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Epilepsy in Pregnancy

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This is the first edition of this guideline, produced by the Royal College of Obstetricians and Gynaecologists (RCOG) and endorsed by the following organisations: Association of British Neurologists, Epilepsy Action, Royal College of General Practitioners, Royal College of Midwives and the Royal College of Physicians.

Executive summary of recommendations

Diagnosis of epilepsy

What aspects of diagnosis are specific to pregnancy and the puerperium, including the definition of seizures for the obstetrician?

The diagnosis of epilepsy and epileptiform seizures should be made by a medical practitioner with expertise in epilepsy, usually a neurologist. ✓

Women with a history of epilepsy who are not considered to have a high risk of unprovoked seizures can be managed as low-risk women in pregnancy. ✓

What is the importance of classifying seizure type and epilepsy syndrome?

Women with epilepsy (WWE), their families and healthcare professionals should be aware of the different types of epilepsy and their presentation to assess the specific risks to the mother and baby. ✓

What other conditions in pregnancy should be considered in the differential diagnosis of epileptic seizures?

In pregnant women presenting with seizures in the second half of pregnancy which cannot be clearly attributed to epilepsy, immediate treatment should follow existing protocols for eclampsia management until a definitive diagnosis is made by a full neurological assessment. ✓

Other cardiac, metabolic and intracranial conditions should be considered in the differential diagnosis. Neuropsychiatric conditions including non-epileptic attack disorder should also be considered. ✓

Prepregnancy counselling and management

What are the risks of congenital malformations in the fetus of pregnant women with epilepsy (WWE) exposed and not exposed to antiepileptic drugs (AEDs)?

WWE who are planning their pregnancy should have a clinician competent in the management of epilepsy take responsibility for sharing decisions around choice and dose of AEDs, based on the risk to the fetus and control of seizures. ✓

WWE should be reassured that most mothers have normal healthy babies and the risk of congenital malformations is low if they are not exposed to AEDs in the periconception period. C

Women should be informed that the risk of congenital abnormalities in the fetus is dependent on the type, number and dose of AEDs. B

What are the long-term neurodevelopmental outcomes of exposure to AEDs and maternal seizure in infants born to WWE?

WWE and their partners need to be informed about the possible adverse impact on long-term neurodevelopment of the newborn following in utero exposure to sodium valproate. C

Based on limited evidence, in utero exposure to carbamazepine and lamotrigine does not appear to adversely affect neurodevelopment of the offspring. There is very little evidence for levetiracetam and phenytoin. Parents should be informed that evidence on long-term outcomes is based on small numbers of children. C

To what extent can congenital abnormalities be minimised in WWE?

All WWE should be advised to take 5 mg/day of folic acid prior to conception and to continue the intake until at least the end of the first trimester to reduce the incidence of major congenital malformation. ✓

Prepregnancy folic acid 5 mg/day may be helpful in reducing the risk of AED-related cognitive deficits. C

The lowest effective dose of the most appropriate AED should be used. B

Exposure to sodium valproate and other AED polytherapy should be minimised by changing the medication prior to conception, as recommended by an epilepsy specialist after a careful evaluation of the potential risks and benefits. ✓

What is the effect of pregnancy on seizures in WWE?

WWE should be informed that two-thirds will not have seizure deterioration in pregnancy. C

Pregnant women who have experienced seizures in the year prior to conception require close monitoring for their epilepsy. D

How should risks be communicated to WWE?

WWE should be provided with verbal and written information on prenatal screening and its implications, the risks of self-discontinuation of AEDs and the effects of seizures and AEDs on the fetus and on the pregnancy, breastfeeding and contraception. ✓

WWE should be informed that the introduction of a few safety precautions may significantly reduce the risk of accidents and minimise anxiety. ✓

Healthcare professionals should acknowledge the concerns of WWE and be aware of the effect of such concerns on their adherence to AEDs. D

Antepartum management

What are the recommended models for antenatal care of WWE and what are the benefits of joint obstetrics and neurology clinics?

Pregnant WWE should have access to regular planned antenatal care with a designated epilepsy care team. ✓

WWE taking AEDs who become unexpectedly pregnant should be able to discuss therapy with an epilepsy specialist on an urgent basis. It is never recommended to stop or change AEDs abruptly without an informed discussion. ✓

All pregnant WWE should be provided with information about the UK Epilepsy and Pregnancy Register and invited to register. ✓

What is the optimum method and timing of screening for detection of fetal abnormalities?

Early pregnancy can be an opportunity to screen for structural abnormalities. The fetal anomaly scan at 18^{+0}–20^{+6} weeks of gestation can identify major cardiac defects in addition to neural tube defects. ✓

All WWE should be offered a detailed ultrasound in line with the National Health Service Fetal Anomaly Screening Programme standards. D

How should women taking AEDs be monitored to avoid worsening of seizures? For WWE taking AEDs, is dose escalation better than expectant management?

Based on current evidence, routine monitoring of serum AED levels in pregnancy is not recommended although individual circumstances may be taken into account. C

What are the adverse effects of AEDs in pregnancy on the mother and how can they be minimised?

Healthcare professionals should be alert to signs of depression, anxiety and any neuropsychiatric symptoms in mothers exposed to AEDs. D

What are the risks of obstetric complications in pregnant WWE, including those taking AEDs?

Healthcare professionals need to be aware of the small but significant increase in obstetric risks to WWE and those exposed to AEDs, and to incorporate this in the counselling of women and the planning of management. B

How should WWE be monitored in pregnancy?

In the antenatal period, WWE should be regularly assessed for the following: risk factors for seizures, such as sleep deprivation and stress; adherence to AEDs; and seizure type and frequency. ✓

If admission is required antenatally, WWE at reasonable risk of seizures should be accommodated in an environment that allows for continuous observation by a carer, partner or nursing staff. ✓

How should the fetus be monitored in pregnancy? What are the effects of AEDs on cardiotocography?

Serial growth scans are required for detection of small-for-gestational-age babies and to plan further management in WWE exposed to AEDs. B

There is no role for routine antepartum fetal surveillance with cardiotocography in WWE taking AEDs. D

What is the role of vitamin K in preventing haemorrhagic disease of the newborn and maternal haemorrhage in WWE taking AEDs?

All babies born to WWE taking enzyme-inducing AEDs should be offered 1 mg of intramuscular vitamin K to prevent haemorrhagic disease of the newborn. ✓

There is insufficient evidence to recommend routine maternal use of oral vitamin K to prevent haemorrhagic disease of the newborn in WWE taking enzyme-inducing AEDs. D

There is insufficient evidence to recommend giving vitamin K to WWE to prevent postpartum haemorrhage. ✓

What is the optimal timing and mode of delivery for WWE based on seizure control?

WWE should be reassured that most will have an uncomplicated labour and delivery. ✓

The diagnosis of epilepsy per se is not an indication for planned caesarean section or induction of labour. D

How should women with non-epileptic attack disorder be counselled in pregnancy and how should their non-epileptic seizures be managed?

Inappropriate medical intervention, including AED administration and iatrogenic early delivery, should be avoided when there is a firm diagnosis of non-epileptic attack disorder. D

Where required, what dose of antenatal corticosteroids should be given to WWE on enzyme-inducing AEDs?

In WWE taking enzyme-inducing AEDs who are at risk of preterm delivery, doubling of the antenatal corticosteroid dose for prophylaxis against respiratory distress syndrome in the newborn is not recommended. D

Intrapartum care

What are the risks and risk factors for seizures in labour in WWE and how can they be minimised?

Pregnant WWE should be counselled that the risk of seizures in labour is low. C

Adequate analgesia and appropriate care in labour should be provided to minimise risk factors for seizures such as insomnia, stress and dehydration. ✓

Long-acting benzodiazepines such as clobazam can be considered if there is a very high risk of seizures in the peripartum period. D

AED intake should be continued during labour. If this cannot be tolerated orally, a parenteral alternative should be administered. ✓

What is the optimum management of epileptic seizures in labour?

Every obstetric unit should have written guidelines on the management of seizures in labour. ✓

Seizures in labour should be terminated as soon as possible to avoid maternal and fetal hypoxia and fetal acidosis. Benzodiazepines are the drugs of choice. D

Continuous fetal monitoring is recommended in women at high risk of a seizure in labour, and following an intrapartum seizure. ✓

What are the recommended methods of analgesia in labour for WWE?

Pain relief in labour should be prioritised in WWE, with options including transcutaneous electrical nerve stimulation (TENS), nitrous oxide and oxygen (Entonox®), and regional analgesia. ✓

Pethidine should be used with caution in WWE for analgesia in labour. Diamorphine should be used in preference to pethidine. D

What are the effects of induction of labour on WWE and do AEDs affect induction agents?

There are no known contraindications to use of any induction agents in WWE taking AEDs. ✓

What is the most suitable place of delivery for WWE?

