean section and infant mortality.

Nevertheless, women with MS may have specific neurological impairments that affect interpretation of symptoms during pregnancy. For example, women with plaques at T11 or lower will have impaired bladder and bowel function but normal sensation of uterine contractions and pain. Lesions between T6 and T10 will impair perception of uterine contractions and where significant lesions are present above T6, other signs of labor will have to be considered, such as worsening lower limb spasticity.

Urinary retention can occur during labor or postpartum, particularly when epidural analgesia is used; consideration should be given to the use of an in-dwelling urinary catheter from early in the labor until after delivery (when the woman is mobile and the effects of any epidural have worn off) in women with impaired bladder function. Difficult (and in particular instrumental) vaginal delivery may exacerbate urinary incontinence, and so should be avoided if this is a pre-existing problem.

In the past there have been theoretical concerns expressed regarding the safety of epidural anesthesia, and exacerbation of MS. Evidence from the PRIMIS study, however, has been reassuring, demonstrating no significant difference in outcomes between women with and without epidural anesthesia¹².

Postpartum

Women who are more mildly affected by MS are more likely to choose to breastfeed. Although there are small studies suggesting otherwise, the general consensus is that breastfeeding does not protect against (or cause) a postpartum relapse¹³. Women who have been taking DMDs before pregnancy balance the benefits of breastfeeding against the risk of relapse without treatment. Women who defer DMD

treatment should be counseled that should they suffer relapse, most centers require good recovery before DMD is restarted and so further delay may occur.

A small number of centers have advocated prophylactic use of IVIG postpartum to prevent relapses¹⁴. Activity of disease in the year prepregnancy and in the first trimester to some extent predicts the risk of relapse in the 3 months' postpartum. Nevertheless, a recent authoritative multivariate model predicts that using this information to make a decision about treatment would lead to 50% of women being treated unnecessarily¹³. IVIG is expensive and is derived from pooled human serum, which presents theoretical risks of infection. Thus, the current consensus is not to treat prophylactically.

STROKE

Definition and incidence

Stroke is an acute neurological impairment that follows interruption of blood supply to a specific part of the brain. Blood supply may be interrupted by thrombosis (either arterial or venous) or embolism, or in a smaller proportion of women by hemorrhage. As previously described, it is the main cause of neurological mortality in pregnancy, and represents a significant proportion of all indirect maternal deaths.

Stroke is an uncommon but serious complication of pregnancy. The incidence of stroke in non-pregnant women aged 15–44 years has been reported to be as low as 10.7 per 100,000 woman-years¹⁵. Multicenter or long-term observational studies are therefore required to establish the incidence in pregnancy. Estimates using such methods produce widely differing rates between 4.3 and 210 strokes per 100,000 deliveries depending on inclusion criteria with most studies suggesting an increased risk of stroke associated with pregnancy^{16–18}. Most

(up to 90%) strokes in these studies occurred peripartum and up to a few weeks after the birth.

Risk factors for stroke

Physiological risk factors

Progressive physiological changes occurring throughout pregnancy predispose to stroke including increasing hypercoagulability, venous stasis and vascular wall changes. Pushing in the active phase of the second stage of labor involves episodes of significantly increased intrathoracic pressure (Valsalva) and elevation of cerebral perfusion pressure, which may lead to changes in cerebral blood flow – particularly where cerebral autoregulation or anatomy is disordered¹⁹.

Obstetric risk factors

The main obstetric factor associated with an increased risk of stroke is pre-eclampsia and eclampsia, in particular uncontrolled systolic hypertension. This is still the major cause of death due to pre-eclampsia in the UK¹. Age more than 35 years, black ethnicity, greater parity and multiple gestation are all risk factors for stroke, although quantifying this risk is not possible from available data.

Co-morbidity risk factors

Women who become pregnant may have co-morbidity that increases the risk of vascular events including stroke; such factors include obesity (BMI >30 kg/m²), diabetes, pre-existing hypertension, renal and heart disease, vasculopathies such as sickle cell disease, vasculitis and collagen or atherosclerotic disease. Alcohol, tobacco and cocaine use may cause a vasculopathy or hypertension.

Migraine with aura (see later) also produces excess risk for stroke, but this condition is common and stroke in pregnancy is rare, so caution should be used when counseling women about this risk factor.

Previous stroke during pregnancy presents a particular dilemma for women considering further pregnancy. Unfortunately, few data are available, although in a follow-up study 13 of 489 (2.7%) women aged 15–40 who had suffered a stroke had a recurrent event, but only two of these occurred during pregnancy²⁰. Full ascertainment of vascular risk factors, including CT or MR angiography prior to pregnancy, is appropriate to best inform the individual of her likely risk of pregnancy related recurrent stroke.

Clinical presentation and management of stroke

Presentation and investigation

Stroke presents as in the non-pregnant woman and clinical features may suggest either infarction or hemorrhage, but neuroimaging is required to confirm the diagnosis. The possibility of stroke should be considered in any woman who presents with any of the symptoms listed in Table 1. While in an imperfect screen with a specificity of 88% and a sensitivity varying from 66 to 100%, the Cincinnati Prehospital Stroke Scale may be a useful screening scale to help guide whether an obstetric patient presenting with headache or other softer neurologic complaints warrants prompt complete neurologic assessment and neuroimaging. This screening scale is summarized in Table 2.

