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 2006–08, 36 women died from diseases of the central nervous system, and 11 of these women were deemed to have had major substandard care. The overall number of deaths is similar to that of previous years, and the proportion with epilepsy was unchanged. Pre-pregnancy counselling should be offered to patients in order to optimise their condition, as well as to make appropriate changes to medication. A thorough history and physical examination should be performed, and specialist advice sought early when looking after these women in their pregnancies. Women should be managed by a multidisciplinary team, ideally including a neurologist, specialist nurse or midwife, obstetrician with an interest in maternal medicine, obstetric physician and an 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 childbearing age and is the commonest neurological disorder seen in pregnancy. In the latest triennial Confidential Enquiry into Maternal Deaths in the UK in 2006–08, 14 epilepsy related deaths were reported among a total of 261 maternal deaths. Most of the 14 deaths involved women stopping their anti-epileptic medication injudiciously. 11 of the 14 women were thought to have had a sudden explained death in epilepsy (SUDEP). This is the commonest cause of death in patients with epilepsy and epidemiological studies show that it occurs most commonly in those with poorly controlled epilepsy.

Epilepsy is classified according to the clinical type of seizure or specific encephalographic (EEG) features. Broadly, seizures are classified into either partial (where the onset is localised to a focal area of the brain) or generalised. Partial seizures can be simple (unimpaired consciousness), complex (consciousness is impaired) or secondarily generalised. A specific type of partial seizure is temporal lobe epilepsy, which is often associated with an aura, duration of one or more minutes, and confusion after the event. Generalised seizures include absence ('petit mal'), tonic–clonic ('grand mal') and myoclonic seizures.

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. Other causes of seizures in pregnancy include eclampsia, thrombotic thrombocytopenic purpura (TTP), cerebrovascular accident, and cerebral venous or sinus thrombosis, hypoglycaemia and electrolyte imbalances (e.g. hypocalcaemia and hyponatraemia). It is also important to consider the possibility of a non-epileptic attack disorder (pseudoseizures) which can be difficult to distinguish from true seizures, but pointers to a pseudoseizure include closed eyelids with resistance to eye opening, biting the tip (rather than the side) of the tongue or the inside of the cheek, side-to-side head shaking, lack of cyanosis and rapid post-ictal orientation. Pseudoseizures may occur at times in people who also have seizures due to epilepsy.

Anti-epileptic medication

Anti-epileptic drugs (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.

In a recent 15-year prospective observational study looking at the MCM risk of AED monotherapies in pregnancy in UK and Ireland, it was shown 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. Studies are ongoing regarding other AEDs in pregnancy, for example, levetiracetam, but published data on MCM risk are currently limited. Data taken from the North American AED Pregnancy Registry showed that among the 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. This suggests that appropriate counselling should be based on the specific AED combinations.

A recent 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. Periconceptional 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.

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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. A meta-analysis showed that freedom from seizures for 9 months prior to pregnancy is associated with an 84–92% likelihood of remaining seizure-free during pregnancy. Women who have been seizure-free for 2 years prior to pregnancy, may consider discontinuation of their anti-epileptic medication, although this should be a fully informed decision after discussion with a neurologist. Women with juvenile myoclonic epilepsy should not discontinue their medication. The teratogenic risks of AEDs and the risks of impaired fetal cognitive development associated with them should be discussed. The aim is to treat with one AED at the lowest effective dose. 5 mg folic acid should be commenced at least 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. The patient should be cautioned against the abrupt discontinuation of AEDs and the risk of SUDEP.

Antenatal management

Once a pregnancy is confirmed, women should be encouraged to book early so they can be referred to an obstetrician as soon as possible to discuss management in the pregnancy. In addition to first trimester ultrasound screening, a detailed anomaly scan at 18–20 weeks, including fetal echocardiography should be performed.

In most women, pregnancy does not affect the frequency of seizures. In data from the European and International Registry of Antiepileptic Drugs and Pregnancy (EURAP), two-thirds of women with epilepsy on monotherapy remained seizure-free throughout pregnancy. There is no relation to the seizure type or course of epilepsy during previous pregnancies. Possible reasons for seizure deterioration during pregnancy include a lack of drug compliance (due to fears of teratogenesis), decreased drug levels related to vomiting in early pregnancy, lower circulating free drug levels, lack of gastrointestinal absorption of AEDs during labour, and lack of sleep. In data from EURAP, women with epilepsy on lamotrigine monotherapy were less likely to be seizure-free (58.2%) and have more generalised tonic–clonic seizures (21.1%) in pregnancy. Women on carbamazepine, and especially lamotrigine which exhibit little protein binding, may need to increase their doses with advancing pregnancy, as free drug levels tend to fall. Levetiracetam levels also fall during pregnancy but the effect on seizure control is not known. Vitamin K (10–20 mg orally) should be prescribed from 36 weeks gestation to women taking hepatic enzyme-inducing drugs (carbamazepine, phenytoin and phenobarbitone) to increase the Vitamin K-dependent clotting factors in the baby and to reduce the incidence of haemorrhagic disease of the newborn.

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. AEDs should be continued during labour, in rectal or intravenous form if necessary, and an early epidural can be offered in order to limit the risk of precipitating a seizure because of pain and anxiety. In the event of a seizure, which is not self-limiting, facial oxygen and intravenous lorazepam, or rectal or intravenous diazepam should be administered.

Postpartum care

The risk of having a seizure in the first 24 hours post delivery is approximately 1–2% so women should, therefore, not be left unattended during this time. 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 used.

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, it may be gradually decreased again over a few weeks in the puerperium.

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, and 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, the vasodilators, nifedipine and hydralazine, as well as analgesia overuse, as other causes of headache.

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 a 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