For WWE at risk of peripartum seizures delivery should be in a consultant-led unit with facilities for one-to-one midwifery care and maternal and neonatal resuscitation. ✓

The decision to use water for analgesia and birth should be made on an individual basis. WWE who are not taking AEDs and who have been seizure free for a significant period may be offered a water birth after discussion with their epilepsy specialist. ✓

Postpartum management

What is the risk of seizure deterioration postpartum and how can this be minimised?

WWE and their caregivers need to be aware that although the overall chance of seizures during and immediately after delivery is low, it is relatively higher than during pregnancy. C

WWE should be advised to continue their AEDs postnatally. ✓

Mothers should be well supported in the postnatal period to ensure that triggers of seizure deterioration such as sleep deprivation, stress and pain are minimised. ✓

Is there a need to modify the dose of AED after delivery?

If the AED dose was increased in pregnancy, it should be reviewed within 10 days of delivery to avoid postpartum toxicity. ✓

What are the effects of AED exposure on the newborn through placental transfer and from breast milk? How should babies of WWE taking AEDs be monitored?

Neonates born to WWE taking AEDs should be monitored for adverse effects associated with AED exposure in utero. C

WWE who are taking AEDs in pregnancy should be encouraged to breastfeed. C

Based on current evidence, mothers should be informed that the risk of adverse cognitive outcomes is not increased in children exposed to AEDs through breast milk. C

What advice should be given regarding safety strategies and care of the baby?

Postpartum safety advice and strategies should be part of the antenatal and postnatal discussions with the mother alongside breastfeeding, seizure deterioration and AED intake. ✓

Postnatal mothers with epilepsy at reasonable risk of seizures should be accommodated in single rooms only when there is provision for continuous observation by a carer, partner or nursing staff. ✓

How should depression be screened for in the postpartum period?

WWE should be screened for depressive disorder in the puerperium. Mothers should be informed about the symptoms and provided with contact details for any assistance. D

Contraception

What contraception can be safely offered to women taking AEDs?

WWE should be offered effective contraception to avoid unplanned pregnancies. ✓

Copper intrauterine devices (IUDs), the levonorgestrel-releasing intrauterine system (LNG-IUS) and medroxyprogesterone acetate injections should be promoted as reliable methods of contraception that are not affected by enzyme-inducing AEDs. D

Women taking enzyme-inducing AEDs (carbamazepine, phenytoin, phenobarbital, primidone, oxcarbazepine, topiramate and eslicarbazepine) should be counselled about the risk of failure with some hormonal contraceptives. C

Women should be counselled that the efficacy of oral contraceptives (combined hormonal contraception, progestogen-only pills), transdermal patches, vaginal ring and progestogen-only implants may be affected if they are taking enzyme-inducing AEDs (e.g. carbamazepine, phenytoin, phenobarbital, primidone, oxcarbazepine and eslicarbazepine). C

All methods of contraception may be offered to women taking non-enzyme-inducing AEDs (e.g. sodium valproate, levetiracetam, gabapentin, vigabatrin, tiagabine and pregabalin). C

WWE taking enzyme-inducing AEDs should be informed that a copper IUD is the preferred choice for emergency contraception. Emergency contraception pills with levonorgestrel and ulipristal acetate are affected by enzyme-inducing AEDs. C

Women taking lamotrigine monotherapy and oestrogen-containing contraceptives should be informed of the potential increase in seizures due to a fall in the levels of lamotrigine. C

What are the preferred contraceptive choices in WWE and what risks need to be conveyed to help them make informed decisions?

The risks of contraceptive failure and the short- and long-term adverse effects of each contraceptive method should be carefully explained to the woman. Effective contraception is extremely important with regard to stabilisation of epilepsy and planning of pregnancy to optimise outcomes. ✓

Other implications

What may affect the driving entitlements of WWE who are pregnant?

WWE should be informed of the effect of changing the dose of AED on seizures and its impact on driving privileges. ✓

What are the implications of disability legislation for WWE and health service providers?

Healthcare providers need to be aware of equality legislation in the UK that protects individuals with a disability from discrimination. ✓

1. Purpose and scope

This guideline summarises the evidence on maternal and fetal outcomes in women with epilepsy (WWE). It provides recommendations on the care of WWE during the prepregnancy, antepartum, intrapartum and postpartum periods. This guideline does not cover the methods of diagnosis of epilepsy, detailed categorisation of seizures or strategies for the management of epilepsy. These are addressed in detail in the national guidelines on epilepsy.[1,2]

2. Introduction and background epidemiology

Epilepsy is one of the most common neurological conditions in pregnancy, with a prevalence of 0.5–1%.[3] An estimated 2500 infants are born to WWE every year in the UK.[4] About one-third of WWE are in the reproductive age group.[5] The risk of death is increased ten-fold in pregnant WWE compared with those without the condition.[3] Fourteen maternal deaths that occurred between 2009 and 2012 were attributed to epilepsy in the 2014 MBRRACE-UK (Confidential Enquiries into Maternal Deaths and Morbidity) report.[6] Twelve of these 14 deaths were classified as SUDEP (sudden unexpected death in epilepsy), with poorly controlled seizures being the main contributory factor. The report highlighted the urgency for developing a multiagency guidance to standardise and improve the care of pregnant WWE.

The risk of major congenital malformation in the fetus is increased in WWE taking antiepileptic drugs (AEDs).[7–13] Exposure to sodium valproate and potentially other AEDs may also have an adverse effect on the neurodevelopment of the newborn in the long term.[14,15] Maternal concerns regarding the effects of AEDs on the baby may lead to discontinuation or reduction in the dose of the AEDs, thereby increasing the woman's risk of seizures and SUDEP. Seizure deterioration and AED exposure in pregnancy have an enormous impact on the life of the mother.

Care of WWE continues to be fragmented. The need for better epilepsy review services, and engagement with WWE during the preconception period and in pregnancy, has been a recurrent focus of Confidential Enquiries into maternal and child health in the UK.[6,16,17] Any service that cares for WWE will need to provide evidence-based information on the risks to the mother and baby and the benefits of appropriate treatment. Such a strategy will empower parents to make the right choices in their care.

3. Identification and assessment of evidence

This guideline was developed in accordance with standard methodology for producing RCOG Green-top Guidelines. MEDLINE, EMBASE and The Cochrane Library were searched from inception until 2015 for relevant randomised trials, cohort studies, registry reports, case series and systematic reviews. The following search terms were included: 'epilepsy', 'pregnancy', 'seizures', 'preconception', 'antenatal', 'intrapartum', 'postnatal', 'antiepileptic drugs', 'complications' and 'fetal.' All relevant Medical

Subject Headings (MeSH) terms and subheadings were included. The search was restricted to humans, and there were no language restrictions.

Where possible, recommendations are based on available evidence. In the absence of published evidence, these have been annotated as 'good practice points'. Further information about the assessment of evidence and the grading of recommendations may be found in Appendix I.

4. Diagnosis of epilepsy

4.1 What aspects of diagnosis are specific to pregnancy and the puerperium, including the definition of seizures for the obstetrician?

The diagnosis of epilepsy and epileptiform seizures should be made by a medical practitioner with expertise in epilepsy, usually a neurologist. ✓

Women with a history of epilepsy who are not considered to have a high risk of unprovoked seizures can be managed as low-risk women in pregnancy. ✓

Health professionals working with WWE should be aware that the epilepsies are a heterogeneous group of brain diseases with the common feature of seizure. A medical practitioner with specialist training in epilepsy, usually a neurologist makes the diagnosis of epilepsy and its categorisation. Any assessment of the condition in pregnancy should include duration and severity, frequency and type of seizures, and impact of epilepsy on the mother such as driving, accidents, family life and employment. A drug history of effective and ineffective medications is relevant, including a history of adverse effects.

Women who have remained seizure-free for at least 10 years (with the last 5 years off AEDs) and those with a childhood epilepsy syndrome who have reached adulthood seizure- and treatment-free are considered no longer to have epilepsy.[18] Evidence level 2–

A medical practitioner with specialist training in epilepsy, usually a neurologist, should also make the decision regarding the resolution of epilepsy on an individual basis. These women can be managed as low-risk individuals in their pregnancy provided that there are no other risk factors.

4.2 What is the importance of classifying seizure type and epilepsy syndrome?

Women with epilepsy (WWE), their families and healthcare professionals should be aware of the different types of epilepsy and their presentation to assess the specific risks to the mother and baby. ✓

The manifestation of epilepsy is highly varied. Classification of the epilepsy syndrome is required to choose the appropriate AED, to determine prognosis in pregnancy and to identify and prevent the factors of seizure deterioration. The most common seizure types reported in pregnancy and their manifestations are detailed in Table 1.