If any of the three elements in the scale or any other neurologic findings are newly abnormal, the possibility of acute stroke is high and the patient should have urgent imaging and evaluation by a neurologist.

Table 1 Symptoms that warrant consideration of stroke

Sudden weakness or numbness of face, arm or leg, especially if on one side of the body

Sudden confusion

Trouble speaking or understanding

Sudden trouble seeing in one or both eyes without a prior history of migraines

Sudden trouble walking

Sudden loss of balance or coordination not readily attributable to pregnancy

Sudden severe headache with no known cause

Table 2 Cincinnati Stroke Scale

Three elements

1. Facial droop
 - a. Have the patient smile and assess for facial droop
 - i. Normal: both sides of face move equally
 - ii. Abnormal: one side of face does not move
2. Arm drift
 - a. Have the patient hold both arms out and up with palms facing upwards
 - i. Normal: both arms move equally
 - ii. Abnormal: one arm drifts compared with the other
3. Speech
 - a. Have the patient repeat a sentence
 - i. Normal: patient uses correct words with no slurring
 - ii. Abnormal: slurred or inappropriate words or mute

As stated above, most pregnancy related cerebral infarction occurs around the time of delivery and early puerperium^{16,21,22} at a time when the mother is often bed bound, still hypercoagulable and may just have had pelvic surgery, i.e. cesarean section or instrumental vaginal delivery. Widespread adoption of postpartum thromboprophylaxis use in the UK has been associated with a decrease in the incidence of cerebral infarction due to emboli, but not that due to uncontrolled systolic hypertension¹.

Stroke is a medical emergency. Patients with acute arterial ischemic stroke from embolism or thrombosis can have their long-term outcome greatly improved by the use of thrombolytic therapy within 180 minutes of the

onset of symptoms. Therefore all patients with symptoms suggestive of stroke require prompt neuroimaging to determine whether they have had an ischemic stroke that may benefit from the use of thrombolytic therapy. Table 3 lists the recommended guidelines for timing of interventions for patients presenting with acute ischemic stroke. Table 4 reviews the other assessments recommended for patients presenting with possible acute stroke. Patients should be positioned with the head of the bed lowered between 0 and 15 degrees and, if blood pressure is greater than 180/105 mmHg, it should be treated acutely with intravenous labetalol. Aspirin should not be given while investigating an acute stroke. Table 5 reviews

Table 3 Patients presenting with symptoms of acute stroke to an emergency room should

Be seen by a provider within 10 min with early notification of local 'stroke team' of possible stroke patient
Have a neurologic assessment and head CT performed within 25 min of presentation
Have the head CT scan read with determination of whether they are candidates for fibrinolytic therapy within 45 min of presentation
Receive fibrinolytic therapy within 60 min of presentation to the A&E and no longer than 180 min since the time of onset of symptoms

Table 4 Additional investigations for patients presenting with possible acute stroke

Assess airway (can the patient protect her own airway or does she require intubation), breathing (what is her respiratory rate and oxygenation) and circulation (are her pulse and blood pressure normal)
Obtain secure intravenous access
Obtain a fingerstick glucose measurement
Obtain a full blood count, urea and electrolytes, liver function tests serum glucose, serum troponin
Consider urine toxicology screen and blood alcohol level
Arterial blood gas if oxygen saturation abnormal
Obtain an ECG

the contraindications for thrombolytic therapy. The use of thrombolysis should be considered for pregnant and postpartum women with severe acute cerebral non-hemorrhagic infarction if it can administered within 180 minutes of onset of the neurologic deficit²³. Thrombolysis is well tolerated by the fetus in pregnancy and does not seem to increase the risk of placental abruption, so should not be withheld if the maternal condition is life-threatening. Postpartum, thrombolytic therapy carries a risk of uterine or pelvic hemorrhage. However, this risk decreases with increasing time after delivery and, in most cases, the benefits of thrombolysis will outweigh the risks. Local hemorrhage can usually be dealt with by local hemostatic measures (such as uterine balloon) or surgery. Close liaison between neurologist, obstetrician and physician is essential in such cases.

It is not recommended to use thrombolytics for acute ischemic stroke in the setting of probable or confirmed pre-eclampsia.

Specific syndromes are considered below, but in most cases pregnant women who have cerebral infarction should be managed within a multidisciplinary stroke unit. Low dose aspirin is the mainstay of treatment for acute ischemic stroke. Aspirin and the other antiplatelet agents (aspirin with dipyridamole, or clopidogrel) are also the most effective preventive treatment of stroke. Unfractionated or low-molecular weight heparin is not recommended for acute stroke or stroke prevention except in the case of stroke from cardioembolism, arterial dissection or large artery intraluminal thrombus. Warfarin is teratogenic and usually avoided in pregnancy.

