Neurological disease in pregnancy

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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 Confidential Enquiry into Maternal Deaths Report 2006–2008, 36 women died from diseases of the central nervous system, and 11 of these women were deemed to have had major substandard care. In the 2016 MBRRACE-UK, neurological diseases were the second most frequent cause of indirect maternal death. There was a non-statistically significant decrease in rate of death between 2009–2011 and 2012–2014. New guidelines from the Royal College of Obstetrics and Gynaecology on managing epilepsy in pregnancy, the most common neurological problem in pregnancy, should help improve care in these women and reduce mortality.

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 multidisciplinary team including a neurologist, specialist nurse or midwife, maternal medicine obstetrician or obstetric physician and obstetric anaesthetist.

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 child-bearing 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 remains the third most frequent cause of indirect maternal deaths and the risk of death is increased ten-fold in pregnant WWE. The 2014 MBRRACE-UK report (Confidential Enquiry into Maternal Deaths and Morbidity) attributed 14 maternal deaths to epilepsy (between 2009 and 2012). Twelve of these were classified as SUDEP (Sudden unexplained death in epilepsy).

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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 known as 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 (pseudoseizures) can be difficult and should be made when other causes of seizure have been excluded (see Table 1). They often occur in patients with epilepsy.

WWE require specific care throughout their pregnancy. First-edition guidelines have been released by the Royal College of Obstetrician and Gynaecologists (RCOG) 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:

- The impact of AEDs on the fetus and its future neurological development
- The effect of pregnancy on metabolism of AEDs and potential changes in seizure frequency
- The importance of good pre-conception seizure control and pregnancy planning including taking folic acid

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

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Seizures in pregnancy

Other causes of seizure	Potential distinguishing features
Eclampsia	High blood pressure; proteinuria
Thrombotic thrombocytopenic purpura (TTP)	Symptoms that may include fever, low platelets, haemolytic anaemia, thrombosis causing renal and neurological impairment
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

hypoplasia. WWE not exposed to AEDs during pregnancy have a similar incidence of MCM to the background population.

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.

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 best where possible.

Long-term neurodevelopmental outcomes

A study looking at the cognitive function at 6 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. Peri-conceptional 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 6 years of age in children whose mothers took folic acid, compared to those children whose mothers did not. The above data support the need to avoid valproate in pregnancy if possible.

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 of carbamazepine and lamotrigine does not appear to adversely affect neurodevelopment of the children, but this is based on limited evidence. 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. 5 mg folic acid should be commenced 3 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 patient.

Antenatal management

Once pregnancy is confirmed, WWE should book early so they can be referred to an obstetrician or maternal physician. 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

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