Accurate documentation of the type of seizures and their frequency will help to identify any provoking factors, plan management and allow retrospective audit of epilepsy care. The rates of seizure deterioration in pregnancy may be associated with the type of seizure.[19] Evidence level 2–

Uncontrolled tonic-clonic seizures are the strongest risk factor for SUDEP, which are the main cause of death in pregnant WWE.[20] SUDEP is defined as 'sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicologic or anatomic cause for death.[21] Evidence level 4

Table 1. Clinical presentation of various seizures types and their effects on the mother and baby

Common types of epilepsy/seizures	Clinical presentation	Effects on mother and baby
Tonic-clonic seizures (previously known as grand mal)	Dramatic events with stiffening, then bilateral jerking and a post-seizure state of confusion and sleepiness.	Sudden loss of consciousness with an uncontrolled fall without prior warning. Associated with a variable period of fetal hypoxia.[22] This seizure type is associated with the highest risk of SUDEP.
Absence seizures	Generalised seizures that consist of brief blank spells associated with unresponsiveness, which are followed by rapid recovery.	Effects mediated through brief loss of awareness although physiological effects are modest. Worsening absence seizures place the woman at high risk of tonic-clonic seizures.
Juvenile myoclonic epilepsy	Myoclonic jerks are the key feature of this form of epilepsy and often precede a tonic-clonic convulsion. These jerks present as sudden and unpredictable movements and represent a generalised seizure.	Occurs more frequently after sleep deprivation and in the period soon after waking or when tired. The sudden jerks may lead to falls or to dropping of objects, including the baby.
Focal seizures (previously defined as 'complex partial' if seizures impair consciousness and 'simple partial' if consciousness not impaired)	Symptoms are variable depending on the regions and networks of the brain affected. Within an individual, the attacks are recognisable and stereotypical. Seizures may impair consciousness. Primary focal seizures can undergo secondary generalisation. An aura is a primary focal seizure.	Impairment of consciousness increases risk of injury such as long bone fracture, dental or head injury, electrocution or burns compared with if consciousness is retained (an epileptic aura only). They can be associated with a variable period of hypoxia and risk of SUDEP.

4.3 What other conditions in pregnancy should be considered in the differential diagnosis of epileptic seizures?

In pregnant women presenting with seizures in the second half of pregnancy which cannot be clearly attributed to epilepsy, immediate treatment should follow existing protocols for eclampsia management until a definitive diagnosis is made by a full neurological assessment. ✓

Other cardiac, metabolic and intracranial conditions should be considered in the differential diagnosis. Neuropsychiatric conditions including non-epileptic attack disorder should also be considered. ✓

The National Institute for Health and Care Excellence (NICE) tertiary referral guidance should be followed if there is diagnostic uncertainty or treatment failure.[1] An incorrect diagnosis exposes the mother and the unborn child to unnecessary and potentially harmful drug treatment in addition to a psychosocial burden, such as inappropriate loss of driving privileges or employment restrictions.[23,24] If there is diagnostic uncertainty, women who present with seizures should have the involvement of a neurologist.[25] Evidence level 4

The diagnosis may be dependent on past history of epilepsy or on risk factors for developing pre-eclampsia.[26,27] Evidence level 3

Imaging modalities such as magnetic resonance imaging (MRI) and computerised tomography (CT) scans are considered safe in pregnancy to assess women presenting with seizures.[28,29] The risk to the fetus from a single exposure is minimal.[30]

Evidence level 3

If there is doubt whether the seizure is secondary to epilepsy or eclampsia, magnesium sulfate, which is the drug of choice for the treatment of eclamptic seizures, should be administered until a definitive diagnosis is made.[31]

Evidence level 1+

The other differential diagnoses for seizures in pregnancy include cerebral venous sinus thrombosis, posterior reversible leucoencephalopathy syndrome, space-occupying lesions and reversible cerebral vasoconstriction syndrome. Other conditions, such as syncope associated with cardiac arrhythmia, aortic stenosis, carotid sinus sensitivity, vasovagal syncope and metabolic conditions such as hypoglycaemia, hyponatraemia and Addisonian crisis will need to be ruled out for first presentation of seizures in pregnancy.[32]

Non-epileptic attack disorder, also referred to as psychogenic non-epileptic seizures, dissociative seizures or pseudoseizures, forms an important differential diagnosis in individuals with drug-resistant attacks.[33] Non-epileptic attack disorder may co-exist with epilepsy and pose complex diagnostic and therapeutic challenges that require multidisciplinary management with access to psychological or psychiatric services.

Evidence level 3

5. Prepregnancy counselling and management

5.1 What are the risks of congenital malformations in the fetus of pregnant WWE exposed and not exposed to AEDs?

WWE who are planning their pregnancy should have a clinician competent in the management of epilepsy take responsibility for sharing decisions around choice and dose of AEDs, based on the risk to the fetus and control of seizures.

✓

WWE should be reassured that most mothers have normal healthy babies and the risk of congenital malformations is low if they are not exposed to AEDs in the periconception period.

C

Women should be informed that the risk of congenital abnormalities in the fetus is dependent on the type, number and dose of AEDs.

B

In WWE not exposed to AEDs, the incidence of major congenital malformations is similar to the background risk for the general population.[34] A prospective Finnish population-based study reported a 2.8% (26/939) rate of congenital malformations in the offspring of WWE who were not taking AEDs in the first trimester.[7]

In WWE who are taking AEDs, the risk of major congenital malformation to the fetus is dependent on the type, number and dose of AED. Among AEDs, lamotrigine, and carbamazepine monotherapy at lower doses have the least risk of major congenital malformation in the offspring.[13]

Evidence level 2+

The most common major congenital malformations associated with AEDs are neural tube defects, congenital heart disorders, urinary tract and skeletal abnormalities and cleft palate.[9,11,13] Sodium valproate is associated with neural tube defects, facial cleft and hypospadias; phenobarbital and phenytoin with cardiac malformations; and phenytoin and carbamazepine with cleft palate in the fetus.

Evidence level 2++

Reproductive decision-making in people with epilepsy can be influenced by an overestimation of the risk of inheritance in their offspring.[35] If there are known risk factors for inheritance of epilepsy, or if there is a fear of inheritance, genetic counselling should be offered.[36]

Evidence level 3

A systematic review and meta-analysis of 59 studies provided estimates of incidence of congenital malformation in fetuses born to women taking various AEDs.[11] The risk was highest for women taking sodium valproate (10.7 per 100, 95% CI 8.16–13.29) or AED polytherapy (16.8 per 100, 95% CI 0.51–33.05) compared with the 2.3 per 100 (95% CI 1.46–3.1) observed in mothers without epilepsy.[11]

Evidence level 2++

Data from the EURAP study group[13] suggest that the lowest rates of malformation were observed in women exposed to less than 300 mg per day of lamotrigine (2 per 100, 95% CI 1.19–3.24) and to less than 400 mg per day of carbamazepine (3.4 per 100, 95% CI 1.11–7.71). The rates of major congenital malformation in the UK and Ireland registers[10] were also lower in the levetiracetam monotherapy group (0.7 per 100; 95% CI 0.19–2.51) than the polytherapy group (5.6 per 100, 95% CI 3.54–8.56).[10]

Evidence level 2+

There is insufficient evidence to provide robust estimates of risk of major congenital malformation for other AEDs in monotherapy such as eslicarbazepine, gabapentin, lacosamide, oxcarbazepine, perampanel, pregabalin, topiramate or zonisamide.

The risk of recurrence for major congenital malformation was increased (16.8 per 100) in WWE with a previous child with major congenital malformation.[37] There was no significant association between epilepsy type and tonic-clonic seizures in the first trimester and major congenital malformations.

Evidence level 2+

5.2 What are the long-term neurodevelopmental outcomes of exposure to AEDs and maternal seizure in infants born to WWE?

WWE and their partners need to be informed about the possible adverse impact on long-term neurodevelopment of the newborn following in utero exposure to sodium valproate.

C

Based on limited evidence, in utero exposure to carbamazepine and lamotrigine does not appear to adversely affect neurodevelopment of the offspring. There is very little evidence for levetiracetam and phenytoin. Parents should be informed that evidence on long-term outcomes is based on small numbers of children.