The differential diagnosis of acute stroke in pregnancy is broad and includes migraine, transient ischemic attacks, head trauma, brain tumor, Todd's palsy (a neurologic deficit

Table 5 Contraindications and cautions to thrombolytic therapy for acute stroke

Contraindications

- Intracranial bleed on CT
- Presentation suggests SAH
- Multilobar infarction on CT
- History of intracranial hemorrhage
- Uncontrolled hypertension (>185/110 mmHg when treatment fibrinolytics to be given)
- Known AVM/neoplasm
- Witnessed seizure at onset of stroke
- Active bleeding/acute bleeding diathesis (platelets <100, PTT elevated, INR >1.7)
- Within 3 months of intracranial or intraspinal surgery/serious head trauma or previous stroke
- Arterial puncture at a non-compressible site in the past 7 days

Cautions

- Consider whether benefits of thrombolytic therapy outweigh risks
 - Minor or clearing stroke
 - Within 14 days of major surgery or trauma
 - Within 21 days of GI/GU hemorrhage
 - Within 3 months of acute MI
 - Post MI pericarditis
 - Glucose <50 or >400 mg/dl
-

SAH, subarachnoid hemorrhage; AVM, arteriovenous malformation; PPT, partial prothrombin time; INR, international normalized ratio; GI, gastrointestinal; GU, gastric ulcer; MI, myocardial infarction

following a seizure), systemic infection, functional deficits ('conversion disorders') and toxic metabolic disturbances (e.g. hypoglycemia, acute renal failure, hepatic insufficiency, drug intoxication). Perhaps the most challenging and common differential diagnosis for stroke in the obstetric population is migrainous aura. Migrainous auras are typically brief and more likely to be positive (the alteration of a sensory perception) rather than negative (the absence of a perception), e.g. wavy lines in vision versus no vision or 'pins and needles' versus numbness. Migrainous auras are most commonly visual (typically scotoma and/or

zig-zag lines) or sensory ('pins and needles') in the perioral region. Less commonly, they are sensory in the upper limbs or difficulties with speech (typically disarticulation with word finding difficulty or use of wrong words but no difficulty with comprehension). Neurologic symptoms other than this should not be casually attributed to migrainous aura. Visual or sensory symptoms should be one sided, gradually progress and last between 5 and 60 minutes. If more than one aura symptom is present, symptoms should occur in succession rather than simultaneously. Importantly, migraine and migrainous aura is by definition

a recurring problem and the diagnosis cannot be made on first presentation of symptoms. If there is doubt about whether a patient's symptoms represent stroke/transient ischemic attack or migrainous aura, an evaluation by a neurologist and neuroimaging is advisable.

Specific stroke syndromes and their management

Pre-eclampsia and eclampsia

Presentation Pre-eclampsia is a multisystem disorder affecting 3–5% of pregnancies²⁴. Although only a tiny proportion of those affected by pre-eclampsia suffer from stroke, up to 45% of women who have pregnancy-related stroke have pre-eclampsia or eclampsia^{16,25}. Uncontrolled systolic hypertension and endothelial dysfunction may lead to hemorrhage or infarction²⁶. Disordered cerebral autoregulation may also play a role, especially postpartum.

Investigation and management Investigation and management of pre-eclampsia will be familiar to the obstetrician and is reviewed elsewhere. Most cases of stroke in the setting of pre-eclampsia are due to arterial hemorrhage (when thrombolytic therapy is contraindicated) but cases of acute arterial thrombosis also occur. While pre-eclamptic stroke is most likely in the setting of severe hypertension (>180/110mmHg), it can occur at blood pressures much lower than this and the acute change in blood pressure may be as important a factor as the absolute pressure. The only definitive treatment for pre-eclampsia is delivery of the fetus and placenta. Prompt neuroimaging should occur in pre-eclamptic women with sudden onset (thunderclap) headache and/or any persistent neurologic deficit. Neurosurgical consultation should be urgently sought if intracerebral blood is found on CT or MRI to guide the need for interventions to

decrease intracranial pressure. Blood pressure is typically brought to a level of 160/90mmHg (a mean arterial pressure of 110 mmHg) and not much lower as some degree of hypertension may be needed to maintain cerebral perfusion and prevent ischemia. The presence of an intracerebral bleed will complicate options for obstetric anesthesia and an obstetric anesthesiologist should be involved early in these cases.

Reversible cerebral vasoconstriction syndrome

Presentation Reversible cerebral vasoconstriction syndrome (RCVS) is an underrecognized and often misdiagnosed syndrome characterized by a sudden-onset, severe headache seen in association with a neurologic deficit. It is caused by reversible vascular narrowing involving the circle of Willis and its immediate branches. RCVS can present in conjunction with hypertensive encephalopathy, pre-eclampsia and reversible posterior leukoencephalopathy, physical exertion or bathing and it can occur in isolation²⁷. Women may have had an uncomplicated pregnancy and present a few days after delivery with headache, cerebral irritation and neurological deficit. Investigations demonstrate infarction and/or hemorrhage.

The differential diagnosis includes subarachnoid hemorrhage, migraine, arterial dissection, vasculitis or infection.

Investigation and treatment CT, MR or catheter angiography may demonstrate multifocal segmental narrowing of the cerebral vessels, which resolves within 4–6 weeks. Spinal fluid should be normal, and this distinguishes this syndrome from subarachnoid hemorrhage (SAH).

Treatment is supportive, although vasodilators and steroids have been used.

Intracranial hemorrhage

Presentation Most intracranial hemorrhage occurring during an otherwise normal pregnancy is the result of aneurysmal SAH and arteriovenous malformation (AVM). Intracranial arterial dissection is a much rarer etiology. Hypertension, smoking, alcohol and family history are all risk factors. The incidence of SAH from aneurysmal rupture is 3–11 per 100,000 pregnancies¹⁶, but 50% of all aneurysmal rupture in women below 40 occurs in the context of pregnancy²⁸. Cavernoma and other venous anomalies are a very infrequent cause of hemorrhagic stroke.

Presentation of intracranial hemorrhage is the same as in the non-pregnant woman. Symptoms are dominated by the sudden onset of headache, often described as ‘the worst headache of my life’; this presentation should always prompt consideration of the diagnosis of SAH. Meningeal irritation (due to blood spreading through the cerebrospinal fluid), altered consciousness, collapse or vomiting at onset, and the absence of lateralizing neurologic findings are features that are characteristic of SAH but not universal.

Investigation and management CT scan is very sensitive for SAH in the first 12 hours after the event, but is less sensitive with smaller bleeds and as the days go by after the initial event. Lumbar puncture is recommended in patients with a history suggestive of SAH who have a normal CT scan, especially if more than a day has passed since the onset of their symptoms. The presence of xanthochromia on cerebrospinal fluid is highly suggestive of a SAH but will not be present until 2–6 hours after the acute event.

CT offers advantages compared with MR in ease of obtaining a study and in the past was viewed as better than MRI at identifying early hemorrhage. However, the use of FLAIR and T2 sequences with MRI may be as good or better than CT at identifying an early SAH, and is

better than CT at identifying a SAH in the days following the acute event.

Ruptured aneurysmal SAH may be complicated by rebleeding – with an associated mortality rate of 50–70%²⁹, so monitoring and management of such patients should take high priority. Four per cent of patients will rebleed within 24 hours of the initial bleed, and up to 20% within the first month. Vasospasm, cerebral infarction, hydrocephalus, increased intracranial pressure, seizures and hyponatremia are other possible complications. Medical treatment usually involves intravenous fluids, bed rest, compression stockings, analgesia, laxatives and nimodipine 60 mg 4-hourly³⁰. Medical management of SAH should be undertaken at or in close liaison with a neurosurgical center.

Once the diagnosis is established, the etiology for the SAH must be determined with cerebral angiography, CT angiography or MR angiography. While cerebral angiography remains the most sensitive test, it is rapidly being replaced by CT angiography due to the ease of testing and steadily improving technology. All of these tests can be safely performed in pregnant or postpartum women when necessary (see earlier discussion).

Definitive treatment usually involves endovascular coiling or surgical clipping and the timing of these interventions will be decided by the neurosurgeon. In most cases, treatment of the mother is the primary concern, although near to or during labor, in some cases the baby may be delivered first^{28,31–33}. Outside pregnancy, coiling is felt to produce better overall outcomes than clipping³⁴. In pregnancy, the risks of periprocedure use of radiation, postprocedure anticoagulation and postcoiling rupture in remaining aneurysm tissue are generally outweighed by the benefit of effective treatment. At the time of SAH, women with aneurysms may temporarily lack capacity to consider these issues, but in any case, detailed discussion between the obstetrician,

the neurosurgical team and the family should take place whenever possible.

Women who have had a previous aneurysm completely obliterated by clipping or coiling may consider vaginal delivery³⁵. Use of epidural anesthesia is advised. Some recommend avoidance of spinal anesthesia in women in whom the aneurysm is not totally obliterated³⁶, based on the hypothesis that the decrease in intracranial pressure caused by dural tap could cause an increase in transmural pressure across the arterial wall, thus facilitating rupture of a potential vascular malformation; however, anesthetic input is required as this fall in pressure is likely to be preventable.

Treatment of unruptured aneurysm

In general, management of unruptured aneurysms should be the same as in the non-pregnant state, and guided by ISUIA (the International Study on Unruptured Intracranial Aneurysms)³⁷. Although rupture of aneurysm is associated with significant mortality, treatment of aneurysms also carries risk. ISUIA data suggest that the risk of treating certain low-risk aneurysms (small (<7 mm), asymptomatic, stable, anterior artery aneurysms) may be greater than the risk of conservative 'watching and waiting'. In common with many trials, pregnancy has not been specifically considered. After discussion with the woman, it may be felt appropriate to treat such aneurysms prior to conception or during pregnancy. While there are no data to guide management of women with untreated aneurysms in labor and at delivery, most clinicians would recommend early good pain control, ensuring blood pressure remains less than 140/90 mmHg and limiting the active phase of the second stage of labor. An untreated aneurysm is not, however, viewed as an indication for cesarean delivery.

Unruptured arteriovenous malformation

Presentation Arteriovenous malformations (AVM) are less common than arterial aneurysms but present similarly with acute SAH. Unruptured AVMs present a lower bleeding risk than aneurysms, and the overall risk of primary hemorrhage occurring during pregnancy is 3.5%, which is similar to the normal population³⁸. Individual case reports suggest that pregnancy is not associated with significant changes to AVM³⁹, although the obstetrician or neurologist should emphasize the paucity of data to guide decisions in this area.

Treatment AVMs are treated with combinations of surgery, endovascular embolization and stereotactic radiosurgery. The decision about treatment is guided by a number of factors including the site and complexity of the lesion.

In most cases, AVMs are managed outside pregnancy. Although there is concern that untreated or partially treated AVMs may be at risk of hemorrhage from the hemodynamic changes of labor, the observed risk of hemorrhage is recognized to be low – particularly when epidural analgesia is used and pushing in the second stage is limited, with early resort to instrumental delivery^{40,41}.