C

A 2014 Cochrane review showed that there were no significant differences in the developmental quotient of children exposed to the AEDs carbamazepine, lamotrigine and phenytoin when compared with infants of mothers without epilepsy or with offspring of mothers with epilepsy not taking AEDs.[38] Children exposed to sodium valproate in utero had a significantly lower developmental quotient when compared with those born to WWE who were not taking AEDs, and to those born to women without epilepsy.[38]

Evidence level 2++

The intelligence quotient (IQ), verbal IQ and performance IQ were lower in children exposed to sodium valproate compared with women without epilepsy and with WWE not taking AEDs.[14,38] Exposure to carbamazepine had no effect on the IQ, verbal IQ or performance IQ of these children compared with the offspring of women without epilepsy or WWE not on medication.[38]

Children exposed to sodium valproate had lower IQ at 6 years of age compared with those exposed to carbamazepine (P = 0.0015), lamotrigine (P = 0.0003) or phenytoin (P = 0.0006).[15] They also performed poorly on measures of verbal and memory abilities compared with children exposed to other AEDs, and had lower nonverbal and executive functions compared with children exposed to lamotrigine (but not carbamazepine or phenytoin).[15] High doses of sodium valproate were negatively associated with verbal ability, IQ, nonverbal ability, memory and executive function and this was not observed with other AEDs.[15]

Evidence level 2++

In utero exposure to sodium valproate is associated with increased rates of childhood autism (adjusted hazard ratio 2.9, 95% CI 1.4–6.0).[39,40]

Evidence level 2+

Very few studies to date have assessed the cognitive abilities of children exposed to levetiracetam, but initial outcomes based on limited numbers have been reassuring.[41,42]

Evidence level 2–

Little is known about other new AEDs or combination therapies and the absence of data should not be taken as an indication of fetal safety.

5.3 To what extent can congenital abnormalities be minimised in WWE?

All WWE should be advised to take 5 mg/day of folic acid prior to conception and to continue the intake until at least the end of the first trimester to reduce the incidence of major congenital malformation. ✓

Prepregnancy folic acid 5 mg/day may be helpful in reducing the risk of AED-related cognitive deficits. C

The lowest effective dose of the most appropriate AED should be used. B

Exposure to sodium valproate and other AED polytherapy should be minimised by changing the medication prior to conception, as recommended by an epilepsy specialist after a careful evaluation of the potential risks and benefits. ✓

Studies evaluating the effects of folic acid supplementation in pregnancy on major congenital malformation have shown varied results.[43,44] Two studies have shown an association between low folate levels[45] or no supplementation[46] and major congenital malformation. A further two studies have failed to show a benefit with folic acid in reducing major congenital malformation.[47,48]

Evidence level 2–

The long-term follow-up of children born to WWE taking lamotrigine, carbamazepine, phenytoin or sodium valproate monotherapies in pregnancy showed that compared with unexposed children (101, 95% CI 98–104), the mean IQs were higher in children exposed to periconceptional folate (108, 95% CI 106–111) (P = 0.0009).[15] Given the potential benefit of folate on long-term cognitive outcomes, the known safety of the supplement and the absence of evidence of its ineffectiveness in preventing major congenital malformation, it is advised that WWE are prescribed high-dose folic acid 5 mg daily from at least 3 months prior to conception to the end of the first trimester.

Evidence level 2+

Women taking sodium valproate or other AED polytherapy should have a detailed discussion with the epilepsy specialist on the risks and benefits of continuing or changing the AED prior to planning pregnancy. Where possible, the aim will be to avoid sodium valproate and AED polytherapy. However, if the risk of maternal seizure deterioration from changing the AED is deemed to be high, women will need to be advised to continue the sodium valproate or AED polytherapy.

5.4 What is the effect of pregnancy on seizures in WWE?

WWE should be informed that two-thirds will not have seizure deterioration in pregnancy. C

Pregnant women who have experienced seizures in the year prior to conception require close monitoring for their epilepsy. D

The majority of women (67%) do not experience a seizure in pregnancy.[19] The seizure-free duration is the most important factor in assessing the risk of seizure deterioration.[49] In women who were seizure free for at least 9 months to 1 year prior to pregnancy, 74–92% continued to be seizure free in pregnancy.[49–51]

Evidence level 2–

The data from the EURAP (International Registry of Antiepileptic Drugs and Pregnancy) study showed that pregnant women with idiopathic generalised epilepsies were more likely to remain seizure free (74%) than those with focal epilepsies (60%).[19] There is insufficient evidence to assess whether the rates of status epilepticus are increased in pregnant WWE compared with nonpregnant women. Status epilepticus is defined as 30 minutes of continual seizure activity or a cluster of seizures without recovery. Currently, there are no tests to predict the risk of seizure deterioration in pregnancy.

Evidence level 2+

5.5 How should risks be communicated to WWE?

WWE should be provided with verbal and written information on prenatal screening and its implications, the risks of self-discontinuation of AEDs and the effects of seizures and AEDs on the fetus and on the pregnancy, breastfeeding and contraception. ✓

WWE should be informed that the introduction of a few safety precautions may significantly reduce the risk of accidents and minimise anxiety. ✓

Healthcare professionals should acknowledge the concerns of WWE and be aware of the effect of such concerns on their adherence to AEDs. D

WWE should be fully aware of the implications of future pregnancy on their epilepsy and the health of their offspring in the short and long term. Any information on prenatal screening for major congenital malformation should highlight the detection rates, limitations of the test performance and the implications, such as termination of pregnancy.

Pregnant WWE tend to overestimate the risks of teratogenicity associated with intake of AEDs in pregnancy. Risk perception is likely to have an effect on adherence to AEDs in pregnancy.[52]

An observational study on pregnant WWE taking levetiracetam or carbamazepine showed that 15% (4/26) of mothers self-discontinued their AED in pregnancy.[53] This rate may be higher for WWE taking sodium valproate due to its high teratogenic potential. The risk–benefit ratio for both mother and baby from seizures and exposure to AEDs should be communicated by providing relevant estimates.

Evidence level 3

Women have concerns regarding the effect of epilepsy and its treatment on motherhood. This includes fear of harming the baby or not being able to fulfil the role of mother to their expectations.[54] Maternal and neonatal death from drowning is a known risk and mothers should be advised to bathe themselves or their children in shallow water and with assistance to minimise this risk.[6]

WWE also feel that there is a lack of understanding among healthcare professionals about epilepsy and the specific issues related to pregnancy. A survey of WWE showed that 87% of women would like to be counselled about the risk of epilepsy and AEDs to their unborn child, and about one-half of them would like a more proactive role in the discussions about treatment decisions.[55]

Evidence level 2–

Both written and oral communications are important to WWE and women consider access to the same care provider to be important.[54]

Evidence level 3

6. Antepartum management

6.1 What are the recommended models for antenatal care of WWE and what are the benefits of joint obstetrics and neurology clinics?

Pregnant WWE should have access to regular planned antenatal care with a designated epilepsy care team. ✓

WWE taking AEDs who become unexpectedly pregnant should be able to discuss therapy with an epilepsy specialist on an urgent basis. It is never recommended to stop or change AEDs abruptly without an informed discussion. ✓

All pregnant WWE should be provided with information about the UK Epilepsy and Pregnancy Register and invited to register. ✓

Confidential Enquiry findings on maternal deaths due to epilepsy have identified the need for collaborative working between obstetricians, midwives and epilepsy specialists in pregnancy.[17] Prompt establishment of pathways between primary care and obstetric units will allow early referral of WWE to a joint clinic.

Evidence level 3

The multidisciplinary setting should involve an obstetrician with a special interest in epilepsy, working alongside a neurologist with specialist training in epilepsy or epilepsy specialist nurses. The team may involve other specialists such as neuropsychiatrists where required. To increase normality where appropriate, it is essential to include a midwife in the care of these women. Other models of care, such as a clinic led by an obstetric physician, or by obstetricians with training in maternal medicine, with input from the midwife and neurology team can also contribute to improved continuity of care.

Such models will need to ensure that they are part of an integrated antenatal care pathway and take into consideration the local resources. Local guidelines and clear mechanisms of communication need to be in place for the care of WWE at all stages of their pregnancy until the postnatal period. There are no studies on the evaluation of clinical effectiveness of joint obstetrics and neurology clinics on maternal and fetal outcomes in WWE.

In women with an unplanned pregnancy, an individualised management plan should be agreed between the woman with epilepsy and the epilepsy specialist. This may include a change in the dose or type of AED aimed at minimising the risk to the fetus. AEDs should not be abruptly stopped or changed without appropriate discussion. Even high-risk drugs like sodium valproate are still the drugs of choice for certain epilepsies and a discussion of risks and benefits is mandatory.

All pregnant women should be invited to join the UK Epilepsy and Pregnancy Register and informed of the anonymity of the data collection and the value of the data for clinical practice and future research.[4]

Evidence level 4

6.2 *What is the optimum method and timing of screening for detection of fetal abnormalities?*

Early pregnancy can be an opportunity to screen for structural abnormalities. The fetal anomaly scan at 18^{+0}–20^{+6} weeks of gestation can identify major cardiac defects in addition to neural tube defects. ✓

All WWE should be offered a detailed ultrasound in line with the National Health Service Fetal Anomaly Screening Programme standards. D

Biochemical screening with maternal serum alphafetoprotein when combined with ultrasonography increases the detection rate for neural tube defects to 94–100%,[56] thereby offering the opportunity to detect these abnormalities in early gestation for WWE.