Cerebral venous thrombosis

Presentation Cerebral venous thrombosis (CVT) may account for approximately 20% of strokes during pregnancy²² and should be considered in any pregnant woman complaining of headache and drowsiness – particularly if focal neurological signs or seizures are evident. Its occurrence is now increasingly recognized with the more widespread use of MRI; the incidence in pregnancy is estimated at 11.6 per 100,000 deliveries in the US. Thrombosis of cerebral veins or dural sinuses causes injury to tissue through increased venous pressures

and (in the case of dural sinus thrombosis) decreased CSF reabsorption and increased intracranial pressure. The presentation is highly variable and may include headache with or without vomiting, focal deficits, seizures and/or mental status changes. Headache is the most common presentation with gradual onset and often localized.

Investigation and management The presence of papilloedema is not a sensitive or specific sign of CVT and diagnosis relies on neuroimaging, which will demonstrate venous distribution infarction with possible hemorrhage. MRI in combination with MR venography is the best test for diagnosing CVT. CT scans can be normal in up to 30% of cases.

Even when hemorrhage is evident on imaging, CVT is treated by anticoagulation for 6–12 months. During pregnancy, therapeutic doses of low molecular weight heparin may be used, although evidence for its benefit is lacking. Data from non-pregnant patients suggest that 80% have complete recovery and that the rate of recurrence is well below 10%.

Paradoxical embolism

Patent foramen ovale (PFO) is an interatrial communication present in approximately 27% of adults, but in up to 50% of young patients presenting with stroke⁴². This abnormal communication may allow right-to-left shunting of venous emboli directly into the arterial circulation, or provide a focus of thrombus formation. While case-control studies consistently show a relationship between stroke and PFO, prospective data show that a PFO is not associated with an increased risk of first or recurrent stroke. While there is still controversy over this issue, most experts would currently recommend that patients with a single prior stroke, a PFO and no other thrombotic risks should receive only the usual stroke prevention treatments, i.e. antiplatelet agents such

as acetylsalicylic acid (ASA). Patients with a PFO (regardless of whether they have had a stroke) should therefore receive anticoagulation with warfarin or heparin only if they have another indication for anticoagulation. Decisions about the management of patients with recurrent stroke and PFO, or those with a PFO with a single stroke but multiple risk factors for recurrence (thrombophilia, atrial septal aneurysms) should be made in collaboration with a cardiologist, hematologist and (when pregnant or considering pregnancy) a high risk obstetrician and obstetric physician. Options to be discussed include full anticoagulation or surgical closure of the PFO prior to pregnancy but there is currently little evidence to guide management in these situations.

EPILEPSY

All women with epilepsy are likely to have considered the impact their condition and its treatment might have on their ability to have and bring up children. For example, a postal survey of 12,000 female members of Epilepsy Action (a UK patient charity) obtained 2000 responses. The most important issues highlighted by women 19–44 years were risk of epilepsy/medication affecting the unborn child (87%), effect of pregnancy on seizure control (49%), and risk of child developing epilepsy (42%).

Anecdotally, these considerations are also affected by broader social and economic factors. For example, women may weigh the effects of pregnancy and family on their employment in a way that differs from women who do not have epilepsy. As has been described previously, women with epilepsy are over-represented in areas of socioeconomic deprivation, and this may affect choice of partner. Furthermore, women may be concerned about their partner and relationship – feeling they may need to rely more on them than other women.

The history of advice given to women with epilepsy about their ability to have children has reflected a great uncertainty and some prejudice against women with this condition. Anecdotally, older women with epilepsy report being told in no uncertain terms not to conceive by their doctors.

Over the past 40 years, women have not been so actively dissuaded from having children. Nevertheless, ideally, a woman should be informed of the full matrix of consequences arising from the interactions of (1) the epilepsy syndrome; (2) seizures; (3) co-morbidities or other relevant health issues, such as smoking or alcohol consumption; and (4) anti-epileptic drugs (AEDs), and these should be discussed with respect to the obstetric and fetal outcome of pregnancy⁴³.

Fertility

Overall, fertility rates among women with epilepsy are slightly lower than the general population. A number of epilepsy and non-epilepsy related explanations for this observation have been offered.

1. Women with epilepsy may find it difficult to establish or maintain relationships with men and therefore not be in a position to consider planned pregnancy. A number of studies demonstrate that such women are less likely to marry or remain in relationships than women without epilepsy⁴⁴.
2. Seizures may have an adverse effect on the menstrual cycle. In one study, over 35% of women with partial seizures of temporal origin had anovulatory cycles when studied over three cycles, compared to 8% of controls. The authors considered that seizures might have a direct effect on the hypothalamic-pituitary axis, independent of drug effects.
3. Certain AEDs have been highlighted to have particular effects on the female reproductive system. Valproate (VPA)

has been associated with polycystic ovary syndrome in a number of species, including humans⁴⁵, although the strength of this association has been contested (see below).

4. Fertility may be reduced because of non-epilepsy related factors. Women may be overweight, smoke or consume too much alcohol – all of which may reduce their ability to conceive.

Thus, female fertility may also be affected by the epileptic syndrome, severity of seizures and other co-morbidities independently of the effects AEDs⁴⁶⁻⁵⁰.

Epilepsy is more prevalent among women of low socioeconomic status (SES), and this may also have an impact on observed fertility rates, although this aspect of care has not been directly investigated. Traditionally, fertility rates among low SES women are higher than among high SES, although pregnancy outcomes are better in the latter group.