Evidence level 2–

No studies have assessed the role of routine fetal echocardiography in detecting congenital heart disease in babies of WWE taking AEDs compared with the 20-week detailed scan that is currently offered.

6.3 *How should women taking AEDs be monitored to avoid worsening of seizures? For WWE taking AEDs, is dose escalation better than expectant management?*

Based on current evidence, routine monitoring of serum AED levels in pregnancy is not recommended although individual circumstances may be taken into account. C

The levels of most AEDs are known to fall in pregnancy due to the changes in the pharmacokinetics of absorption, metabolism, haemodilution and excretion in pregnancy.[57–59] The levels of lamotrigine are known to fall by up to 70% in pregnancy.[60]

Evidence level 2–

Some have postulated that falling drug levels may contribute to worsening seizures, leading some clinicians to prophylactically increase lamotrigine dosing during pregnancy. Other clinicians have concerns about the potential harms of increasing drug doses in pregnancy without clear evidence of benefit over risk. Current practice in AED monitoring is either regular therapeutic drug monitoring[61] or monitoring based on clinical features to adjust the AED dose.[1,2] There is no clear evidence to show that therapeutic drug monitoring reduces the risk of seizure deterioration compared with monitoring based on clinical features.

Evidence level 4

The findings of a systematic review on the effectiveness of the above two monitoring methods in pregnant women taking lamotrigine were limited due to the inclusion of poor quality observational studies with small numbers of women.[62] The systematic review included five studies that were heterogeneous in population and intervention. Only one (a case series of 15 patients) of the five studies directly compared the two strategies in WWE taking lamotrigine. Given the paucity of evidence, there is no clear indication to undertake therapeutic drug monitoring in pregnancy routinely. Clinicians will need to take into account other features such as suspicion of non-adherence, toxicity and intractable seizures in their decisions on therapeutic drug monitoring.

Evidence level 2–

6.4 *What are the adverse effects of AEDs in pregnancy on the mother and how can they be minimised?*

Healthcare professionals should be alert to signs of depression, anxiety and any neuropsychiatric symptoms in mothers exposed to AEDs. **D**

Clinicians caring for mothers with epilepsy taking AEDs should be aware of the effects of the drugs, particularly those relating to cognitive and psychiatric problems.[63] WWE should be advised that certain epilepsies as well as particular AEDs carry an increased risk of depression with features such as low mood, inability to plan and organise thoughts, poor concentration, tiredness, irritability or anger.[64] Self-monitoring for these symptoms and early intervention may improve quality of life.

Evidence level 2–

AEDs have the potential to affect maternal cognition, especially where high doses or polytherapy are used. Additional factors such as psychosocial problems, low esteem and fear of having seizures may have a negative impact on cognitive performance.[65] Appropriate and early referral to the perinatal mental health team is required if there are any concerns regarding cognitive functions such as attention and memory in combination with mood disturbance.

6.5 *What are the risks of obstetric complications in pregnant WWE, including those taking AEDs?*

Healthcare professionals need to be aware of the small but significant increase in obstetric risks to WWE and those exposed to AEDs, and to incorporate this in the counselling of women and the planning of management. **B**

A 2015 systematic review[66] identified 38 studies (2 837 325 women) examining pregnancy and reproductive outcomes in relation to epilepsy and pregnancy. In WWE compared with women without epilepsy, the odds of spontaneous miscarriage (OR 1.54, 95% CI 1.02–2.32), antepartum haemorrhage (OR 1.49, 95% CI 1.01–2.20), hypertensive disorders (OR 1.37, 95% CI 1.21–1.55), induction of labour (OR 1.67, 95% CI 1.31–2.11), caesarean section (OR 1.40, 95% CI 1.23–1.58), any preterm delivery (less than 37 weeks; OR 1.16, 95% CI 1.01–1.34), fetal growth restriction (OR 1.26, 95% CI 1.20–1.33) and postpartum haemorrhage (OR 1.29, 95% CI 1.13–1.49) were increased. There were no differences between the two groups in the odds of gestational diabetes or perinatal death.

Compared with WWE not exposed to AEDs,[66] those taking AEDs demonstrated higher odds ratio of induction of labour (OR 1.40, 95% CI 1.05–1.85), fetal growth restriction (OR 3.51, 95% CI 1.23–10.01) and postpartum haemorrhage (OR 1.33, 95% CI 1.16–1.54). The odds of admission to the neonatal intensive care unit were increased in the same group (OR 1.42, 95% CI 1.13–1.78). There were no significant differences between the two groups for hypertensive disorders, caesarean section, spontaneous miscarriage, antepartum haemorrhage, preterm delivery, or fetal death.

Evidence level 2++

In studies that compared WWE receiving monotherapy with those receiving polytherapy,[66] the odds of caesarean section were increased in the polytherapy group (OR 1.47, 95% CI 1.07–2.02). There were no differences in the odds of spontaneous miscarriage, preterm delivery before 36 or 37 weeks of gestation, antepartum haemorrhage or postpartum haemorrhage. The two groups showed no difference in the odds of fetal outcomes such as small-for-gestational-age fetuses, stillbirths or admissions to the neonatal intensive care unit.

6.6 How should WWE be monitored in pregnancy?

In the antenatal period, WWE should be regularly assessed for the following: risk factors for seizures, such as sleep deprivation and stress; adherence to AEDs; and seizure type and frequency. ✓

If admission is required antenatally, WWE at reasonable risk of seizures should be accommodated in an environment that allows for continuous observation by a carer, partner or nursing staff. ✓

At subsequent visits after the booking appointment, the following need to be evaluated: the mother's wellbeing, including ability to cope, memory, concentration and sleep; symptoms such as tiredness and dizziness; the AEDs being taken, including dose and dosing schedule; and seizure frequency and type, including auras.

Early and appropriate discussion with the epilepsy specialist nurse or neurologist is required if there is a deterioration in seizure control. Precipitants of seizures such as fasting, sleep deprivation and stress should be identified and managed accordingly.[67] Specialist advice may include altering drug doses, addition of new drugs or recommending admission to hospital.

Evidence level 4

In WWE with active seizures, advising on care to minimise the period of time they go unobserved should be considered. Individuals with unwitnessed seizures are at high risk of SUDEP, with nocturnal seizures being an independent risk factor.[68] This may include advising WWE who are at reasonable risk of seizures to not to sleep alone at night. Inpatient nursing should be in an environment in which continuous care from a partner or nursing observations takes place.

Evidence level 3

6.7 How should the fetus be monitored in pregnancy? What are the effects of AEDs on cardiotocography?

Serial growth scans are required for detection of small-for-gestational-age babies and to plan further management in WWE exposed to AEDs. B

There is no role for routine antepartum fetal surveillance with cardiotocography in WWE taking AEDs. D

The odds of having a small-for-gestational-age fetus are increased in WWE (OR 1.26, 95% CI 1.20–1.33) compared with those without the condition. The odds are 3.5 times higher in WWE exposed to AEDs (OR 3.51, 95% CI 1.23–10.01) compared with those not taking AEDs.[66] Given the increased risk in WWE exposed to AEDs, serial growth scans should be offered from 28 weeks of gestation for detection of growth restriction.

Evidence level 2++

Fetal heart rate changes such as bradycardia and reduced variability during a seizure have been reported due to possible fetal hypoxia.[22,69,70] A small study comparing the cardiotocography pattern in pregnant WWE taking AEDs did not show any difference in fetal heart rate parameters such as baseline heart rate, number of accelerations or duration of high and low variation episodes.[71] There is therefore no evidence for routine antepartum fetal surveillance with cardiotocography in WWE taking AEDs.

Evidence level 2–

6.8 *What is the role of vitamin K in preventing haemorrhagic disease of the newborn and maternal haemorrhage in WWE taking AEDs?*

All babies born to WWE taking enzyme-inducing AEDs should be offered 1 mg of intramuscular vitamin K to prevent haemorrhagic disease of the newborn. ✓

There is insufficient evidence to recommend routine maternal use of oral vitamin K to prevent haemorrhagic disease of the newborn in WWE taking enzyme-inducing AEDs. D

There is insufficient evidence to recommend giving vitamin K to WWE to prevent postpartum haemorrhage. ✓

Enzyme-inducing AEDs (carbamazepine, phenytoin, phenobarbital, primidone, oxcarbazepine, topiramate and eslicarbazepine) are considered to competitively inhibit the precursors of clotting factors and affect fetal microsomal enzymes that degrade vitamin K, thereby increasing the risk of haemorrhagic disease of the newborn. A systematic review to assess the effect of prenatal vitamin K in preventing haemorrhagic disease of the newborn in WWE taking enzyme-inducing AEDs did not identify any randomised trials.[72] Two observational studies failed to show a beneficial effect for prenatal vitamin K to prevent haemorrhagic disease of the newborn,[73,74] although it is worth noting that babies in these studies were also routinely administered 1 mg of vitamin K injection at birth. Despite the lack of objective evidence, however, it seems reasonable to offer parenteral vitamin K supplementation routinely to all babies born to mothers on enzyme-inducing AEDs.