Effect of pregnancy on epilepsy

Anecdotally, most women express concern about how becoming pregnant might affect seizure control. Even women who are seizure-free while taking an AED are concerned about the medical implications (injuries, mortality, psychiatric effects) or the social consequences (for example loss of driving licence) of a breakthrough seizure.

The risk that seizure control may deteriorate has been considered in a number of studies, recently summarized in a comprehensive literature review⁵¹. In this review, the percentage of patients with unchanged seizure frequency in these studies ranged from 54 to 80%. The highest rate of unchanged seizure frequency was the 80% reported in AED-compliant patients, documented by serum levels. The rate of seizure decrease ranged from 3 to 24%. The rate of seizure increase ranged from 14 to 32%. Unfortunately, interpretation of these

studies is limited as none included a ‘control’ group of women with epilepsy who were not pregnant: epilepsy is well known to ‘ebb and flow’ with seizure frequency spontaneously changing over periods of months or years.

There are several reasons why women with epilepsy may suffer increased risks of seizures during pregnancy. Specifically, AEDs which have previously controlled epilepsy, may become less effective for a number of reasons:

1. Women may take their treatment less regularly or stop altogether because of first trimester nausea, or fear of the potential risks from AEDs to the fetus⁵². As is always the case with non-adherence, this may not be reported at the time to the physician.
2. Particularly in the later stages of pregnancy, women may be more sleep deprived, which can trigger seizures in susceptible individuals even when AEDs are taken.
3. Drug metabolism and drug effects are different in pregnancy. The state of pregnancy induces significant changes in protein binding of hormones and exogenous compounds such as AEDs – leading to a fall in ‘free’ drug concentrations – particularly in the final trimester. Additional pharmacokinetic changes in drug clearance may result in reduction in available drug. Certain AEDs, such as lamotrigine (LTG) are particularly prone to this effect⁵³.

Delivery is a time of particular concern. Seizures occurring around the time of delivery can result in both maternal and fetal harm⁵⁴ compounding the hemodynamic and physical stresses associated with labor. It is commonly quoted that for 2–4% of women with epilepsy, delivery will be associated with seizures during labor or in the following 24 hours, although the evidence for this statement is approximately 20 years old⁵⁵ and may reflect previous obstetric practice with respect to women with epilepsy.

Effect of seizures occurring during pregnancy

Women with epilepsy are familiar with the effect that seizures may have on their own person. They are typically aware but less certain about the effects seizures may have on the developing fetus.

There has been a longstanding awareness that tonic–clonic seizures may cause abnormalities in fetal heart rate^{56,57}. Higher miscarriage rates have been observed, but have also been associated with there being family history of epilepsy, particularly either parent having epilepsy⁵⁸. The published data include case reports where pregnant women have suffered seizures while the fetal heart rate has been monitored, and fetal distress was documented⁵⁴. Nevertheless, population studies to inform clinicians and patients about the relationship between seizures and adverse fetal outcomes are less clear.

It is the generally held view that the occurrence of generalized tonic–clonic seizures during pregnancy may harm the fetus; although the absolute risk is low, it is likely to depend on the frequency and severity of seizures. There is insufficient evidence to quantify this risk. Partial seizures (simple or complex), absence seizures, or myoclonus are not harmful to the fetus⁴³.

Nevertheless, a more recently published prospective study of cognitive function in children exposed to AEDs *in utero* reported that the type of seizure (focal or generalized) or occurrence of more than five convulsive seizures during pregnancy was not significant within a regression model⁵⁹. This finding contrasts with previous data⁶⁰ and its significance is further limited because in common with all previous work the study was not statistically ‘powered’ to consider this association, indeed the proportion of patients with poorly controlled epilepsy was small: only eight pregnancies of 303 mothers were exposed to more than eight convulsive seizures.

The effects that might be induced by prolonged seizures are also not well documented. For example, early reports suggested prolonged seizures in the form of status epilepticus may result in significant fetal (and maternal) mortality rates. Status epilepticus is defined as a seizure persisting for more than 30 minutes. An early report by Teramo *et al.*⁵⁴ documented 29 cases from the literature of which nine of the mothers and 14 fetuses died.

More recently, the EURAP study⁶¹ reported that seizure frequency presented a low risk of adverse pregnancy outcomes such as spontaneous abortions, stillbirth and perinatal deaths. Of 36 cases of status epilepticus (12 convulsive) there was one stillbirth but no cases of miscarriage or maternal mortality. Although they reflect the findings of a large and respected pregnancy registry, these findings provide only limited guidance to neurologists and women with epilepsy: status epilepticus is usually associated with significant metabolic and hemodynamic compromise, and risk of death is high. For example, a large North American epidemiological study demonstrated overall mortality rates associated with status epilepticus were 22%⁶² – similar to results obtained from other studies over many years. In contrast the EURAP study recorded a mortality rate of 0%, which suggests that the episodes of status epilepticus recorded in the EURAP study differed significantly from those considered in previous studies. It must be assumed that the cases of status epilepticus in EURAP were somehow milder, or differed in definition from other studies.

Overall, one of the key issues that doctors and women with epilepsy struggle with is the need to balance control of seizure frequency and severity with the potential adverse effects of AEDs during pregnancy. In particular, women on high doses of AEDs, on non-first line AEDs and/or polytherapy are generally those with the most severe or enduring epilepsy. VPA presents a particular challenge for clinicians and women with epilepsy. VPA is

a first-choice treatment for many idiopathic generalized epilepsies, which may relapse if treatment is changed or stopped. The failure of the reported studies to account adequately for the effect of seizure frequency and severity on pregnancy outcome makes counseling individual patients particularly difficult.

In general, however, the main aim for women with epilepsy in pregnancy is to remain seizure free, and they are therefore advised to continue AEDs during pregnancy to avoid seizures. Exceptions occur if the risk of seizures is very low, the seizures can be avoided in some other way or the seizures are mild (i.e. non-convulsive seizures)⁴³. This decision making is summarized below.

Significance of epilepsy type in pregnancy

Some epilepsies are associated with underlying conditions that have a strong genetic predisposition. In these cases, women will need to be given genetic counseling about the likelihood that their children may suffer epilepsy, or the condition that may underlie the woman's epileptic condition.

For example, women whose epilepsy is caused by Mendelian genetic conditions, such as subependymal heterotopia, neurofibromatosis or tuberous sclerosis will need to be aware that these disorders may have up to a 50% chance of being expressed in any child.

Women with learning disabilities for whom the underlying diagnosis is not clear – and whose neurological problems are likely to be due to a combination of the effects of several genes and environment – are more difficult to counsel. Nevertheless, maternal IQ and home social environment are the strongest predictors of a child's IQ⁶³: maternal learning difficulties are likely to adversely affect child neurodevelopment in both respects.

Women with idiopathic generalized epilepsies, particularly absence epilepsies and juvenile myoclonic epilepsy are told that the

likelihood of their children developing a similar disorder is in the order of 5–20%. It is not normal practice to counsel women about the subtle cognitive abnormalities that have been noted in some neuropsychometric studies of women with these conditions – as too little is known about the magnitude of these effects.

Effect of co-morbidities and other health-related issues on pregnancy outcome

Women with epilepsy who are pregnant or who are planning pregnancy may present with non-epilepsy related factors that may affect pregnancy outcome.

Many of the co-morbidities frequently seen in people with epilepsy (such as mental health disorders, learning difficulties and osteopenia) and their treatments may be relevant in terms of predicting or counseling about pregnancy outcome. For example, some antidepressants or antipsychotics may have established teratogenic potential.

Women may also present with specific obstetric risk factors (such as history of premature labor, spina bifida or occurrence of other birth defects), which may modify advice given in relation to epilepsy and AEDs.

Low SES is a further risk factor that is known to be associated with poor pregnancy outcomes. As has been described, women with epilepsy frequently come from low SES households (i.e. partners may be of low SES) or neighborhoods. Low SES is known to be associated with adverse obstetric and fetal outcomes including low birth weight, perinatal, neonatal and postnatal mortality, and also of non-chromosomal congenital malformations^{64–66}.

Furthermore, low SES and poor early household environment are also associated with poor early neurodevelopment. This issue is relevant when considering the teratogenic effects of drugs used during pregnancy. For example, children exposed to cocaine *in utero* were assessed and consideration given to

whether they had been placed in foster care or remained with parents. Children placed in foster care were likely to have been exposed to higher doses of cocaine. But postnatal neurodevelopment among the fostered group was superior (although not equivalent to ‘normal’) highlighting the importance of the early environment.

Certain behaviors such as alcohol consumption and smoking are well known to be detrimental to pregnancy outcome⁶⁷. Folic acid should be taken⁶⁸, although whether it protects the fetus from neural tube defects in epilepsy is less clear.

The above non-epilepsy related factors can have a significant effect on the outcome of a pregnancy. It is important that those interpreting the research data and guidelines, and counseling women with epilepsy about pregnancy are aware that non-epilepsy related factors may modify risks presented to women in this context. The extent to which this is the case in neurology (and obstetric) practice in the UK is not certain.

Effect of anti-epileptic drugs on pregnancy outcome

Without epilepsy, and without AEDs, on average women face an overall risk of approximately 2% of bearing a child with a major congenital malformation (MCM). Furthermore, it is estimated that 3.6% of children at school age will be identified as having a primary special educational need associated with learning difficulties. A higher proportion, in the region of 20%, will require some form of learning support at school.

The possibility that AEDs may adversely affect the development of the fetus to increase the risk of congenital malformations has been recognized for many years in a range of studies, published since before the 1970s⁶⁹. In particular, a number of pregnancy registries in North America, Europe, UK and Australia have

been set up to monitor pregnancy outcomes in women taking AEDs⁷⁰⁻⁷³ and one company register was set up to monitor LTG only⁷⁴. These registries are described in the report of Morrow⁷¹. These registries share in common the fact that only first trimester exposures are considered, and that the greatest focus is on the presence of MCMs. Meta-analysis of their findings suggests that the risk of MCM is increased approximately three-fold⁷⁵. In particular women taking two or more drugs ('polytherapy') have more than a 10% chance of having a child with a congenital malformation.

It has been this range of studies, combined with the warnings about potential teratogenicity from the manufacturer, and latterly data from the registry studies that has led clinicians to warn patients about potential teratogenic effects and, where possible, to restrict the dose of AED treatment to a single agent, and, if possible, to review dose or consider withdrawal. This strategy depends significantly on the patient's condition. For example, many of the idiopathic epilepsies – and particularly juvenile myoclonic epilepsy – are likely to relapse if the dose is reduced too much or treatment is stopped. Importantly, it is also these epilepsies that best respond to VPA.