Evidence level 2+

No studies have evaluated the effectiveness of antenatal administration of oral vitamin K in preventing postpartum haemorrhage.

6.9 *What is the optimal timing and mode of delivery for WWE based on seizure control?*

WWE should be reassured that most will have an uncomplicated labour and delivery. ✓

The diagnosis of epilepsy per se is not an indication for planned caesarean section or induction of labour. D

In WWE with no underlying obstetric risk factors whose seizures are well-controlled seizures, there is no indication for early delivery. In a small proportion of women with significant deterioration of seizures, which are recurrent and prolonged, and who are at high risk of status epilepticus, elective caesarean section may be considered. There is no evidence on the optimal timing and mode of delivery in WWE.

6.10 *How should women with non-epileptic attack disorder be counselled in pregnancy and how should their non-epileptic seizures be managed?*

Inappropriate medical intervention, including AED administration and iatrogenic early delivery, should be avoided when there is a firm diagnosis of non-epileptic attack disorder. D

Diagnostic awareness of non-epileptic attack disorder is an important first step in management.[75] Non-epileptic attack disorder is considered to have a psychological aetiology, most commonly dissociation. It is not caused by epileptiform electroencephalography (EEG) discharge and will not respond to AEDs. Management of women with non-epileptic attack disorder should include access to specialist psychiatric or psychological services.

Evidence level 3

Epilepsy and non-epileptic attack disorder have very different management strategies. In women with known non-epileptic attack disorder presenting with seizure-like episodes in labour, obstetricians will need to rely on the previous diagnosis, which was documented as non-epileptic attack disorder, and avoid emergency obstetric and medical interventions such as delivery, AEDs or diazepam. Close liaison is required with the neurology and mental health teams for further management where appropriate.

6.11 Where required, what dose of antenatal corticosteroids should be given to WWE on enzyme-inducing AEDs?

In WWE taking enzyme-inducing AEDs who are at risk of preterm delivery, doubling of the antenatal corticosteroid dose for prophylaxis against respiratory distress syndrome in the newborn is not recommended. D

WWE taking enzyme-inducing AEDs, such as phenytoin, carbamazepine and phenobarbital, may increase their metabolism of corticosteroids, with reduced therapeutic effectiveness.[76] No studies have assessed the effectiveness of higher or frequent doses of corticosteroids on neonatal outcomes in WWE exposed to enzyme-inducing AEDs and at risk of preterm delivery. In the absence of evidence of benefit with increased dose of steroids, and the potential harm with high steroid doses, routine doubling of steroid is not recommended.

Evidence level 4

7. Intrapartum care

7.1 What are the risks and risk factors for seizures in labour in WWE and how can they be minimised?

Pregnant WWE should be counselled that the risk of seizures in labour is low. C

Adequate analgesia and appropriate care in labour should be provided to minimise risk factors for seizures such as insomnia, stress and dehydration. ✓

Long-acting benzodiazepines such as clobazam can be considered if there is a very high risk of seizures in the peripartum period. D

AED intake should be continued during labour. If this cannot be tolerated orally, a parenteral alternative should be administered. ✓

Tonic-clonic seizures occur in about 1–2% of WWE in labour and within 24 hours of delivery in a further 1–2%.[77] The EURAP registry reported the occurrence of seizures in 3.5% (60/1956) of WWE in labour.[78]

Seizures in labour may lead to maternal hypoxia (due to apnoea during the seizure), and fetal hypoxia and acidosis secondary to uterine hypertonus.[22,79]

Evidence level 3

Sleep deprivation and non-intake of AEDs are risk factors for seizures in labour, and it is thought that pain, tiredness, stress and dehydration may be factors as well.[80] Healthcare professionals will need to ensure that doses of AEDs are not missed during labour and delivery, and should consider parenteral alternatives in cases of excess vomiting. Adequate hydration and pain relief with an epidural will minimise the risks of seizures in labour and provides maximum safety in the event of a seizure. Avoidable delays should be minimised for planned induction of labour or elective caesarean section.

Evidence level 2–

Women at a very high risk of seizures can be managed with an additional benzodiazepine such as clobazam.[81] Prophylactic clobazam is considered in the following circumstances: recent convulsive seizures, recent history of seizure provocation by stress or sleep deprivation, or a history of seizures in previous labour. The risks from clobazam, such as respiratory depression in the newborn, need to be balanced against the benefit due to seizure prevention.

Evidence level 4

Women should be advised to continue taking regular AEDs orally during induction of labour and during labour. If not tolerated orally, AEDs may be given parenterally (this includes phenytoin, phenobarbital, sodium valproate and levetiracetam).

7.2 What is the optimum management of epileptic seizures in labour?

Every obstetric unit should have written guidelines on the management of seizures in labour. ✓

Seizures in labour should be terminated as soon as possible to avoid maternal and fetal hypoxia and fetal acidosis. Benzodiazepines are the drugs of choice. D

Continuous fetal monitoring is recommended in women at high risk of a seizure in labour, and following an intrapartum seizure. ✓

Any seizure lasting more than 5 minutes is unusual and represents a high risk of progressing to convulsive status epilepticus, a life-threatening medical emergency which affects around 1% of pregnancies in WWE.[82] Treatment should be initiated as soon as reasonably possible before status epilepticus and pharmacoresistance is established.[83,84]

Evidence level 2–

Left lateral tilt should be established alongside maintenance of airway and oxygenation at all times.

There are no studies on the optimal management of epileptic seizures in labour. Outwith pregnancy, benzodiazepines are the drug of choice in status epilepticus:

- In those with intravenous access, lorazepam given as an intravenous dose of 0.1 mg/kg (usually a 4 mg bolus, with a further dose after 10–20 minutes) is preferred. Diazepam 5–10 mg administered slowly intravenously is an alternative.
- If there is no intravenous access, diazepam 10–20 mg rectally repeated once 15 minutes later if there is a continued risk of status epilepticus, or midazolam 10 mg as a buccal preparation are suitable.

If seizures are not controlled, consider administration of phenytoin or fosphenytoin. The loading dose of phenytoin is 10–15 mg/kg by intravenous infusion, with the usual dosage for an adult of about 1000 mg. Guidance on the management of seizures is available in the NICE guideline on epilepsy.[1]

Evidence level 2++

If there is persistent uterine hypertonus, consider administration of tocolytic agents. After the mother is stabilised, continuous electronic fetal monitoring should be commenced. If the fetal heart rate does not begin to recover within 5 minutes or if the seizures are recurrent, expedite delivery. This may require caesarean delivery if vaginal delivery is not imminent.

The neonatal team should be informed, as there is a risk of neonatal withdrawal syndrome with the maternal use of benzodiazepines and AEDs.[85]

Evidence level 2–

7.3 What are the recommended methods of analgesia in labour for WWE?

Pain relief in labour should be prioritised in WWE, with options including transcutaneous electrical nerve stimulation (TENS), nitrous oxide and oxygen (Entonox®), and regional analgesia. ✓

Pethidine should be used with caution in WWE for analgesia in labour. Diamorphine should be used in preference to pethidine. D

TENS, Entonox® and regional analgesia (epidural, spinal, combined spinal epidural) are suitable and safe methods of analgesia in labour.[86] An epidural can be considered early to minimise precipitating factors for seizures during labour such as overbreathing, sleep deprivation, pain and emotional stress.

Evidence level 4

Diamorphine should be used in preference to pethidine for analgesia in labour. Pethidine is metabolised to norpethidine, which is known to be epileptogenic when administered in high doses to patients with normal renal function. Pethidine should therefore be avoided or used with caution.[87,88]

If general anaesthesia becomes necessary, it is prudent to avoid anaesthetic agents such as pethidine, ketamine and sevoflurane. The first two are known to lower seizure threshold and the third may have epileptogenic potential.[89–91]

Evidence level 3

7.4 What are the effects of induction of labour on WWE and do AEDs affect induction agents?

There are no known contraindications to use of any induction agents in WWE taking AEDs. ✓

Epilepsy per se is not an indication for induction of labour. The rates of induction of labour are higher in WWE than in those without epilepsy.[92] Healthcare professionals will need to be aware that risk factors such as stress, insomnia and dehydration are high in women with prolonged induction and aim to minimise them.

Evidence level 2+

There is no evidence that AEDs affect induction agents.