Over the past 15 years, new AEDs have become available to treat different types of epilepsy. With greater choice of AEDs, there has been corresponding interest in the differential effects individual AEDs may have on fetal development, in terms of rates of both congenital malformations and neurodevelopment. It is hoped that women who may become pregnant can be commenced on, or switched to, AEDs with potentially less teratogenic effects.

Data have been derived from animal studies⁷⁶, from a range of case reports, retrospective observational studies and prospectively collected from women with epilepsy. Over many years, many AEDs have been implicated in causing additional MCM and neurodevelopmental delay – for example phenytoin^{77,78}, phenobarbital and carbamazepine (CBZ)⁷⁹.

But over the past 5 years, there has been increasing emphasis on the possible differential effect of VPA.

The pregnancy registries, together with other published series, also imply a differential effect of AEDs on fetal outcomes. This has intuitive appeal, as although AEDs all have in common a capacity to suppress or prevent seizures, they are often very different chemical entities. In all the registry studies, consistently higher rates of congenital malformations are seen with VPA compared with CBZ or LTG^{70-73,80}. The data provided do not indicate any particular pattern of malformations, with the exception of neural tube defects being more strongly associated with VPA, an association which has long been suspected^{81,82}.

There are many difficulties with the interpretation of these data and their application to clinical practice. The most commonly cited problem is 'indication' bias and the possibility that outcomes measured by the epilepsy registries, or even prospective cohorts may be confounded by factors including co-morbidities, parental (including paternal) genetic and mental health, and socioeconomic status.

Three specific areas of concern about indication bias have been expressed. First, women treated with VPA differ in terms of the underlying epileptic condition. Until recently, VPA was first choice treatment for women with idiopathic generalized epilepsy, as it was perceived to be more effective, whereas partial onset epilepsies (with or without secondary generalization) were treated with CBZ (or latterly LTG). Idiopathic generalized epilepsies have a strong genetic propensity, and concerns have been expressed that any increased rate of MCM or neurodevelopmental delay may reflect the underlying condition rather than a specific teratogenic effect.

Second, there is clear evidence that use of VPA has fallen significantly since concerns have been raised about its teratogenicity. Publications and guidelines now routinely highlight VPA as having poorer fetal outcomes,

and practice has been observed to change⁸³. These trends in prescribing have also been demonstrated by the pregnancy registries. For example, the Non-Epileptic Attack Disorder (NEAD) registry reported that whereas in 1999, 17% of subjects reported using VPA in the first trimester, by 2008 this proportion had fallen to just 3%. Although no study has investigated the types of patient now treated with VPA, it must strongly be suspected that those who have continued to be treated with VPA over the past 10 years must differ significantly from those who are not. It is likely they have more difficulty to treat epilepsy (with co-morbidities) and do not tolerate or achieve seizure control on alternative drugs. Poorly educated women, with poor access to medical services – who might be expected to have poorer outcome in any case – might remain on VPA through omission to change the AED, although evidence to support this assertion is only anecdotal.

Third, the dose-dependent effect observed for VPA (and some other AEDs) may also in part be due to patients with more severe underlying conditions requiring a greater dose of VPA. Plasma concentrations are not helpful in this regard as serum levels of VPA vary by more than 100% through a 24-hour period and their measurement is of little clinical utility save for the purpose of identifying possible non-compliance with treatment regimens.

Significant confounders, such as co-morbidity, may be relevant.

Obstetric outcomes

Poorly controlled epilepsy is generally held to be associated with poor fetal and obstetric outcomes. For example, an authoritative review stated that women with epilepsy have been observed to have a greater incidence of complications such as eclampsia, preterm delivery, spontaneous abortion and induced labor⁶⁸. In the UK between 2003 and 2005, women with

neurological conditions accounted for 37 out of a total 87 maternal deaths, with epilepsy ($n = 11$)¹ accounting for a significant proportion of these deaths.

These statistics underpin general advice that the obstetric care of women with epilepsy should include close liaison between obstetrician and neurologist.

In common with many other epilepsy outcomes clinicians and patients struggle to extrapolate the observations in published research and of general guidelines to their own specific cases. Many women with epilepsy seek to avoid an over medicalized pregnancy, which they may perceive to be ‘spoilt’ by numerous medical appointments and investigations.

A recent authoritative consensus document^{67,84} reviewed all evidence in this area. The conclusions were vague, and were unable to distinguish between women with mild epilepsy and those who suffered frequent generalized seizures: ‘for WWE [women with epilepsy] who are taking antiepileptic drugs (AEDs), there is probably no substantially increased risk (>2 times expected) of cesarean delivery or late pregnancy bleeding, and probably no moderately increased risk (>1.5 times expected) of premature contractions or premature labor and delivery. There is possibly a substantially increased risk of premature contractions and premature labor and delivery during pregnancy for WWE who smoke...’

Thus in everyday practice, it is recommended that there is good liaison between obstetrician and epilepsy specialist, that care should be taken to optimize AED doses at different stages through the pregnancy, and that delivery should take place in an obstetric unit with facilities for maternal and neonatal resuscitation and treating maternal seizures⁴³. The optimization of AED dose is case specific. Individuals vary in terms of their seizure threshold and metabolism of drugs. The consequence of a seizure for that individual must also be considered. For example, a woman with a history of status epilepticus, or who has been seizure

free for more than 12 months and holds a driving licence, is usually extremely reluctant to reduce drug doses to a level that may compromise seizure threshold.

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