7.5 What is the most suitable place of delivery for WWE?

For WWE at risk of peripartum seizures delivery should be in a consultant-led unit with facilities for one-to-one midwifery care and maternal and neonatal resuscitation. [GPP] ✓

The decision to use water for analgesia and birth should be made on an individual basis. WWE who are not taking AEDs and who have been seizure free for a significant period may be offered a water birth after discussion with their epilepsy specialist. [GPP] ✓

If seizure deterioration is anticipated in the peripartum period, delivery should take place where there are facilities for maternal and neonatal resuscitation and treatment of maternal seizures.[1] Continuous electronic fetal monitoring is recommended in these mothers in labour. This should be documented in the care plan. In women who are at low risk of intrapartum seizures, fetal monitoring may be carried out by intermittent auscultation.

Evidence level 4

One-to-one midwifery care is recommended to allow close monitoring of WWE in labour and to prevent known precipitants of seizure in labour such as overbreathing, poor control of pain, dehydration and omission of AED intake.

The decision to use water for analgesia and birth must be made based on the seizure risk status of the mother after discussion between the parents and team caring for the woman, with attention given to how the risk of drowning can be minimised in the unlikely event of seizure. Appropriate safety measures such as a hoist should be available. Healthcare professionals and parents will need to be aware of the difficulties in managing a seizure in labour in this situation and the small potential risk of drowning.

8. Postpartum management

8.1 What is the risk of seizure deterioration postpartum and how can this be minimised?

WWE and their caregivers need to be aware that although the overall chance of seizures during and immediately after delivery is low, it is relatively higher than during pregnancy. C

WWE should be advised to continue their AEDs postnatally. ✓

Mothers should be well supported in the postnatal period to ensure that triggers of seizure deterioration such as sleep deprivation, stress and pain are minimised. ✓

The immediate postpartum period is a high-risk period for exacerbation of seizure frequency due to increased stress, sleep deprivation, missed medication and anxiety. A prospective study of 1297 pregnancies in WWE showed that the period of maximal seizure exacerbation was the 3-day peripartum period in women with generalised and partial seizures. The risk was highest in women who had seizures in the month prior to pregnancy compared with those who were free of seizures during the same period (OR 3.7, 95% CI 2.4–5.9).[93]

Evidence level 2+

Women should ensure that they take their AEDs as prescribed in the postnatal period. Nausea and vomiting should be treated and if there is no oral intake, consideration should be given to parenteral administration of AEDs. Sleep deprivation-related seizures could be reduced by arranging help for the mother, especially for night-time feeds. If the mother breastfeeds, storage of breast milk pumped during the day might be beneficial. Reviewing the daily activities of the mother and identifying high-risk situations can reduce the risks to the mother and baby due to seizures.

8.2 Is there a need to modify the dose of AED after delivery?

If the AED dose was increased in pregnancy, it should be reviewed within 10 days of delivery to avoid postpartum toxicity. ✓

Many women are on higher doses of AEDs at the end of pregnancy compared with their prepregnancy dose. In the postpartum period, the physiological changes that occurred in pregnancy, such as increased renal and hepatic clearance and haemodilution, are reversed and these women become at risk of toxicity from high AED doses.[94,95]

Evidence level 3

The increase in the dose of AED that occurred in pregnancy should be clearly documented in the notes, with a comprehensive plan to liaise with the neurological team to taper the dose in the first 10 days after delivery. If symptoms of AED toxicity develop in the puerperium (e.g. drowsiness, diplopia or unsteadiness), urgent neurological review is needed.

8.3 *What are the effects of AED exposure on the newborn through placental transfer and from breast milk? How should babies of WWE taking AEDs be monitored?*

Neonates born to WWE taking AEDs should be monitored for adverse effects associated with AED exposure in utero. D

WWE who are taking AEDs in pregnancy should be encouraged to breastfeed. C

Based on current evidence, mothers should be informed that the risk of adverse cognitive outcomes is not increased in children exposed to AEDs through breast milk. C

The rates of transfer of AEDs to the neonate through the placenta and breast milk vary. Many of the old generation AEDs, such as phenobarbital, carbamazepine and phenytoin, and the new generation drugs, such as lamotrigine, oxcarbazepine and topiramate, have an umbilical cord to maternal serum AED concentration (U/S) that is close to one, suggesting free transfer of AED across the placenta.[96] The fetal accumulation is mildly increased for levetiracetam, sodium valproate and gabapentin.[96] Evidence level 3

Babies born to mothers taking AEDs may have adverse effects such as lethargy, difficulty in feeding, excessive sedation and withdrawal symptoms with inconsolable crying. Individualised assessment should be made for the level of post-delivery monitoring required for withdrawal symptoms, and for any signs of toxicity. This is especially important in premature babies, and serum levels of AEDs in the baby should be checked where appropriate.[97] Evidence level 4

The magnitude of AED transfer to the baby through breast milk that is required to affect neonatal and childhood outcomes is not known. The American Academy of Neurology/ American Epilepsy Society panel considered an AED transfer rate of 0.6 (neonatal to maternal plasma concentration ratio or a milk to maternal serum [M/S] concentration ratio) or increasing concentrations of AED in the neonate by 25% during the follow-up period (3 days up to 1 month) to be clinically important.[61]

Lamotrigine (M/S 0.6), levetiracetam (M/S 1–3.09) and topiramate (M/S 0.66–1.1) transfer to a larger extent to the child from breast milk compared with sodium valproate (M/S 0.01–0.1), carbamazepine (M/S 0.36–0.41) and phenytoin (M/S 0.06–0.19), which have minimal transfer.[96] Evidence level 3

Breastfeeding has not been shown to affect the cognitive outcomes at 3 years of age in children who were exposed in utero to lamotrigine, sodium valproate, phenytoin or carbamazepine monotherapy.[98] Evidence level 2+

A prospective study on babies who were exposed to AEDs in utero showed that the psychomotor development of the breastfed children was better at 6 and 18 months compared with those who were not breastfed or were breastfed for less than 6 months.[99] Other options such as alternating breast and bottle milk could be considered if there are any concerns about AED exposure. Evidence level 2++

8.4 What advice should be given regarding safety strategies and care of the baby?

Postpartum safety advice and strategies should be part of the antenatal and postnatal discussions with the mother alongside breastfeeding, seizure deterioration and AED intake. ✓

Postnatal mothers with epilepsy at reasonable risk of seizures should be accommodated in single rooms only when there is provision for continuous observation by a carer, partner or nursing staff. ✓

The safety of the mother and baby in the puerperium is the most important issue to be addressed. Generalised seizures, as well as partial seizures and myoclonic jerks, can result in accidental injuries to the mother and the baby, such as drowning, falls, burns and electrocution. The discussions around caring for the baby should be initiated in the preconception period, continued antenatally and reinforced in the postnatal period.

Safety strategies include nursing the baby on the floor, using very shallow baby baths, laying the baby down if there is a warning aura, not bathing the baby unaccompanied, wearing identification tags, and avoiding sleep deprivation, and alcohol if prone to myoclonic jerks. Women should ensure that family and friends have knowledge of first aid and emergency contact procedures.

8.5 How should depression be screened for in the postpartum period?

WWE should be screened for depressive disorder in the puerperium. Mothers should be informed about the symptoms and provided with contact details for any assistance. D

WWE are at an increased risk of depression in the postnatal period compared with mothers without epilepsy. Rates of postpartum depression are higher in WWE than women without epilepsy (29% versus 11% in controls),[100] and in a prospective study of 56 WWE, risk factors for depression were found to be multiparity (OR 12.5, 95% CI 1.9–82.7) and exposure to AED polytherapy (OR 9.3, 95% CI 1.5–58).[101] Self-monitoring for these symptoms and subsequent early intervention may improve quality of life.

Evidence level 2–

9. Contraception

9.1 What contraception can be safely offered to women taking AEDs?

WWE should be offered effective contraception to avoid unplanned pregnancies. ✓

Copper intrauterine devices (IUDs), the levonorgestrel-releasing intrauterine system (LNG-IUS) and medroxyprogesterone acetate injections should be promoted as reliable methods of contraception that are not affected by enzyme-inducing AEDs. D

Women taking enzyme-inducing AEDs (carbamazepine, phenytoin, phenobarbital, primidone, oxcarbazepine, topiramate and eslicarbazepine) should be counselled about the risk of failure with some hormonal contraceptives. C

Women should be counselled that the efficacy of oral contraceptives (combined hormonal contraception, progestogen-only pills), transdermal patches, vaginal ring and progestogen-only implants may be affected if they are taking enzyme-inducing AEDs (e.g. carbamazepine, phenytoin, phenobarbital, primidone, oxcarbazepine and eslicarbazepine). C

All methods of contraception may be offered to women taking non-enzyme-inducing AEDs (e.g. sodium valproate, levetiracetam, gabapentin, vigabatrin, tiagabine and pregabalin). C

WWE taking enzyme-inducing AEDs should be informed that a copper IUD is the preferred choice for emergency contraception. Emergency contraception pills with levonorgestrel and ulipristal acetate are affected by enzyme-inducing AEDs. C

Women taking lamotrigine monotherapy and oestrogen-containing contraceptives should be informed of the potential increase in seizures due to a fall in the levels of lamotrigine. C

The expected failure rate of oral contraception is three times higher (3.1 per 100 woman-years) in WWE taking enzyme-inducing AEDs compared with the normal population.[102–104] A systematic review of studies on WWE taking combined oral contraceptives reported that the levels of ethinylestradiol and levonorgestrel were reduced with carbamazepine, oxcarbazepine, felbamate and vigabatrin.[105] There were no changes in the serum levels of hormones in women taking levetiracetam, gabapentin, zonisamide and tiagabine.[105] Topiramate in therapeutic doses below 200 mg/day does not interact with oral contraceptives containing norethisterone and ethinylestradiol.[106] Higher doses of topiramate (200–800 mg/day) may modestly increase the clearance of ethinylestradiol.[106]

In women who are taking enzyme-inducers and choose to use oral contraception, the contraceptive efficacy may be improved by increasing the oestrogen component to 50 micrograms (maximum 70 micrograms), reducing the pill-free interval from 7 days to 4 days and tricycling (taking three packs back to back).[107] There are no data on the success rates of such measures.

Barrier contraception should be additionally used if WWE taking enzyme-inducing AEDs use oral contraceptives (combined hormonal contraception or progestogen-only pills), transdermal patches, vaginal rings or progestogen-only implants.[108] Evidence level 4

For emergency contraception for WWE taking enzyme-inducing AEDs, only the copper IUD is recommended. It is unclear whether a higher dose of levonorgestrel or ulipristal acetate is a sufficiently effective strategy. A double dose of levonorgestrel (3 mg as a single dose within 120 hours of unprotected sexual intercourse) may be used pragmatically. Ulipristal acetate should not be used.[108]

Oral hormonal contraceptives can alter the efficacy of some AEDs by increasing the metabolism of glucuronidated drugs through induction of uridine diphosphate-glucuronosyl transferase (UGT1A4). Although lamotrigine is not an enzyme-inducer, oral contraceptive use has been associated with a 25–70% decrease in lamotrigine trough levels, with a drop of more than 20% in the first 3 days after taking the pill.[109] The fall in levels has the potential to increase seizure deterioration.[110] Such a fall in lamotrigine levels is more likely to occur in WWE taking lamotrigine monotherapy and oestrogen-containing contraception. Lamotrigine concentrations are not known to change in WWE receiving progestogen-only pills, progestogen implants and injections and the LNG-IUS.[105] Evidence level 3

There are no data available on the interaction between progestogen-only pills and enzyme-inducing AEDs. Enzyme-inducing AED intake is associated with decreased oestrogen and progesterone levels.[102,111,112] There is insufficient evidence to recommend progestogen-only pills to WWE taking enzyme-inducing AEDs. There are reports of true contraceptive failures in women using AEDs and progestogen-only implants (Implanon®, Nexplanon®, Merck Sharp & Dohme Ltd., Hoddesdon, Hertfordshire).[113,114]

The medical eligibility criteria for use of a contraceptive are primarily based on the safety of the drug. These may not take into consideration the drug interactions which may affect 'efficacy' of the contraceptive, rendering it less effective.

Table 2. Recommended methods of contraception in WWE taking AEDs

AED	Combined hormonal methods	Progestogen-only pill	Progestogen-only implant	Progestogen-only injectable	LNG-IUS	Copper IUD
Enzyme-inducing AEDs[a]	3[b]	3[b]	2[b]	Depot medroxyprogesterone acetate – 1 Norethisterone enanthate – 2[b]	1	1
Non-enzyme-inducing AEDs[c]	1	1	1	1	1	1
Non-enzyme-inducing AEDs: lamotrigine	3	1	1	1	1	1

Adapted from Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit. *Antiepileptic Drugs and Contraception*. CEU Statement (January 2010). [London]: FSRH; 2010.[107,115]

[a] Carbamazepine, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, rufinamide, topiramate.

[b] The consistent use of condoms is recommended.

[c] Benzodiazepines, ethosuximide, gabapentin, lacosamide, levetiracetam, sodium valproate, tiagabine, vigabatrin, zonisamide.

UK Medical Eligibility Criteria (UK MEC) Category 1:	A condition for which there is no restriction for the use of the contraceptive method with the condition or in that circumstance.
UKMEC Category 2:	A condition where the advantages of using the method generally outweigh the theoretical or proven risks.
UKMEC Category 3:	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist provider, since use of the method is not usually recommended unless other methods are not available or not acceptable.
UKMEC Category 4:	A condition that represents unacceptable health risk if the method is used.

9.2 What are the preferred contraceptive choices in WWE and what risks need to be conveyed to help them make informed decisions?

The risks of contraceptive failure and the short- and long-term adverse effects of each contraceptive method should be carefully explained to the woman. Effective contraception is extremely important with regard to stabilisation of epilepsy and planning of pregnancy to optimise outcomes. ✓

A survey of 537 WWE showed that 85% were aware that some AEDs interact with hormone-based contraceptives, 51% were given information that AEDs could make hormone-based contraception less effective, only 9% were told that their AEDs would not interact with their hormone-based contraception and 25% were given no information.[116] Evidence level 2–

10. Other implications

10.1 What may affect the driving entitlements of WWE who are pregnant?

WWE should be informed of the effect of changing the dose of AED on seizures and its impact on driving privileges. ✓

The general driving regulations for individuals with epilepsy apply to pregnant WWE. Mothers will need to be informed that stopping or reducing the dose of AED in pregnancy may result in seizure deterioration, including the first episode of seizures. This will have an impact on driving privileges and may affect parenting and work plans.[117] Evidence level 4

10.2 What are the implications of disability legislation for WWE and health service providers?

Healthcare providers need to be aware of equality legislation in the UK that protects individuals with a disability from discrimination. ✓

Discrimination on the grounds of disability is illegal, with the relevant legislation being the Equality Act 2010 in England, Scotland and Wales, and the Disability Discrimination Act 1995 in Northern Ireland. Pregnancy offers a unique opportunity to work closely with pregnant mothers with epilepsy. Support by healthcare professionals is crucial to WWE, including access to provisions such as water birth if appropriate.

11. Recommendations for future research

- Identify the optimal monitoring strategy (therapeutic drug monitoring versus monitoring based on clinical features) for pregnant WWE taking AEDs with regards to maternal and fetal outcomes by a randomised trial.
- Development and validation of a prognostic model for seizure deterioration in pregnancy.
- Qualitative study on women's views on epilepsy in pregnancy, their perceptions of risk and their concerns regarding AED intake in pregnancy, and the views of partners and families.
- The role of vitamin K in preventing postpartum haemorrhage in WWE taking AEDs.
- The use of double dose steroids to induce fetal lung maturity in WWE taking enzyme-inducing AEDs.
- Effects of AED exposure (for various types and doses) in utero and through breast milk on the long-term neurodevelopment of the offspring and on later diagnosis of cardiac anomalies by a prospective cohort study.
- Optimal dose of AED that minimises the long-term adverse effect on the child.
- Epigenetic effects of AEDs on fetal outcomes.
- Effects of newer AEDs such as levetiracetam on the fetus in the short and long term.
- Neuropsychiatric effects of epilepsy and AEDs as assessed by WWE and their families.

12. Auditable topics

Standards for audit of practice should include the following:

- Provision of written information on the effects of epilepsy and AEDs on pregnancy outcomes and seizures (100%).
- Multidisciplinary input into prepregnancy, antenatal, intrapartum and postnatal care of WWE (100%).

Standards for audit of documentation should include the following:

- Written protocols for management of status epilepticus in all obstetric units (100%).
- Documented discussion on risks to the mother and baby from epilepsy and AEDs in the short and long term (100%).
- Proportion of women enrolled in the UK Epilepsy and Pregnancy Register (100%).

13. Useful links and support groups

- Epilepsy Action. *Epilepsy and having a baby* [https://www.epilepsy.org.uk/info/women/having-baby].
- Epilepsy Society. *Pregnancy and parenting* [http://www.epilepsysociety.org.uk/pregnancy-and-parenting].
- UK Epilepsy and Pregnancy Register [http://www.epilepsyandpregnancy.co.uk/].

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Appendix I: Explanation of guidelines and evidence levels

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1 *Development of RCOG Green-top Guidelines* (available on the RCOG website at http://www.rcog.org.uk/green-top-development). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1–	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendations

A	At least one meta-analysis, systematic review or randomised controlled trial rated as 1++, and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good practice point

✓	Recommended best practice based on the clinical experience of the guideline development group

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The final version is the responsibility of the Guidelines Committee of the RCOG.

The review process will commence in 2019, unless otherwise indicated.

